Evaluation and comparison of magnesium stearate and sodium stearyl fumarate (Pruv®) as lubricants in directly compressible tablet formulations: Their effect on tablet properties and drug dissolution

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Dedicated to my parents, Kallie and Wilma Louw

Thank you for your love and encouragement which blessed me with the self-esteem and ability to continue this journey in search of excellence and wisdom.

The essence of living is to make a positive difference. To make a difference, you need to take action. Knowledge means nothing if you don't take action. People who make a difference are people who don't just wish, they act. There are dreams, visions, plans and ideas in every one of us which need to be released. By the sheer ability of you to think it, you can do it. But it is important to understand that thinking doesn't get it done. Thinking only implies that you can do it. You need to transform your thought into an idea, and take that idea and put it into a plan and then you need to put your plan into action. In science the idea usually evokes around our ever searching need to create perfection by coordinating chaos, both of which are difficult to distinguish. You must take the word impossible out of your dictionary. Anything is possible! Our acts can be no wiser than our thoughts and our thinking can be no wiser than our understanding. In understanding your potential, you must decide whether or not you are going to rob the world or bless it with rich, valuable, untapped resources locked away within you.

The potential of a thing is not determined by opinions, assumptions or prejudices, but only by the demands placed on it by the inventor. Your true ability should not be measured by the limitations of an academic test or an IQ score. Nor should it be determined by your family or society. They did not create you. Therefore, they do not have the right to determine how much potential you really possess. If you want to know how much potential you have, first discover who created you. We all have a deposit of God's ability for we were created in the image of God dynamic, creative and living.

Success becomes our enemy as we settle for what we have. Refuse to be satisfied with your last accomplishment, because potential never has a retirement plan. Any person, who sets a limit on what he can do, also sets a limit on what he will do. Success is traditionally defined by external measures of how much money you make or by your status in society. Being successful seemingly always involves being measured against others. Fulfilled success is not a comparison of what you have done compared to that which others have done. It is simply coming up to the level of our best, making the most of our abilities and possibilities. Success is knowing your purpose in life, growing to reach your potential and sowing seeds that benefit others. Success is not a destination; it is not a place you arrive at one day. Instead, it is the journey you take; and whether or not you succeed, comes from what you do day to day.

Why do most of us battle to make the most of our abilities and possibilities? I believe that in most cases it is because of fears we have. I have discovered that every time I find myself stuck in a place not being able to make progress, it was because of some fear. It might be fear of rejection or fear of being wrong. We are often more willing to do damage to a relationship by arguing than to admit that we were wrong. It might be fear of being emotionally uncomfortable due to the fear of failure.

Fear for failure leads to inaction. It paralyses you. It leads you to procrastinate on an important issue. Someone once called procrastination the fertilizer that makes difficulties grow. Because you don't act, you don't gain personal experience in that situation, which is the key to learning and overcoming obstacles. And the lack of experience breeds an inability to handle similar situations and that ultimately feeds and increases the fear of making it more and more difficult to break the cycle of fear. Failure works the same way as success. It's not some place you arrive. It's how you deal with life, along the way. Every person's life is filled with errors and negative experiences, but errors become mistakes when we perceive them and respond to them incorrectly. Mistakes become failures when we continually respond to them incorrectly. People who succeed are able to see errors or negative experiences as a regular part of life, learn from them, and then move on with self-confidence. Self-confidence is the fuel for productivity and creativity, decisiveness (taking action) and speed. The difference between average people and achieving people - those who consistently shine as apposed to those who don't - is their perception of, and response to, failure.

Each of us has to make a choice. We can sleep life away, avoiding failure at all costs. Or we can wake up and realize that failure is simply a price we pay in achieving success. George Bernard Shaw wrote "A life spent in making mistakes is not only more honourable but more useful than a life spent doing nothing".

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Abstract

Evaluation and comparison of magnesium stearate and sodium stearyl fumarate (Pruv®) as lubricants in directly compressible tablet formulations: Their effect on tablet properties and drug dissolution

The most widely used lubricant in the pharmaceutical industry is probably magnesium stearate. Magnesium stearate exhibits its lubricating properties by forming a film of low shear strength between the die wall and the compact, thus reducing the friction (Banker & Anderson, 1986:306). It also exhibits anti-adhesive and flow enhancement properties by preventing tablets from sticking to the die wall and punch faces and ensuring uniformity of tablets. Besides these advantageous properties, the lubricant forms a hydrophobic film around the carrier particles which can negatively affect the tablet properties such as crushing strength, disintegration time, friability and dissolution (Bolhuis *et al.*, 1975:324; Levy & Gumtow, 1963:1142). Due to the deleterious effects on the tablet properties, lubricant concentrations must be restricted to an absolute minimum. These effects are known to increase with prolonged mixing, and in practice one tries to keep the lubricant mixing time as short as possible (Ragnarsson *et al.*, 1979:130). It has been shown that the die wall film of magnesium stearate is resistant to wearing off and the lubricating effect remains for several compactions when an unlubricated granulation is added to a lubricated die (Hölzer & Sjögren, 1981b:276). The lubricant film around the particles is formed during the final mixing, while the film at the die wall is formed during the compaction. This implicates that the lubricant is mixed for shorter (mixing) times with the other excipients in the formulation.

Sodium stearyl fumarate (Pruv®) has been suggested as a suitable lubricant in tableting (Mendell, 2002:5) and it is claimed not to have the disadvantages of magnesium stearate in respect of tablet strength, disintegration and dissolution (Lindberg, 1972:213). These properties could prove advantageous regarding tablet strength as well as drug release properties (especially for immediate release tablet formulations). Since the primary function of lubricants is the reduction of friction, it was this property that provided the challenge that was circumvented in this study. The addition of the sparingly water-soluble, hydrophobic drug, furosemide, perplexed the formulation of tablets, however, provided a mode of evaluation of the effects of formulation variables on tracer substance dissolution behaviour.

Systematic evaluations of various commercially available excipients were investigated to determine their effects on the physical tablet properties as well as on tracer dissolution. Magnesium stearate or Pruv® was incorporated into Avicel® PH-200, Emcompress® and Tablettose® fillers/binders. Mixing time was varied between 1 and 16 minutes and mixing speed between 33 and 97 rpm under certain specified testing environments in a Turbula® mixer. Compression was done with a Manesty® F3 single station tablet press with biconcave punches (10 mm). Evaluation on the powder and the compressed formulation was done. The aim was to evaluate and compare the lubricant, glidant and antiadherent properties of magnesium stearate and Pruv®, as well as the effect both had on tablet properties (crushing strength, friability and disintegration) and drug release.

It was found that magnesium stearate had superior glidant properties compared to its counterpart as a result of its flatter particle shape and larger specific surface area. Lubricant concentrations below 0.5% w/w gave optimum glidancy for both lubricants and mixing times between 4 and 8 minutes was sufficient to optimize this glidant effect.

Tablet strength decreased when lubricant concentration increased, due to less interparticulate binding surface between the carrier particles. This decrease subsided when lubrication surpassed the 1.5% w/w concentration level. Mixing, however, had the opposite effect on Pruv® than on magnesium stearate, since Pruv® increased the tablet strength with continuous mixing.

Disintegration and dissolution deteriorated with the addition of magnesium stearate and Pruv®. This was due to the hydrophobic nature of magnesium stearate and increase in tablet strength observed with Pruv®. The evaluation of the extent of drug release (AUC) and rate of release (DR_i) indicated of an average increase of 50% in drug release in formulations with Pruv® compared to magnesium stearate as lubricant.

Magnesium stearate had superior lubricant and antiadherent properties as opposed to Pruv® and optimum lubricant efficiency was experienced at low concentrations (< 1% w/w) and low mixing times (< 4 minutes). The apparatus and methods for lubricant evaluation were newly developed and gave accurate, repeatable measurements.

Uittreksel

Evaluering en vergelyking van magnesiumstearaat en natriumstearielfumaraat (Pruv®) as smeermiddels in direk-saampersbare tabletformules: Effek op tableteienskappe en geneesmiddeldissolusie

Die mees algemeen gebruikte smeermiddel in die farmaseutiese industrie is waarkynlik *magnesiumstearaat*. Magnesiumstearaat tree op as smeermiddel deur die vorming van 'n laag van lae skuifkrag tussen die matryswand en die tablet om sodoende wrywing te verlaag (Banker & Anderson, 1986:306). Smeermiddels toon ook (1) antiklewingseienskappe, om klewing van tablette aan die matryswand en stempeloppervlaktes te voorkom, en (2) vloei-eienskappe om sodoende uniforme tabletmassa te verseker. Benewens dié voordelige eienskappe moet die smeermiddel 'n hidrfobiese laag rondom die draerdeeltjies vorm wat tableteienskappe soos breeksterkte, disintegrasie tyd, afsplyting and dissolusie negatief kan beïnvloed (Bolhuis *et al.*, 1975:324; Levy & Gumtow, 1963:1142). As gevolg van die nadelige effekte op tableteienskappe moet smeermiddelkonsentrasies tot 'n absolute minimum beperk word. Die effekte is bekend daavoor om toe te neem met verlengde vermenging en in die praktyk word daar probeer om die vermengingstyd so kort moontlik te hou (Ragnarsson *et al.*, 1979:130). Dit is bewys dat die matryswandlaag van magnesiumstearaat weerstand bied teen afwering en dat die smeermiddel se effek voortduur vir tablette, al word granules sonder smeermiddel in die smeermiddel-bedekte matrys gekompakteer (Hölzer & Sjögren, 1981b:276). Die smeermiddellaag rondom deeltjies word gevorm in die finale vermengingsproses, terwyl die laag op die matryswand tydens tablettering gevorm word. Dit impliseer dat smeermiddels vir korter tye met die ander hulpstowwe in die formule vermeng moet word.

Natriumstearielfumaraat (Pruv®) is as geskikte smeermiddel vir tablettering voorgestel (Mendell, 2002:5) en daar word beweer dat dit nie die nadelige eienskappe van magnesiumstearaat het nie ten opsigte van breeksterkte, disintegrasie en dissolusie (Lindberg, 1972:213). Die eienskappe kan voordelig wees ten opsigte van breeksterkte en geneesmiddel vrystelling en -dissolusie (veral vir vinnig vrystellende formules). Aangesien die primêre funksie van smeermiddels die verlaging van wrywing is, was dit die evaluering van hierdie eienskap wat as uitdaging vir die studie gedien het. Die toevoeging van die swak-wateroplosbare, hidrofobiese geneesmiddel, furosemied, het bykomende uitdagings

gebied wat betref die fomulering van tablette. Die geneesmiddel het egter die geleentheid geskep om die effek van formuleringsveranderlikes se effek op dissolusiegedrag te evalueer.

Sistematiese evaluering van verskeie hulpstowwe is uitgevoer om hulle effekte op fisiese tableteienskappe sowel as dissolusiegedrag van die analiet te bepaal. Magnesiumstearaat of Pruv® is vermeng met Avicel® PH-200, Emcompress® en Tablettose® (tablet vulstowwe). Mengtyd (in 'n Turbula® menger) het gevarieer tussen 1 en 16 minute en mengspoed tussen 33 en 97 opm. Tablettering is gedoen op 'n Manesty® F3 enkeltabletpers met bikonkawe stempels (10 mm). Evaluering van die poeier en gekompakteerde formules is gedoen. Die doel was om die smeer-, gly- en antiklewingseienskappe van magnesiumstearaat en Pruv®, asook om die effek wat beide op die tableteienskappe (breeksterkte, afsplyting en disintegrasie) en geneesmiddelvrystelling gehad het, te evalueer en te vergelyk.

Daar is gevind dat magnesiumstearaat oor beter glymiddel eienskappe beskik het as Pruv®, as gevolg van eersgenoemde se platter deeltjies en groter spesifieke oppervlak area. Smeermiddel konsentrasies onder 0.5% m/m het optimum glymiddeleienskappe vir beide smeermiddels gelewer en mengtye tussen 4 en 8 minute was genoegsaam om die gly-eienskappe verder te optimaliseer.

Tabletbreeksterkte het afgeneem soos smeermiddel konsentrasie toegeneem het as gevolg van minder interpartikulêre bindingsareas tussen draerdeeltjies. Hierdie verlaging het afgeneem indien die smeermiddel konsentrasie bokant 1.5% m/m verhoog het. Vermenging het egter die teenoorgestelde effek op Pruv® gehad as op magnesiumstearaat, aangesien Pruv® tabletbreeksterkte verhoog het met verlengde mengtyd.

Disintegrasie en dissolusie het verswak met die toevoeging van magnesiumstearaat en Pruv®. Dit was as gevolg van die hidrofobiese eienskappe van magnesiumstearaat en die toename in breeksterkte soos met Pruv® gevind is. Twee dissolusieparameters, naamlik die aanvanlike dissolusietempo (DR_i) en die mate van dissolusie (AUC) was nuttig in die bepaling van 'n gemiddelde 50% toename in geneesmiddelvrystelling van formules met Pruv® in plaas van magnesiumstearaat as smeermiddel.

Magnesiumstearaat het better smeermiddel en antiklewingseienskappe gehad in vergelyking met Pruv® en doeltreffende smeermiddeleffektiwiteit was by lae konsentrasies (< 1% m/m) en kort mengtye (< 4 minute) gevind. Die apparatuur en metodes van smeermiddelevaluering is nuut ontwikkel en het akkurate en herhaalbare metings verseker.

Aim and objectives of this investigation

AIM

The aim of this study was to compare and evaluate magnesium stearate and sodium stearyl fumarate (Pruv®) as lubricants in directly compressed Avicel® PH-200, Emcompress® and Tablettose® tablet formulations in terms of their effect on the physical properties of the powders and tablets and on drug dissolution.

BACKGROUND

The oral route still provides a relative easy way of administering drugs for a systemic effect. Of all the oral dosage forms available, tablets still remain the most popular dosage form. As a dosage form class, tablets are one of the most challenging pharmaceutical products to design and manufacture, with the main objective to orally administer the correct amount of drug in the proper form at or over the correct time and in the desired location (Banker & Anderson, 1986:293).

Direct compression as method of tablet manufacture presents several advantages to the formulator, but also certain challenges. Amongst the latter are (1) finding new tablet excipients suitable for use in directly compressible formulations to further improve on the advantages of the direct compression and (2) improving drug release through the selection of the correct combination during the formulation phase, especially in the case of sparingly water-soluble and poorly water-wettable drugs.

The lubricant plays an important and sometimes critical role in directly compressible tablet formulations, both in terms of the final tablet properties and in terms of its effect on drug release and dissolution. Therefore, a lubricant is almost invariably needed in directly compressible tablet formulations. As the powder/granules are compressed and thus deformed during tableting, it exerts a radial stress on the die wall, the magnitude of which can be large enough to prevent ejection of the tablets from the die. A lubricant as a substance, which deforms easily when sheared between two surfaces and hence, when sheared between the tablet and the die wall, provides a readily deformed film (Armstrong, 1988:65). Whilst most conventional lubricants, and magnesium stearate in particular, provide sufficient lubrication during tableting, they impart certain negative characteristics in tablets, including lack of solubility, incompatibility, a decrease in the mechanical strength of tablets accompanied by an increase in tablet friability and hydrophobicity which lead to an increase in tablet disintegration time thereby reducing drug dissolution and eventually drug

bio-availability. Their adverse effect on drug dissolution in particular, is well known and a mistake as simple as overmixing can have disastrous consequences (Bolhuis *et al.*, 1975:324).

Sodium stearyl fumurate has been suggested as a suitable lubricant for direct compression (Mendell, 2002:5). It is claimed not to have the disadvantages of magnesium stearate in respect to tablet strength, disintegration and drug dissolution (Lindberg, 1972:213). This excipient exhibits the following characteristics and advantages:

- Due to its hydrophilic properties is does not prolong tablet disintegration compared to magnesium stearate.
- It is a boundary lubricant with an efficiency comparable to magnesium stearate in terms of reduction of die wall friction during tablet ejection.
- It is particularly suitable in formulations where rapid disintegration is desirable.
- It is less hydrophobic than most other lubricants and because of its excellent lubrication properties has beneficial effects on the lubrication characteristics of other tablet components. This might allow for a reduction in the concentration of sodium stearyl fumarate (Mendell, 2002:5). It does, however, appear to be slightly less effective to counteract the adhesion of powder to the punches.
- Prolonged mixing with the compound appears to improve its lubricating and anti-adhesive effects with less negative impact on tablet disintegration compared to magnesium stearate, although it might reduce tablet strength somewhat (Hölzer & Sjögren, 1979:152).

It is accepted that a micronized lubricant is more efficient than a coarse fraction, and it is therefore important that the surface area is standardized to obtain reproducible effects. Thus, the particle size of sodium stearyl fumurate is an important factor to be considered during formulation, especially to achieve the fore mentioned properties and effects. The effects of the excipient correlate better with the relative surface area of added lubricant than with the actual amount (Hölzer & Sjögren, 1981:147). When sodium stearyl fumarate is incorporated into formulations, one must aim for a concentration of 1.5 - 2.0% w/w to achieve optimum lubrication (Mendell, 2002:5).

OBJECTIVES

To achieve the aim of the study, the following had to be undertaken:

- Optimization of mixing conditions (mixing time and mixing speed) for mixture preparation. Preparation of powder mixtures containing a directly compressible filler (Avicel® PH200, Emcompress® or Tablettose®) and different concentrations of magnesium stearate or sodium stearyl fumurate.
- Physical characterization of the particle shape and size of fore mentioned excipients and formulations with magnesium stearate or sodium stearyl fumarate (Pruv®).
- Determination of the physical properties of tablets prepared from the fore mentioned formulations as a function of compression force. This phase will also include the determination of lubricant efficiency as a function of lubricant type and concentration, filler type and compression force.
- Determination of drug dissolution from tablets to evaluate the effect of lubricant type and concentration on drug release/dissolution profiles.
- Evaluation of the lubricant, antiadhesion and flow properties of magnesium stearate and Pruv® a function of lubricant concentration and mixing conditions (mixing time and speed) in different carrier systems. This evaluation included the design and development of assessment apparatus and methods.

CHAPTER 1

Lubricants and their use in directly compressed tablets

1.1 INTRODUCTION

Lubrication has always been one of the most complicated and frustrating aspects of tablet formulation. The lubrication of direct compression powder blends is, if anything more complicated than that of classical granulating. In general the problems associated with lubricating direct compression mixtures can be divided into two categories; namely (1) the type and amount needed to produce adequate lubrication and (2) the softening effects which result from lubrication (Sheth *et al.*, 1980:64), due to the lubricant particles coating the larger excipient particles and interrupting interparticulate bonding (Velasco *et al.*, 1997:112).

The overall mean particle size of direct compression blends is less than that for granulation, and higher concentrations of lubricants are thus often needed. The recognized need for small particle size of lubricants in granulations is of even greater importance in direct compression (Shah & Mlodozeniec, 1977:1377).

Particle surfaces are covered with more lubricant in direct compression blends, to magnify the softening effect upon compression. This is particularly true in direct compression fillers, which exhibit almost no fracture or plastic flow on compression. Even when a layer of lubricant covers all surfaces of a granulation, significant clean surfaces are formed during compression. In most instances standard blending times will result in complete coverage of these surfaces. The same blending times in direct compression blends may or may not cover all primary surfaces. Thus, the length of blending becomes much more critical in direct compression than in preparation of tablet granulations. If blended long enough, alkaline stearate lubricants will shear off and completely cover all exposed particle surfaces. It may be necessary to avoid the alkaline stearate lubricants completely in some compression formulations, due to incompatibilities and adverse effects of lubricants on tablet properties. The influence of the duration of lubricant and excipient mixing on the processing characteristics of powders – and on the properties of compacts prepared by direct compression – was studied by Shah and Mlodozeniec (1977:1377). They found that ejection force, hardness, disintegration, and dissolution of directly compressed tablets of lactose and microcrystalline cellulose were all significantly affected by blending times. Lubrication of direct compression formulations is one of the more complex and difficult problems faced by the pharmaceutical formulator.

1.2 DEFINITION AND ROLES IN TABLET FORMULATIONS

In the broadest sense, lubricants are agents added in small quantities to tablet formulations to improve certain processing characteristics. In this connection, three roles are usually identified:

1. Prevention of sticking to surfaces, e.g. the faces of tablet punches, die wall, hopper, etc. ("antiadherent role").
2. Reducing friction between sliding surfaces, traditionally at the tablet die wall interface during tablet formation and ejection ("true lubricant role").
3. Improving flow properties by modifying the interaction between particles ("glidant role") (Strickland *et al.*,1956:51).

Most lubricant materials possess one or more of these attributes to varying degrees (see table 1.1), and combinations are often used to maximize the overall lubricant effect.

Table 1.1: *Characteristics of some lubricants (Gunsel & Kanig, 1976:329).*

Lubricant	True lubricant	Antiadherent	Glidant
Metallic stearates	Excellent	Good	Poor
Stearic acid	Good	Good	None
Colloidal silicas	None	Good	Excellent
Talc	Poor	Excellent	Good
Corn starch	Poor	Excellent	Excellent

Such a classification, together with appropriate means of evaluation would provide a rational basis for the selection and utilization of combinations of materials, to meet the specific needs of a given formulation and process.

Despite the many advances made in pharmaceutical technology, essentially the same materials are being used as lubricants as were used as long as 50 years ago. Yet, several important problems exist with traditional lubricants with which the formulator have (more or less) learned to live:

1. The most effective of these lubricants are hydrophobic.
2. There has been no tableting grade lubricant specifically designed to meet pharmaceutical requirements. For instance, official grades of magnesium stearate from different sources are well known to possess different lubricating qualities.

3. Our basic understanding of the relationship between lubricant physicochemical properties and function is incomplete.
4. Laminar lubricants, such as magnesium stearate, tend to delaminate under agitation, thereby making the degree of coverage of host particles a function of blending time or intensity of mixing.
5. Hydrophobic lubricants are well known to soften tablets, the degree of this effect depending on the specific lubricant, its concentration and the deformation characteristics of the matrix.

No acceptable alternative to the inclusion of a lubricant or lubricant system as a part of tablet formulations currently exists. Research in more recent years has been concerned with developing better methods of evaluating lubricants, a better understanding of magnesium stearate, and the use of new or non-traditional substances as lubricants, such as sodium stearyl fumarate, produced by Mendell as Pruv®.

1.3 LUBRICANTS

Lubricants act by interposing an intermediate layer between the tablet constituents and the die wall, which yields preferentially when the tablet surface moves relative to the die on compression and on ejection. The smaller the amount of stress needed to shear the material, the better its lubricant properties will be.

1.3.1 CLASSIFICATION

Lubrication is considered to occur by two mechanisms. The first is termed fluid (or hydrodynamic) lubrication, because the two moving surfaces are viewed as being separated by a finite and continuous layer of fluid lubricant. A hydrocarbon such as mineral oil, although a poor lubricant, is an example of a fluid-type lubricant. Hydrocarbon oils do not readily lend themselves to application of tablet granulations and, unless atomized or applied as a fine dispersion, will produce tablets with oil spats. The second mechanism, that of boundary lubrication, results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces of the die wall. Magnesium stearate is an example of a boundary lubricant. Boundary-type lubricants are better than fluid-type lubricants since the adherence of a boundary lubricant to the die wall is greater than that of the fluid type. This is to be expected since the polar end of the boundary lubricant should adhere more tenaciously to the oxide metal surface than the non-polar fluid type (Banker *et al.*, 1980:88).

Lubricants may be further classified according to their water solubility (as water-soluble or water-insoluble). The choice of a lubricant may depend in part upon the mode of administration and the type of tablet being produced, the disintegration and dissolution properties desired, the lubrication and flow problems and requirements of the formulation, various physical properties of the powder system being compressed, drug compatibility considerations, and cost (Banker *et al.*, 1980:89).

1.3.1.1 Water-insoluble lubricants

Some of the more common anti-frictional agents encountered in direct compression are hydrophobic and consequently might affect the release of the drug. In practice this is often markedly so, and for this reason it cannot be overemphasized that lubricant concentration and mixing time should be kept to the absolute minimum. They may also significantly reduce the mechanical strength of the tablet. Stearic acid and its magnesium and calcium salts are widely used, but the latter can be sufficiently alkaline to react with certain amine salts such as aminophylline, resulting in the release of the free base and discoloration of the tablets. In these cases substitution with stearic acid will overcome the problem. Published formulas show levels of these lubricants between 1 and 4 %, but there is evidence to show that in many cases they could be reduced to as little as 0.25% without significantly affecting the lubrication of the system (See table 1.2).

Table 1.2: *Water- insoluble lubricants (Banker et al., 1980:90).*

Material	Usual range (% w/w)
Stearates (magnesium, calcium, sodium)	0.25-2
Stearic acid	0.25-2
Sterotex®	0.25-2
Talc	1-5
Waxes	1-5
Stearowet®	1-5

Liquid paraffins, particularly those of low viscosity, have been used and are said to be of value for coloured tablets, and even modified vegetable oils have been tried. However, they appear in general to offer little advantage over solid lubricants and their incorporation into the pre-compression mixture is more difficult, requiring solution in a volatile liquid, which is then sprayed onto the unlubricated material (Marshall & Rudnic, 1990:381).

Isolated references in the literature describe the use of talc as a lubricant, but this material is better regarded as a glidant. It has several disadvantages including an abrasive quality

unless the finest grade is specified. It is, of course, entirely insoluble in body fluids and therefore the absolute minimum amount should be incorporated in the formulation, often found to be 3 to 5%. Finally, tablets containing talc cannot be readily reworked without further quantities being added, as it loses some of its effectiveness after compression and incorporation in the granulation (Marshall & Rudnic, 1990:381).

Stearowet® has demonstrated remarkable resistance to the effect of overmixing. Exaggerated mixing times of up to 1 hour have resulted in no increase in dissolution time ($T_{50\%}$) when compared to a 2 hour mix (Banker *et al.*, 1980:90).

Since the best lubricants are hydrophobic, the presence of the lubricant coating may cause an increase in the disintegration time and a decrease in the drug dissolution rate. Usually as the concentration of the lubricant increases, these undesirable effects increase, as the ability of water to penetrate the tablet is reduced. Since the strength of a tablet depends on the area of contact between the particles, the presence of a lubricant may also interfere with the particle-to-particle binding and result in a less cohesive and mechanically weaker tablet (Banker *et al.*, 1980:89). Matsuda *et al.* (1976:1155) reviewed the effect on hardness and ejection force of two methods of applying four lubricants (stearic acid, magnesium stearate, calcium stearate, and talc) to statically compressed tablets prepared from a lactose granulation. In one method of addition the lubricant was incorporated into the granulation during preparation, while in the other it was added to (mixed with) the final granules. The mixing method gave better results for ease of ejection and tablet hardness than the incorporation method.

1.3.1.2 Water-soluble lubricants

Alternative more hydrophilic materials have been investigated due to the natural association of lubricant properties with lipophilic materials (and hence with poor aqueous solubility). Water-soluble lubricants are in general used only when a tablet must be completely water-soluble (e.g. effervescent tablets) or when unique disintegration or, more commonly, dissolution characteristics are desired. Possible choices of water-soluble lubricants are shown in table 1.3. Boric acid is a questionable member of the list due to the recognized toxicity of boron.

Perhaps not surprisingly, none appears to possess as much lubricity as that of the water-insoluble lubricants, although synergism may be of help in some combinations.

Table 1.3: *Water-soluble lubricants (Banker et al., 1980:91).*

Material	Usual range (% w/w)
Boric acid	1
Sodium benzoate + sodium acetate	1-5
Sodium chloride	5
DL-leucine	1-5
Carbowax 4000® (PEG)	1-5
Carbowax 6000® (PEG)	1-5
Sodium oleate	5
Sodium benzoate	5
Sodium acetate	5
Sodium lauryl sulphate	1-5
Magnesium lauryl sulphate	1-2

Receiving increasing attention in this context is a group of soluble but less effective lubricants, which also possess surfactant qualities and are typified by the lauryl sulphates. For example, sodium lauryl sulphate has been shown to have a very significant opposite effect to that of magnesium stearate on the dissolution rate of drug from salicylic acid tablets. Physical mixtures of this lubricant with stearates may give the best compromise in terms of lubricity, tablet strength, and disintegration. Recently, magnesium lauryl sulphate has been found to have an attractive balance of these properties. Although a concentration of 5% magnesium lauryl sulphate was required to be equivalent to 2% magnesium stearate in terms of lubricant efficiency, improved mechanical strength and disintegration were observed. Further investigations have shown that magnesium lauryl sulphate possesses superior properties to both magnesium stearate and sodium lauryl sulphate as flow inducers in terms of weight uniformity in capsules and tablets (Marshall & Rudnic, 1990:382).

Some of the synthetic soluble wax-like polymers, typified by the polyethylene glycols (PEGs), have been used as soluble lubricants. Carbowax® 4000 and 6000 have been investigated but their lubricant efficiency is less than, say, 2% magnesium stearate. In attempts to find the optimum lubricant from all standpoints, combinations of polymers like the polyoxyethylene monostearates and polyoxyethylene lauryl sulphates have undergone limited trials, with some encouraging signs, but more information is required (Marshall & Rudnic, 1990:382).

The sodium salts of certain other organic acids (such as benzoic, oleic, and even lactic) and esters such as glyceryl triacetate and sucrose monolaurate have been used in isolated

instances, but little has been published on their performance. The most promising of these sodium salt-organic acid combinations so far was sodium stearyl fumarate, or better known as Pruv® (Marshall & Rudnic, 1990:382). Table 1.4 gives an overview of the physicochemical characteristics of the most widely used lubricants used in both tablet and capsule production.

Table 1.4: *Physicochemical characteristics of capsule/tablet lubricants (Allen, 2000:405).*

Lubricant	Density ($g.cm^{-3}$)			Melting point (°C)	Usual range (% w/w)
	True	Bulk	Tapped		
Calcium stearate	1.064-1.096	0.16-0.38	0.2-0.48	149-160	≤ 1
Glyceryl (glycerin) behenate	-	-	-	70	0.5-5
Glyceryl (glycerin) palmitostearate	-	-	-	52-55	-
Magnesium stearate	1.092	0.159	0.286	117-159	0.25-5
Mineral oil, light	0.818-0.88	-	-	-	-
Polyethylene glycol	1.15-1.21	-	-	Varies	-
Sodium stearyl fumarate	1.107	0.20-0.35	0.3-0.5	224-245	0.5-2
Stearic acid	0.98	0.537	0.571	≥ 54	-
Stearic acid, purified	0.847 (70 °C)	-	-	66-69	-
Talc	2.7-2.8	-	-	-	1-10
Vegetable oil, hydrogenated, type I	-	-	0.57	61-66	1-6
Zinc stearate	1.092	-	0.26	120-122	0.5-1.5

1.3.2 *BASIC FRICTION MODEL*

As two surfaces are brought together, pressure is large at the initial few points of contact. Deformation occurs which increases the area of contact, thereby lowering the pressure. Deformation continues until the pressure has fallen to the characteristic yield pressure (P_m) of the softer material (Bowden & Tabor, 1950:90) as demonstrated in equation 1.1.

$$A = \frac{L}{P_m} \qquad 1.1$$

where:

A is the actual area of contact, P_m is the mean yield pressure and L is the normal load.

The friction force generally will consist of two terms, namely the force required to shear the junctures (due to metallic junctions formed between sliding bodies) at point contacts and a small ploughing term related to the force required to displace the softer material from in front of the harder material. This latter term is small and usually ignored. Thus:

$$F = AS_m \qquad 1.2$$

where:

F is the shearing force and S_m is the shear strength per unit area.

From equations 1.1 and 1.2 it is clear that frictional force is independent of the apparent area of the sliding bodies and directly proportional to the load and actual area of contact. This is known as Amontons's first law (Bowden & Tabor, 1950:98).

Substituting equation 1.1 into 1.2, results in equation 1.3:

$$F = L\left(\frac{S_m}{P_m}\right) = \mu L \qquad 1.3$$

where:

F is the approximation of the friction force and μ is the coefficient of friction.

Thus the frictional force is directly proportional to the load, so that the coefficient of friction (μ) is virtually independent of the load. This is Amontons's second law, and it holds over an extremely wide range of experimental conditions (Bowden & Tabor, 1967:98).

1.3.3 SHEAR STRENGTH OF LUBRICANTS

True lubricants act by means of one or a combination of the following mechanisms:

1. Separation and coverage of surfaces,
2. Hydrodynamic lubricants, and/or
3. Boundary lubricants

Irrespective of the mechanism, die wall lubricants function by interposing a film of low shear strength at the interface between the tableting mass and the die wall to lower the friction force (F) as illustrated in figure 1.1 and quantified in equation 1.4.

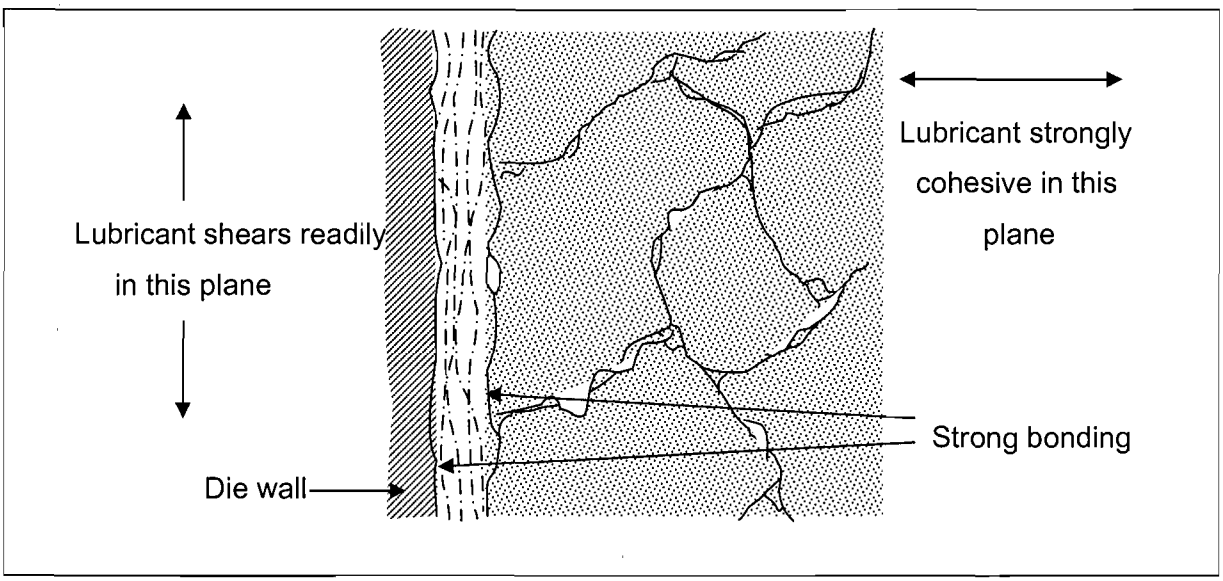


Figure 1.1: *Illustration of the preferred characteristics of die wall lubricants (Marshall, 1986:81).*

$$F = AXS_m + A(1-X)S_1 \qquad 1.4$$

where:

X is the fraction of area over which the contact point junctures are formed, S_m is the shear strength of the material, AXS_m is the force required to shear junctures at contact points and $A(1-X)S_1$ is the shear strength of the lubricant.

Ideally, for a good boundary lubricant, X should be very small.

Die wall lubricants thus can be envisaged as interposing a film of low shear strength at the interface between the tableting mass and the confining wall.

Table 1.5 gives the shear strength of some commonly used lubricants as measured by a punch penetration test.

According to Marshall (1986:81) there is, preferably, some chemical bonding between the lubricant and the surface of the die wall as well as at the edge of the tablet. The best lubricants are those with low shear strength but strong cohesive tendencies in directions at right angles to the plane of shear. By utilizing materials with low shear strength as lubricants, shear failure occurs in the lubricant layers and not at the compressed powder or resultant wall interfaces (figure 1.1).

Table 1.5: *Shear strength of selected lubricants as measured by a punch penetration test ([a]Lewis & Shotton, 1965:80S; [b]Marshall, 1986:81).*

Lubricant	Shear strength	
	$(kg.cm^{-2})^a$	MPa^b
Stearic acid	13.70	1.32
Calcium stearate	15.00	1.47
Hard paraffin	19.00	1.86
Magnesium stearate	20.00	1.96
Sodium stearate	33.90	3.32
Talc, with grain	63.20	6.20
Boric acid	73.00	7.16
Graphite	75.00	7.35
Talc, across grain	80.00	7.85

1.3.4 ASSESSMENT OF LUBRICACY

1.3.4.1 Evaluation based on resolution of forces in compaction

When external mechanical forces are applied to a powder mass, there is normally a reduction in its bulk volume as a result of one or more of the following effects:

1. The onset of loading is usually accompanied by closer repacking of the powder particles, and in most cases, this is the main mechanism of initial volume reduction, as shown diagrammatically in figure 1.2.
2. As the load increases, however, rearrangement becomes more difficult, and further compression involves some type of particle deformation.
3. If on the removal of the load, the deformation is to a large extent spontaneously reversible, i.e. if it behaves like rubber, then the deformation is said to be elastic.

All solids undergo some elastic deformation when subjected to external forces. With several pharmaceutical materials, such as acetylsalicylic acid and microcrystalline cellulose, elastic deformation becomes the dominant mechanism of compression within the range of maximum forces normally encountered in practice (Marshall, 1986:72).

In other groups of powdered solids, an elastic limit, or yield point, is reached, and loads above this level result in deformation not immediately reversible on removal of the applied force. Bulk volume reduction in these cases results from plastic deformation and/or viscous flow of the particles, which are squeezed into the remaining void spaces, resembling the

behaviour of modeling clay. This mechanism predominates in materials in which the shear strength is less than the tensile or breaking strength.

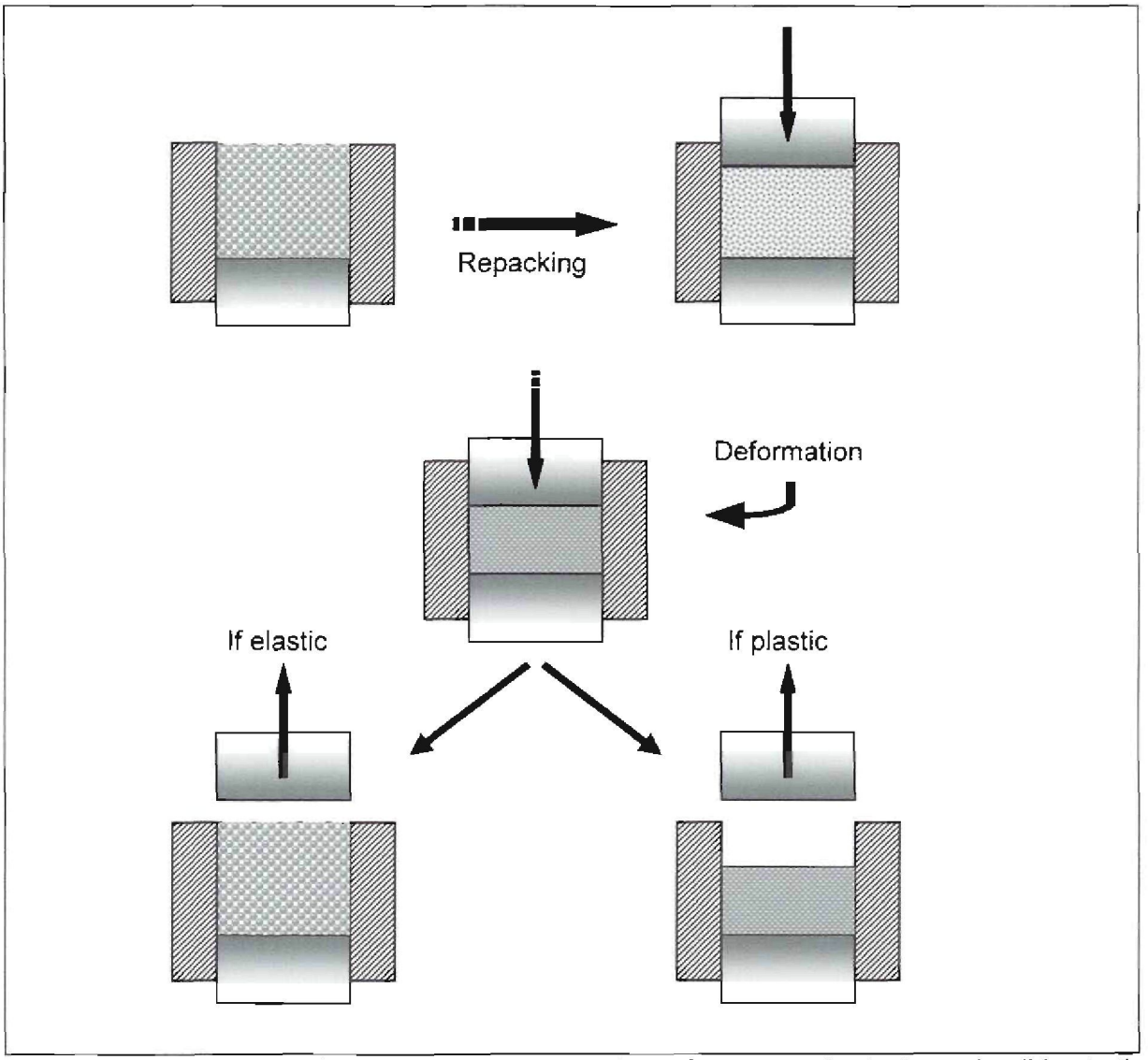


Figure 1.2: *Illustration of the effect of compressional force on a bed of powder (Marshall, 1986:72).*

Irrespective of the behaviour of large particles of the material, small particles may deform plastically, a process known as microsquashing, and the proportion of fine powder in a sample may therefore be significant.

The above account describes all the possible mechanisms that can contribute to a reduction in the bulk volume of a bed of powder, when subjected to external mechanical forces. The physicochemical characteristics of the material being studied determine the contribution each effect makes as the compressional load is increased. All of the deformation effects

may be accompanied by the breaking and formation of new bonds between the particles which gives rise to consolidation as the new surfaces are pressed together.

1.3.4.1.1 Parameters

Most investigations of tableting physics have been carried out on single station presses (sometimes called eccentric presses) or at least in punch and die sets mounted in hydraulic presses or "physical testing" machines which function much like single punch presses (Augsburger *et al.*, 1987:4). The system, represented diagrammatically in figure 1.3, is typical of such arrangements with force being applied to the top of a cylindrical powder mass.

The single ended uniaxial compaction model applicable in such cases makes an accounting of the effects of friction and has provided parameters that have been used to assess lubricity. Since there must be an axial (vertical) balance of forces, the following relationships apply (equation 1.5):

$$F_A = F_L + F_D \qquad 1.5$$

where:

$F_A > F_L$

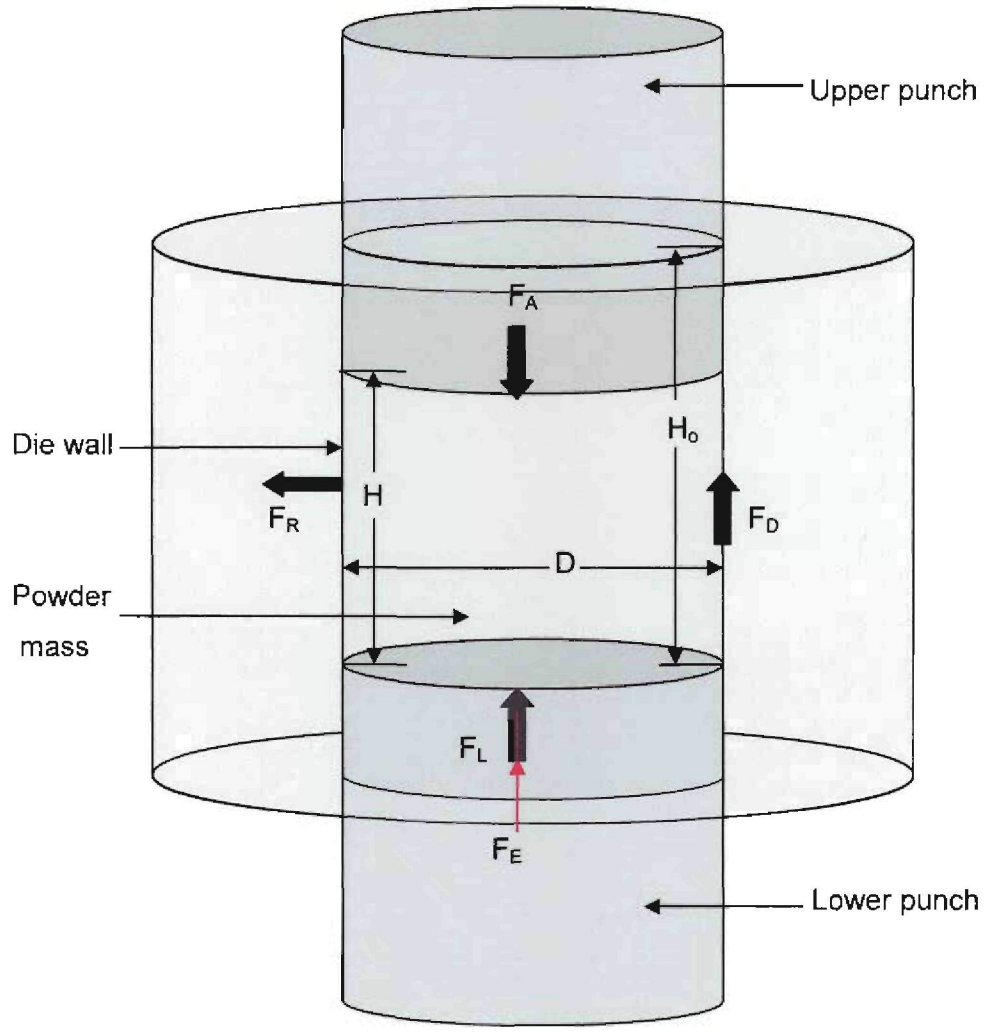
As the compressional force is increased and any repacking of the tableting mass is completed, the material may be regarded to some extent as a single solid body (tablet). Then, as with all other solids, compressive force applied in one direction (e.g. vertical) results in a decrease in the height (ΔH). In the case of an unconfined solid body, this would be accompanied by an expansion in the horizontal direction of D (ΔD).

The ratio of these twodimensional changes is known as the Poisson ratio (λ) of the material, defined as:

$$\lambda = \frac{\Delta D}{\Delta H} \qquad 1.6$$

The Poisson ratio is a characteristic constant for each solid in the following way. Under the conditions illustrated in figure 1.3, the material is not free to expand in the die. Consequently, a radial die wall force F_R develops perpendicular to the die wall surface, thus, materials with larger Poisson ratios give rise to higher values of F_R. Classic friction theory

can then be applied to deduce that the axial frictional force (F_D) is related to F_R by equation 1.7.



F_A : Force applied to the upper punch

F_L : Force transmitted to the lower punch

F_D : Force at the die wall due to friction at this surface

F_R : Radial die wall force due to confinement of powder mass in die

F_E : Ejection force

H_o : Initial powder height in mm

H : Compacted powder height / tablet height in mm

D : Tablet diameter in mm

Figure 1.3: *Diagram of a typical single station punch and die assembly used for compaction studies (Marshall, 1986:79).*

$$F_D = \mu_W F_R \qquad 1.7$$

where:

μ_W is the coefficient of die wall friction.

It is thus important to note that F_R is reduced when materials of small Poisson ratios are used, and that in such cases the axial force transmission is optimal (Marshall, 1986:80). The frictional effect represented by μ_W arises from the shearing of adhesions that occurs as the particles slide along the die wall. It follows that its magnitude is related to the shear strength of the particles (or the die wall particle adhesion, if these are weaker) and the total effective area of contact between the two surfaces. Therefore, force transmission is also realized when F_D values are reduced to a minimum, which is achieved by ensuring adequate lubrication at the die wall and maintaining minimum tablet height.

The residual force (F_L) is the force remaining on the lower punch following compression and prior to ejection (Sadjady *et al.*, 1993:105). Although the residual force should be measured in the die wall, as radial and axial forces are related by the Poisson's ration (equation 1.6), the residual force recorded from the lower punch can also evaluate this phase of the tableting production. According to Hölzer and Sjögren (1977:35), the use of the residual force as a measure of friction is not recommended as it is dependent not only on the friction at the die wall but also largely on expansion of the tablet and machine parts. They also suggested that the maximum ejection force gives better prediction of the adhesional problems in tableting. On the other hand, Shah *et al.* (1986:1345) used the residual force measuring the tendency for picking and sticking.

1.3.4.1.2 Coefficient of lubrication

The coefficient of lubrication, or "R-value," is defined (Nelson *et al.*, 1954:596) as follows:

$$R = \frac{F_L}{F_A} \qquad 1.8$$

Under theoretical conditions of perfect lubrication, $\mu_W = 0$, $F_A = F_L$ and $R = 1$. Thus, R provides an index, which approaches one as a limit as lubrication efficiency increases. Values of R can only be considered in relation to the particular system that generates them. R-values can be affected by such variables as compression force, die wall contact and compression speed. Values below 0.8 probably indicate a poorly lubricated system (table

1.6). The conditions under which these R-values were obtained are important since it is affected by variables, such as compressional force and tablet dimensions (H/D ratio).

Table 1.6: *R-values for selected lubricants ([a]Lindberg, 1972:207; [b]Lewis & Shotton, 1965:82S; [c]Nelson et al., 1954:596).*

Lubricant	1% w/w lubricant, P_A = 12 kN.cm^{-2}, AA granules[a]	2%, P_m = 10 kN.cm^{-2}, sucrose granules[b]	1%, P_A = 13 kN.cm^{-2}, sulfonamide granules[c]
Magnesium stearate	0.91	0.93	0.99
Calcium stearate	-	0.93	0.97
Sodium stearate	-	0.93	0.94
Stearic acid	0.80*	0.94	-
Sodium lauryl sulphate	0.92	-	-
Sodium stearyl fumarate (Pruv®)	0.93	-	-
Boric acid	-	0.63	-
Talc	-	0.59	0.59**
Unlubricated	-	0.55	0.67

**8.8 kN.cm^{-2}, evidence of sticking; *18 kN.cm^{-2}; Values from Nelson et al. (1954:596) are averages.*

The force remaining on the lower punch after decompression (prior to ejection) is sometimes used as a parameter of lubrication. It is a measure of the force that develops as the tablet expands elastically against the lower punch under the restraining influence of the die wall friction. The lower the die wall friction, the more freely the tablet is able to slip as it expands, and the lower the force exerted on the lower punch will be.

1.3.4.1.3 Work of friction

One of the factors not contributing directly to tablet formation is the friction occurring during compression. Several arguments can be given for its elimination. Although of minor importance, the tablet press has to deliver an extra amount of work to compress an unlubricated instead of a lubricated mass. Sticking to the die wall of the mass will result in jamming of the machine and in damage to punches and die. From this point of view, however, the negative influence of friction on tablet properties is of more interest. The reason is found in an uneven force transmission and distribution throughout the tablet mass, which results in regions of different density as well as of different bonding strength.

Therefore, the dissolution pattern may be inhomogeneous (De Blaey, 1972:233). The uneven force distribution throughout the tablet mass may also result in regions of different strength. This may be caused not only by differences in the compression force but also in elastic recovery. A higher compression force will result in a higher amount of work delivered to the tablet or parts of it and therefore increase the strength. On the other hand the elastic recovery will also be increased and this may result in a decrease of the strength. The outcome of this competition will depend on several factors determining their relative importance.

During compression, the transmission of work is studied in equilibrium, either in a column at rest or on the moment of maximum displacement at which the speed of the punch is zero in the compression process. The general observation made by De Blaey (1972:237) is that it is important to study the transmission not only on one moment, but throughout the whole process with equation 1.9.

$$W_{Fr} = \int_{D_o}^{D_m} (F_A - F_L)\, dD \qquad 1.9$$

where:

W_{Fr} is the amount of work required to overcome friction during compression and D is the upper punch displacement.

1.3.4.1.4 Dependence of parameters on contact area

Since the coefficient of die wall friction (μ_W) develops from the shearing of adhesions, its magnitude must be a function of both the shear strength of the adhesions and the effective contact area between the surfaces, such parameters as F_D and R would be expected to be dependent on the tablet-die wall contact area (Hölzer & Sjögren, 1978:62). For cylindrical tablets equation 1.10 is valid.

$$R = \frac{F_L}{F_A} = e^{-KH/D} \qquad 1.10$$

where:

H is tablet height, D is tablet diameter, and $K = \mu_W N$, where N = ratio between the radial and axial stresses.

1.3.4.2 Measurement of ejection force

The maximum ejection force, which is the maximum force exerted on the lower punch during ejection of the tablet, is most probably the most widely used measure of tablet friction (Sadjady *et al.*, 1993:105). In this case, it is only possible to evaluate friction during tableting from the ejection phase. Several authors have used this parameter to evaluate lubricants as it corresponds more directly to actual tablet production (Juslin & Krogerus, 1971:261; Hölzer & Sjögren, 1979a:145; and Mitrevej & Augsburger, 1982:237).

1.3.4.2.1 Relationship to model

The direct measurement of the ejection force has become commonplace today, and can be easily measured in single station presses and in rotary presses. In general, based on the model above, the ejection force should be related to the residual die wall force (RDWF) at the time of ejection. RDWF is the force that remains on the die wall after removal of the upper punch. Ejection force (F_E) also is related to tablet dimensions.

$$F_E = \mu_W \, RDWF \qquad 1.11$$

$$F_E = \mu_W \, RDWP \times A \qquad 1.12$$

where:

RDWP is the residual die wall pressure and A is the apparent area of contact from tablet dimensions.

A dynamic coefficient of friction (μ_W^*) may be estimated from the ejection force and RDWF*, the residual die wall force during ejection (Hölzer & Sjögren, 1981a:139, 1979b:221):

$$\mu_W^* = \frac{F_E}{RDWF^*} \qquad 1.13$$

In opposition to theory, μ_W^* values exceeded static μ_W values in certain cases (Hölzer & Sjögren, 1981b:269).

There are two schools of thought as to whether the static (residual) or dynamic (ejection) force is more appropriate for the evaluation of lubricant properties. It is also suggested that the former is a more suitable parameter for comparing the efficiency of different lubricants while the latter is a more suitable parameter for the optimization of lubricant concentrations

(Waring *et al.*, 1987:116). Thus, measurement of the R-value is a differentiating measurement between lubricants, while μ_W^* measurement will help to optimize lubricant usage. Simultaneous measurement of these lubrication and compression forces is also difficult because of the different magnitudes of the forces involved. This problem can be overcome by measurement of residual area, which includes both the static residual and dynamic ejection event following compaction. Residual area is defined as the displacement area of the lower punch from the baseline during decompression and ejection (figure 1.4).

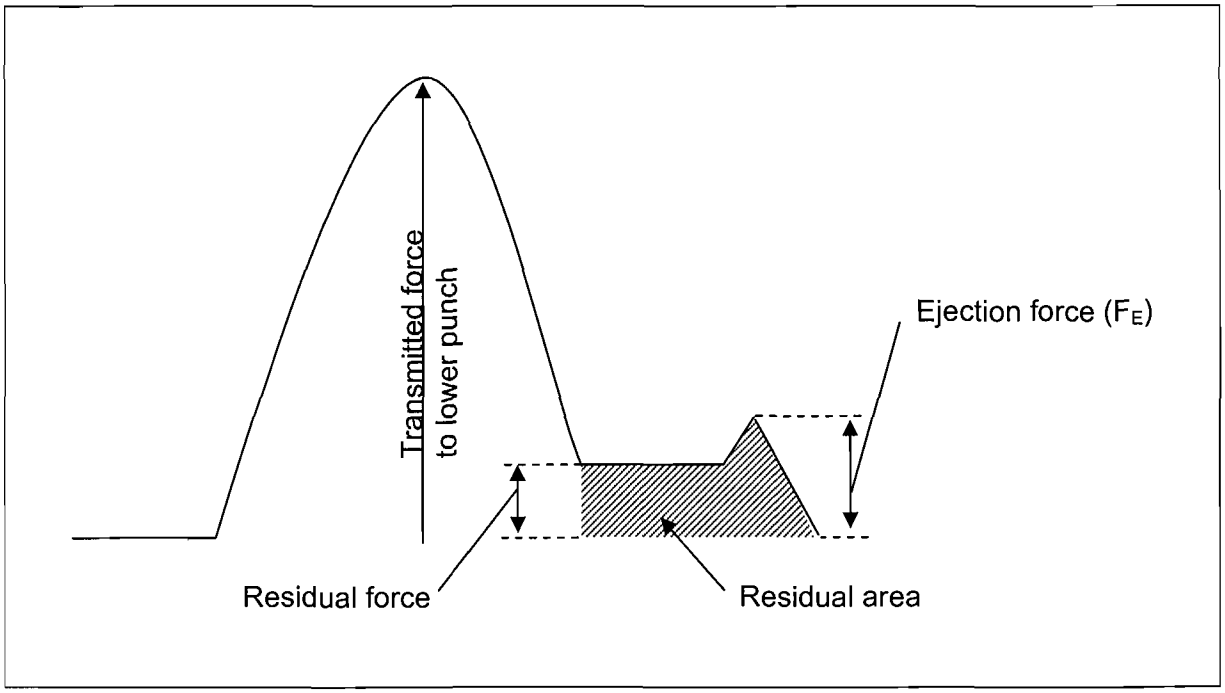


Figure 1.4: *Residual area measurement (Waring et al., 1987:120).*

Table 1.7 shows the friction coefficients of some lubricants (0.5%) in sodium chloride tablets as measured by Hölzer & Sjögren (1981a:142). They measured friction coefficients during maximum compression, also known as the static friction coefficient (μ_W), during ejection, also known as the dynamic friction coefficient (μ_W^*), stress ratios, better known as coefficient of lubrication (R-value), tensile strength (σ_x) and disintegration times. Tensile strength is a measure which brings the tablet dimensions into consideration when measuring crushing strength, as indicated in equation 2.2:

As indicated in table 1.7, μ_W is smaller than μ_W^*, and since all the lubricants lowered the friction coefficients and the effect was qualitatively the same on both μ_W and μ_W^*, it indicated that no adhesion problems affected the results. Magnesium stearate had the smallest friction coefficient, followed by sodium stearyl fumarate, which indicated their superior lubrication efficiency. There was no correlation between the friction coefficient of the lubricant itself and the ability to lubricate the sodium chloride tablets. Due to the very small

forces in operation during the ejection stage of the tablets, it was not possible to measure μ_W^* with acceptable precision. The lubricants increased the stress ratio (R-value) in relation to the reduction of the friction coefficient (μ_W). The correlation coefficient between η and the reduction of μ_W were 0.897 (n = 43). It was also found by Hölzer & Sjögren (1981a:146) that there was a reduction in friction coefficients with prolonged mixing which also increased disintegration times. The tensile strength was also strongly decreased with prolonged mixing, with the most pronounced effect obtained for sodium stearyl fumarate, stearic acid, Ryoto S-370 and magnesium stearate. There was a direct correlation between the tensile strength and friction coefficient μ_W.

Table 1.7: *Friction coefficients (μ_W and μ_W^*), stress ratio (η), tensile strength (σ_x) and disintegration time for tablets of sodium chloride and 0.5% lubricant (Hölzer & Sjögren, 1981a:142).*

Lubricant	μ_W	μ_W^*	R-value (%)	σ_x (MPa)	Disintegration (min)
None	1.37	0.83	46	1.41	3.3
Cutin HR	0.57	0.45	50	0.90	7.9
Dynasan 118	0.51	0.46	52	0.83	10.4
Precirol	0.57	0.39	51	0.81	5.9
Ryoto S-370	0.47	0.37	55	0.58	5.8
Stearic acid	0.59	0.37	51	0.76	4.2
Magnesium stearate	0.31	0.23	57	0.20	18.6
Magnesium lauryl sulphate	0.73	0.53	50	0.84	3.6
Sodium lauryl sulphate	0.60	0.47	52	0.67	3.9
Sodium stearyl fumarate	0.40	0.29	56	0.37	7.7
Teflon P-PFA	1.25	0.77	48	1.25	3.6

1.3.4.2.2 Ejection force-time traces

The force necessary to eject a finished tablet follows a distinctive pattern of three stages (figure 1.5):

- Stage 1: Initial peak – peak force required initiating ejection by breaking of tablet/die-wall adhesions.
- Stage 2: Sliding friction region – force required to push the tablet up the die wall.

- Stage 3: Declining force region - emergence of tablet from die.

As the lower punch rises and pushes the tablet upward there is a continued residual die wall pressure and considerable energy may be expanded due to the die wall friction. As the tablet is removed from the die, the lateral pressure is relieved, and the tablet undergoes elastic recovery with an increase (2 to 10%) in the volume of that portion of the tablet removed from the die. During ejection that portion of the tablet within the die is under strain, and if this strain exceeds the shear strength of the tablet, the tablet caps adjacent to the region in which the strain had just been removed (Parrott, 1990:207).

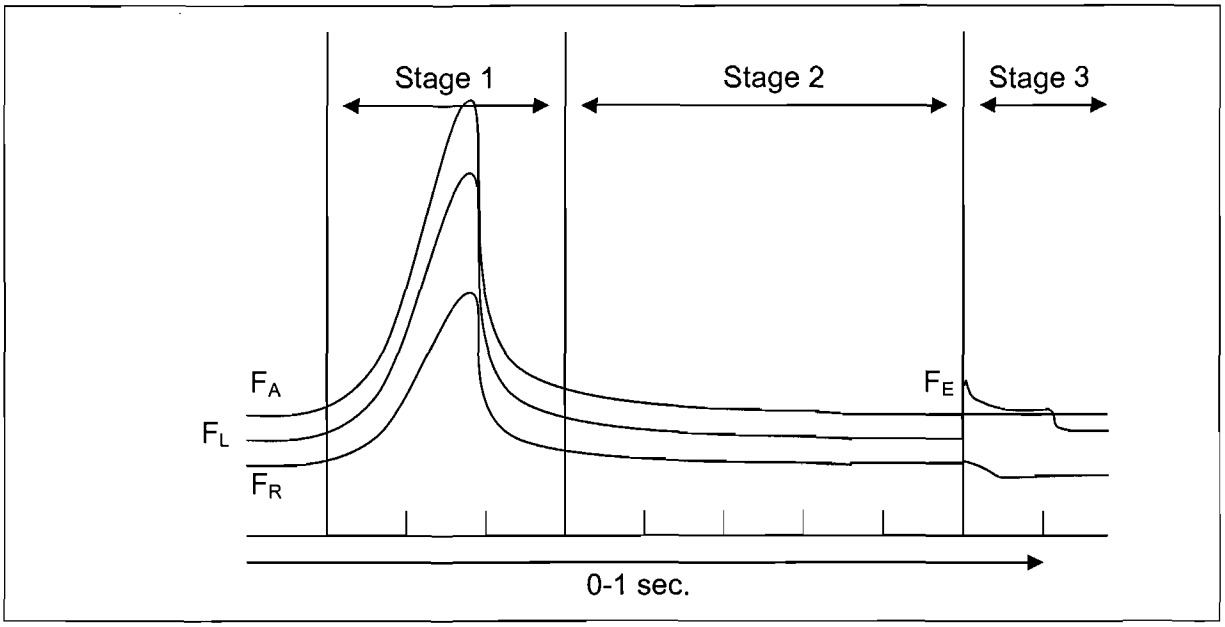


Figure 1.5: *Typical traces from instrumented single station tablet press. Reproduction of typical traces obtained from a multichannel UV recording oscillograph connected to the graph (Marshall, 1986:94).*

1.3.4.2.3 Work of ejection

Just as with work measurement during compression, work during ejection is a dynamic process which can be measured by equation 1.14.

$$W_{Ej} = \int_{D_{1o}}^{D_{1m}} F_E \, dD_1 \qquad 1.14$$

where:

W_{Ej} is the amount of work required to overcome friction during ejection and D_1 represents the displacement of the lower punch.

1.3.4.3 Basic instrumentation models for measurement of die wall stress

There are basically four types of die modifications which were built for friction coefficient measurements, *viz.* Nelson's three-punch die, Winheuser's segmented die, Ringway's photoelastic die and Kruger's oil pressure system. The Nelson three-punch die contained a stationary punch and die assembly, and used a slow-acting hydraulic press to apply the necessary compressive force to produce single tablets (Nelson, 1955:497). Innovative as it was, the technique was open to criticism on the grounds that, to some extent, the measured signal would be related to the extrusion properties of the material under compression; and, that only two granulations had been examined in this way. Windheuser's segmented die avoided the problems of extrusion by leaving the bore of the die intact. A segment of the outer wall was cut away to provide a site for strain gauges as seen in figure 1.6 (Windheuser, *et al.*, 1963:767). Another model used was Rigway's photoelastic die. Using the technique of photoelasticity, it viewed stresses generated in a Perspex die during compression by means of polarized light (Ridgway, 1966:181S). Needless to say, very impressive, but also unpractical. Recently Kruger (2000:29) demonstrated a thin-wall oil pressured system where radial pressure were carried over to surrounding oil in a casing around the die. This oil pressure was detected by pressure gauges and transmitted back to a computer. This innovative idea had lots of practical problems, like viscosity problem with the oil, unstable tube configurations and obvious indirect, inaccurate measurements.

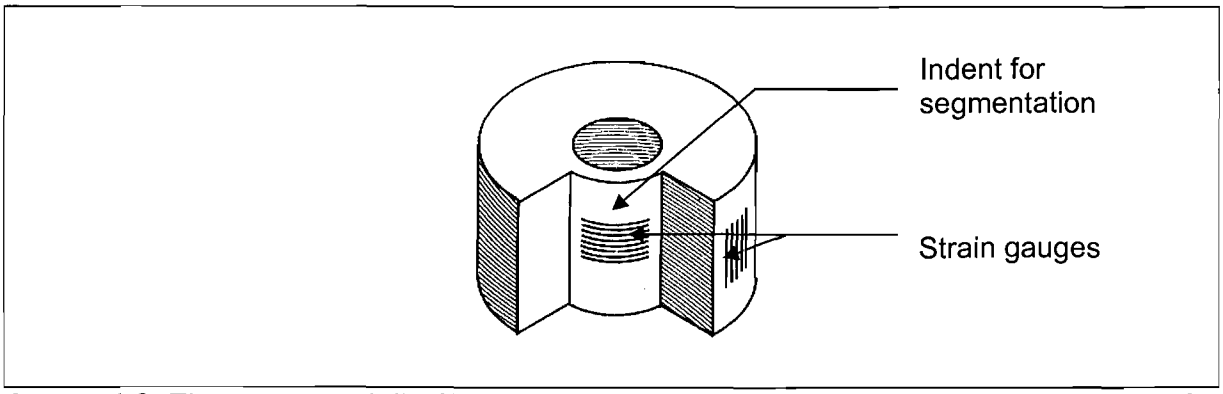


Figure 1.6: *The segmented die: Windheuser. This was the first of several cut-away dies for the measurement of hoop stress or die wall force (Watt, 1988:290).*

The only model discussed, which could have been implemented and integrated in the instrumentation and funds available for this study, was the Windheuser's segmented die, which is also used as current practice in instrumented tablet presses (unfortunately not available or affordable at academic institutions). As with Nelson's model, Windheuser used the slow-acting hydraulic press for experiments, and was, therefore, operating under distinctly unreal conditions (Windhauser *et al.*, 1963:772). However, this hydraulic press

allowed for constant press pressure, in other words the pressure could be kept constant for all powder systems, unlike in the case with enteric presses where displacement of the upper punch is a constant. This was favourable since higher pressure due to different densities of powder systems (thus giving different volume capacities) would have an influence on the applied die wall pressure. It is thus important to keep pressure constant during compression. Although the area of contact will also influence the stress gauge results, tablet dimensions can be measured, to compensate for this variable. Problems, however, occurred as this one-sided segmentation only allowed for a single set of strain gauges, thus not compensating for temperature changes. Another shortcoming of this model is that the segmented shape will always distort asymmetrically under load, and there must therefore be an argument for retaining its original circular symmetry. Reducing the wall thickness uniformly, rather then segmenting the die, can be practical if semiconductor gauges of adequate sensitivity are used. Naturally, the thinning process must not be taken too far, since the die might expand appreciably under internal pressure. Although this model had some shortcomings (alteration will be described in section 5.2), it was the most promising and relevant for the study at hand.

1.3.4.4 Measurement of die wall pressure with strain gauges

Force measurements in the tableting field are normally indirect, and depend on physical changes produced by the force in question. When a force is applied to an elastic component it deforms that component to a certain extent, depending on its elasticity. Stress, in other words, produces strain. Both stresses and strains have direction as well as magnitude, and this must always be borne in mind when measuring systems are devised. There are various means available for the assessment of strain in structures and components, but the term 'strain gauge', when used without qualification, is generally taken to imply the *electrical resistance strain gauge.*

If a length of resistive alloy wire is placed under tension, its length increases; at the same time, its cross-sectional area decreases by the proportion defined as Poisson's ratio, generally in the region of 0.3 for most of these alloys. As a result of these two changes, the electrical resistance of the wire increases and an output signal is generated. This signal represents a certain force. To put an exact value to this signal-force ratio, calibration of the system is necessary. To compensate for Poisson's ratio, a second strain gauge need to be included into and electric circuitry, tangential to the first strain gauge (Watt, 1988:29).

At this stage it is important to distinguish between force and pressure, since the later one is actually measured with strain gauges and force is dependent of the area of the applied pressure.

The primary constraints imposed by a strain gauge are the elongation and gauge fatigue limits. All strain gauges have elongation limits, which, if exceeded, will permanently damage the strain gauge. It is thus important to use strain gauges sensitive enough to detect small measurable signals during ejection, but it must also withstand bigger input pressure as seen during the compression phase.

1.3.4.5 The Wheatstone bridge circuit

Strain gauges, strained within their normal limits, only exhibit small proportional changes in resistance. In order to produce a convenient signal from these changes, it is usual to connect one or more strain gauges together in the 'Wheatstone bridge' circuit.

The Wheatstone bridge circuit is shown in the accompanying diagram (figure 1.7), and comprises four resistors arranged along the sides of a square. They are connected to each other at the corners of the square. Power is supplied across one diagonal, and a signal is taken from the opposite diagonal.

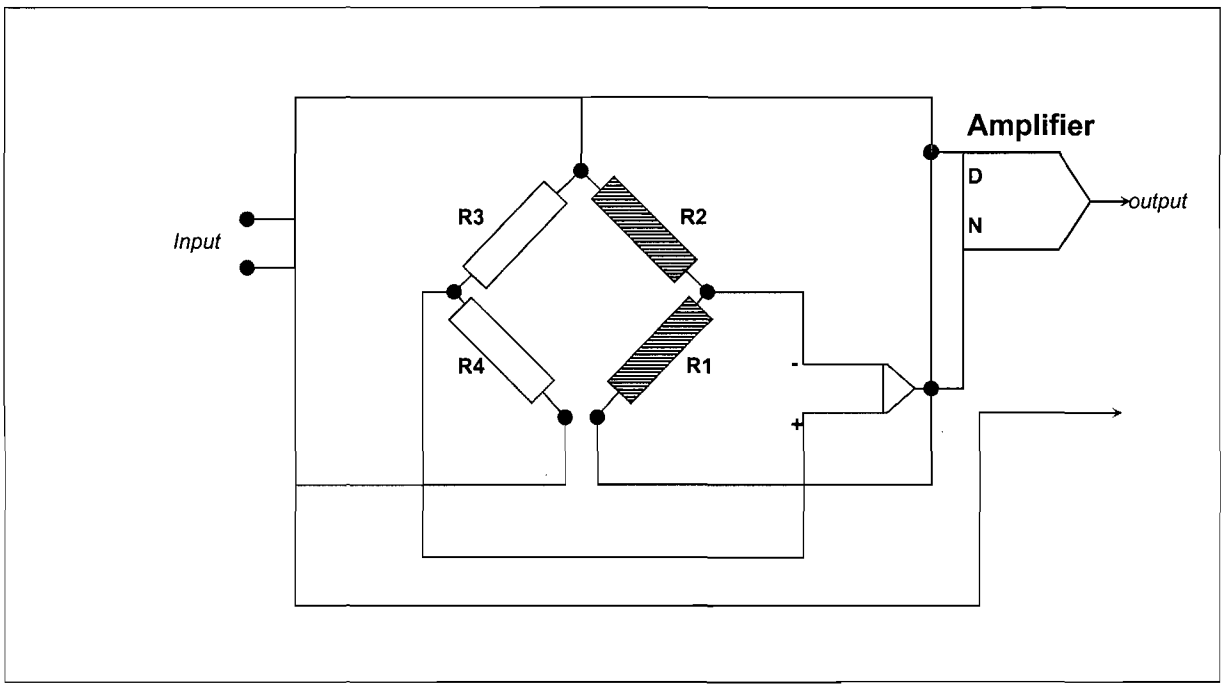


Figure 1.7: *Active linearizing circuitry with half-bridge Wheatstone configuration (Watt, 1988:105).*

When the resistors are all of equal value, the bridge circuit is symmetrical, and there is no potential difference across the output terminals. However, should one or more of the resistors change in value, the bridge will no longer remain in balance: an output voltage will then appear.

Using only one of the strain gauges as an "active" gauge provides what is generally described as a "quarter-bridge" configuration. Two active gauges give a half-bridge, and four, a full bridge. The gauges may be active or passive, but, in each case, the bridge output will be related to the number of active gauges. Active gauges are those which are bonded to a substrate (in this case the thinned die wall) in such a position that they respond to strain in that substrate. Passive gauges are not intended to respond in that way, being primarily intended to provide temperature compensation for the active gauges. They may be attached to an adjacent, unstressed surface. Changes in length of a stressed component will be accompanied by corresponding changes in cross-sectional area, as indicated by Poisson's ratio. If one gauge is bonded along an axis of principal strain, and the compensating gauge is bonded at right angles to it, the second gauge will not be passive, but will contribute a signal of opposite sign from that of the first gauge, at about one third of its magnitude. Such a gauge is often described as a 'Poisson' gauge (Watt, 1988:97).

To compensate for zero drift in the electric current the half-bridge configuration was used with circuitry set up as in figure 1.7. Amplification of signals, especially those during ejection, was necessary due to the small scale of the signals when compared with compression signals (approximately 10 - 100 times amplified). Since the strain gauges had to measure for both signals, it had to withstand the pressure of compression radial pressure, but with amplification had to give accurate ejection radial pressure. This was a major problem and was further complicated by the die wall thickness. A die wall too thick gave unmeasurable signals and when too thin it damaged the die wall, which brings us to the instrumentation of the die.

1.3.4.6 Studies outside of the die

Although the most popular approach to testing lubricity has involved studies within the die, or using a tablet press, several investigators have considered studies conducted in other devices (table 1.8) to be more practical.

Table 1.8: *Representative non-tableting friction studies.*

Type of test	System reported	Reference
Moving flat plate clamped between two cylindrical compacts	PTFE, ASA (unlub) Ferric oxide, plate coated with stearic acid films	James & Newton (1983:29) and Strijbos *et al.* (1977:187)
Partially ejected tablet dragged against surfaces (I-mass friction tester)	Magnesium stearate lubricated dicalcium phosphate	Baichwal & Augsburger (1985:191)
Simple shear cell – weighted disk pulled over powder bed	Carbon black filled polyesters	Budney (1979:197)
Modified Jenike wall friction test – loaded, preconsol. Bed pushed over metal surface	Magnesium stearate	Miller *et al.* (198:42S)
Modified annular shear cell (MASC)	Magnesium stearate, other lubricants	Baichwal & Augsburger (1988:569)

Some criticisms of compaction studies are (James & Newton, 1983:29):

1. A simple resolution of forces merely indicates the magnitude of the problem and provides no information on causative mechanisms.
2. Calculation of F_D, R-values, etc. are dependent on the stress transmission characteristics of the materials, which are unknown for most particulate systems.
3. Measures such as REF, F_E and W_{Ej} are indirect measures of friction and they are dependent on the magnitude of the applied force.

1.4 ANTIADHERENTS

Some materials were found to have strong adhesive properties toward the metal of the punches and dies. Although not a frictional effect, this results in material preferentially sticking to the punch faces and gives rise to tablets with rough surfaces. This effect, called "picking ", can also arise in formulations containing excess moisture. Normally the lubricants present in tableting masses also act as antiadherents, but in the worst cases it may be necessary to add more starch or even talc to overcome the defect.

So by judicious choice of a combination of antiadherents (table 1.9), all these complicating undesirable effects of the tableting process can be minimized (Marshall & Rudnic, 1990:383).

Table 1.9: *Antiadherents (Banker et al., 1980:92).*

Material	Usual range (% w/w)
Talc	1-5
Cornstarch	3-10
Cab-O-Sil®	1-3
Syloid	0.5-3
DL-leucine	3-10
Sodium lauryl sulphate	<1
Metallic stearates	<1

1.4.1 ASSESSMENT OF GLIDANCY

1.4.1.1 Subjective

Antiadhesion activity continues to be evaluated primarily by inspection of tooling. Hölzer and Sjögren's (1979a:148) evaluation of sodium stearyl fumarate is typical. This method of evaluation is not a quantative measure and is very subjective. It is therefore not a very suitable method of measuring adhesion of powder on tooling.

1.4.1.2 Direct measurement

A few attempts have been made to quantitate the sticking of formulations to punch faces. These attempts are summarized in table 1.10.

Table 1.10: *Measuring sticking to punch faces.*

Type of test	Reference
"Slipping force" between the upper punch face and tablet surface (single station press)	Naito *et al.* (1969, 2507; 1971:1956)
"Tablet strippability" measured with strain gauge measuring arm (rotary press)	Ritter *et al.* (1978:1181)
"Adhesion" of tablets to lower punch face with strain gauged cantilever beam	Mitrevej & Augsburger (1982:237)
As above, but using a piezoelectric load washer	Schmidt *et al.* (1983:800)
Surface roughness measurement with surface analyser (Surfcom 700B Tokyo Seimitsu Co, Japan)	Toyoshima *et al.* (1988:212)

The results of such studies generally showed that differences in true lubricant efficiency, as reflected in ejection force measurement, do not necessarily reflect differences in adhesion.

1.4.1.3 Estimation from Coulomb's law

Kikuta and Kitamori (1983:196) suggested that ejection force might be represented by a modification of Coulomb's law (equation 1.15):

$$F_E = \mu_W F_R + C \qquad 1.15$$

where:

C is the adhesive force. F_E and F_R were determined in a physical testing machine.

Plots were linear, with μ_W estimated from the slope and C from the intercept (figure1.8). Values were compared with the subjectively evaluated extent of binding tendency during tableting on a rotary press. A lactose granulation was studied and results are shown in table 1.11.

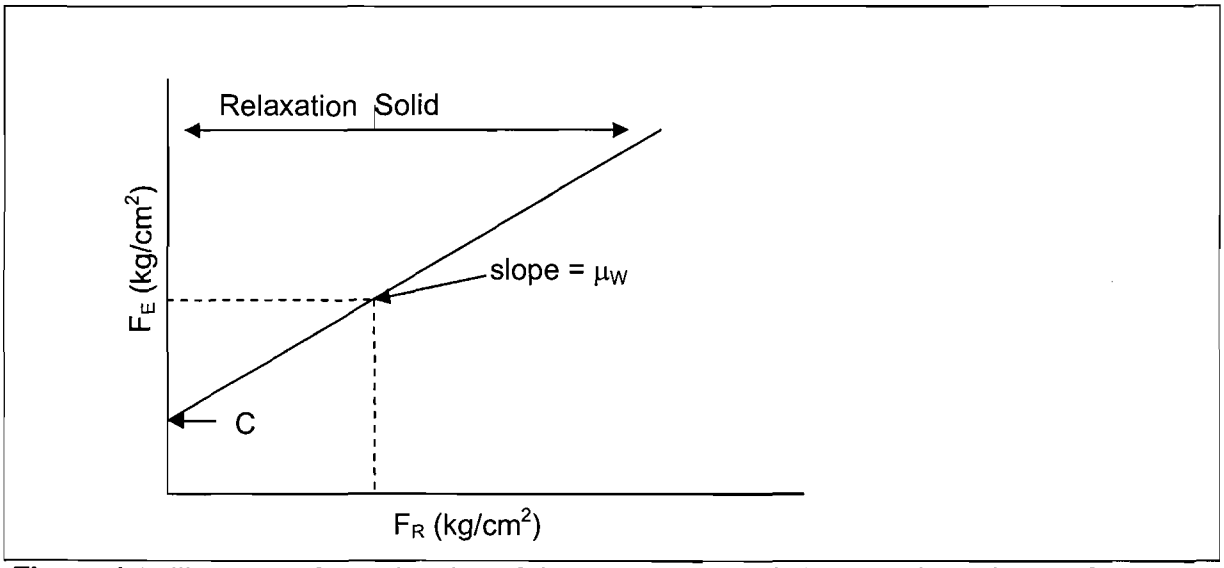


Figure 1.8: *Illustration for estimation of the coefficient of friction and the adhesive force from simultaneous measurements of ejection and radial forces for a tablet compressed as a definite compressive force (Kikuta & Kitamori, 1983:196).*

Since simultaneous measurement of the ejection and the radial forces in an ordinary ejection process would give only a single pair of values of F_E and F_R in equation 1.15, namely a single point in a plot of F_E versus F_R as in figure 1.8, this approach would not permit μ_W and C to be determined individually. Therefore a series of measurements of the ejection forces against varying radial forces is necessary in order to estimate the coefficient of friction and the adhesive force between the tablet compressed by a definite compressive force and the die wall. The generation of various values of the radial force at the ejection of the tablet having a constant structure can be attained by recompression or relaxation of the tablet in

the die in which the tablet has been compressed. When the tablet in the die is allowed to stand for a certain time, the radial force of the tablet decreases and relaxation forces can be measured (Carless & Leigh, 1973:289). When the tablet in the die is recompressed by a force smaller than the initial compressive force, the radial force of the tablet increases without any change in interaction between the tablet and die wall (Kikuta & Kitamori, 1983:196). If no adhesive force if present, the straight line would went through the origin (Kikuta & Kitamori, 1985:848). The straight line further indicates the direct relationship between F_E and F_R.

Table 1.11: *Relation between μ_W and C obtained by the proposed method, and the binding tendency during tableting on a rotary press (Kikuta & Kitamori, 1983:200).*

% Concentration lubricant		Mixing time (min.)	μ_W	C ($kg.cm^{-2}$)	Binding*
MgSt	0.1	1	0.20	12	++
		10	0.19	8	±
		30	0.18	4	-
	0.3	1	0.22	5	-
		10	0.17	3	-
		30	0.12	2	-
Talc	1.0	10	0.48	23	++
	2.0	10	0.38	14	++
	4.0	10	0.35	7	±

* *Qualitative expression of the inspection: ++ = severe; + = moderate; ± = slight; - = none.*

Another important measurement of adhesion is to evaluate the change in ejection force with increasing tableting number as indicated by Kikuta & Kitamori (1985:850) in figure 1.9.

The affinity of magnesium stearate to the die wall was superior to that of calcium stearate, which may be attributed to smaller primary particle size of the magnesium stearate. Magnesium salt itself may have intrinsically greater affinity to the metallic die wall than the calcium salt. The strong affinity of magnesium stearate is inconsistent with their frictional properties, that is, a small friction coefficient and practically no adhesion force. This phenomenon is due to the mono- or multi-layer film of the lubricant which is being left behind on the surface of the die wall, and is reasonable since it is thought that magnesium stearate is a boundary type lubricant (Kikuta & Kitamori, 1985:851). Due to this adhesion of lubricant on the die wall it is common practice to start evaluating the friction coefficient (μ_W) only after

the 10th tablet for 5 tablets thereafter. Measurements from tablet 10-15 give very low adhesion so that adhesive forces (C) decrease and equation 1.15 simplifies to equation 1.7.

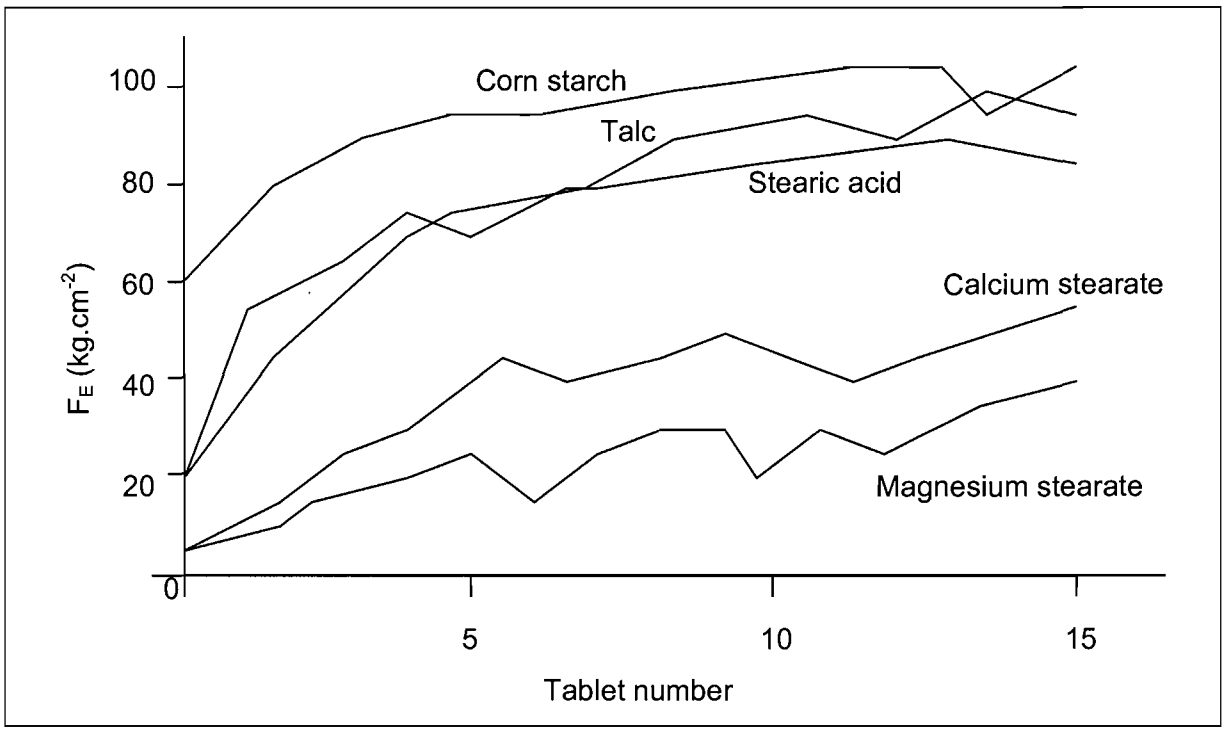


Figure 1.9: *Change in ejection force in serial tableting of unlubricated lactose granulates after tableting with different lubricants (Kikuta & Kitamori, 1985:850).*

1.5 GLIDANTS

Most of the pharmaceutical industry processes require powder movements. For this reason, flowability is of critical importance in obtaining identical, repeatable solid dosage forms. Flowability is obtained and bettered by adding glidants to powder masses. Glidants are added to the formulation in order to improve the flow properties of the materials to be fed to the die and sometimes to aid particle rearrangement within the die during the early stages of compression. They may act by interposing their particles between those of the other components and so, by virtue of their reduced adhesion tendencies, lowering the overall interparticulate friction of the system. In addition there may be some effect due to the rounding off of the surface of irregular particles by adsorption of glidant into the irregularities of the other materials. It follows that, like lubricants, they are required at the surface of feed particles and that they should be in a fine state of division and appropriately incorporated in the mix. In general, materials that are good glidants are poor lubricants. Table 1.12 lists a few of the common glidants.

Table 1.12: *Glidants (Banker et al., 1980:92).*

Material	Usual range (% w/w)
Talc	5
Cornstarch	5-10
Cab-O-Sil®	1-3
Syloid	1.5-3
Aerosil®	1-3

Starches remain a popular choice, in particular those with the larger grain sizes such as potato or cornstarch, possibly because of their additional value as a disintegrant in the formulation. Concentrations up to 10% are common, but it should be appreciated that excess may result in exactly the opposite effect to that desired, i.e., the flow properties will be worse.

Talc is also widely used and has the advantage that it is superior to starches in minimizing any tendency for material to stick to the punch faces (antiadherant). Because of its totally insoluble nature and hence potential retarding effect on dissolution, concentrations must be strictly limited and should rarely exceed 5%. In fact, the best overall compromise may be realized by using a mixture of starch and talc.

Recently certain silicaceous materials have been used successfully as flow inducers; among these quoted in the literature is pyrogenic silica in a concentration as low as 0.25% and hydrated sodium silicoaluminate (0.75%) (Marshall & Rudnic, 1990:382).

A review by Augsburger and Shangraw (1966:418) of a series of silica-type glidants used decreased weight-variation as a criterion of evaluation. In general, many materials commonly referred to as lubricants possess only a minimal lubricating activity, and are better glidants or antiadherents. Thus, a blend of two or more materials may be necessary to obtain the three properties.

York (1975:1216) presented data indicating the relative efficiency of glidants for two powder systems and reported the following order of effectiveness: fine silica > magnesium stearate > purified talc.

The mechanism of action of glidants have been hypothesized by various investigators and include:

1. The dispersion of electrostatic charges on the surface of granulations.[a,b]
2. The distribution of glidant in the granulation.[c]

3. The preferential adsorption of gases onto the glidant versus the granulation.[c]
4. The minimizing of Van der Waals forces by separating the granules.[a]
5. The reduction of the friction between particles and the surface roughness by the glidant adhering to the surface of the granulation [a,b] ([a]Jones, 1968; [b]Paleng & Mannheim, 1972:45; [c]Neuman, 1967:194).

Usually, there is an optimum concentration for flow, generally less than 1% and typically 0.25 - 0.50%. The optimum concentration may be related to that just needed to coat the host particles. Exceeding this concentration usually will result in either no further improvement in flow, and even worsening of flow. Talc, the colloidal silicas, and cornstarch have been employed as glidants.

1.5.1 EFFECT OF PARTICLE SIZE, SHAPE AND DISTRIBUTION ON FLOW PROPERTIES OF POWDERS

The factors which influence the flow characteristics of powders are diverse and range from particle properties (shape, size, size distribution and density), environment (for instance humidity) to the test method used to evaluate it. Particle size and size distribution of the unit particles have considerable impact on the flow properties of powders and therefore on the dynamics of mixing. Table 1.13 shows, in general, the effect of particle size on the flow properties of powders.

***Table 1.13**: Effect of particle size on powder flow (Lantz & Schwartz, 1990:34).*

Particle size	Type of flow[a]	Reason
200 – 250 μm (10 - 60 mesh)[b]	Flow is usually good if shape is not interfering	Mass of individual particles is relatively large
250 – 75 μm (60 mesh – 200 μm)	Flow properties may be a problem with many pure substances and mixtures	Mass of individual particles is small and increased surface area amplifies effects of surface forces
< 100 – 75 μm	Flow becomes a problem with most substances	Cohesive forces or free surface energy forces are large as well as static electrical forces relative to particle size

[a]Assumed that particle shape is constant and does not interfere with flow; [b]U.S. standard mesh size

Large dry particles (sieve size range > 60 mesh) have a tendency to flow better then the smaller dry particles, because they have greater mass. Smaller particles (< 100 mesh) may create mixing problems because surface areas are very large, and may give rise to strong

electrostatic forces as a result of processing and/or interparticle friction from movement. These forces may prevent the desired distribution of these smaller particles throughout a mixture because of fine particle agglomeration.

As the particle size approaches 10 μm and below, weak polarizing electrical forces, called Van der Waals forces or cohesive forces, also begin to affect the flow of the powder. Both Van der Waals and electrostatic forces usually inhibit powder flow through particle agglomeration as mentioned above. However, in some instances improved flow results because the agglomerated particles behave as a single large mass particle (figure 1.10). Flow may be better in this case, but the dynamics of distributing these small particles during mixing is very poor (Lantz & Schwartz, 1990:32).

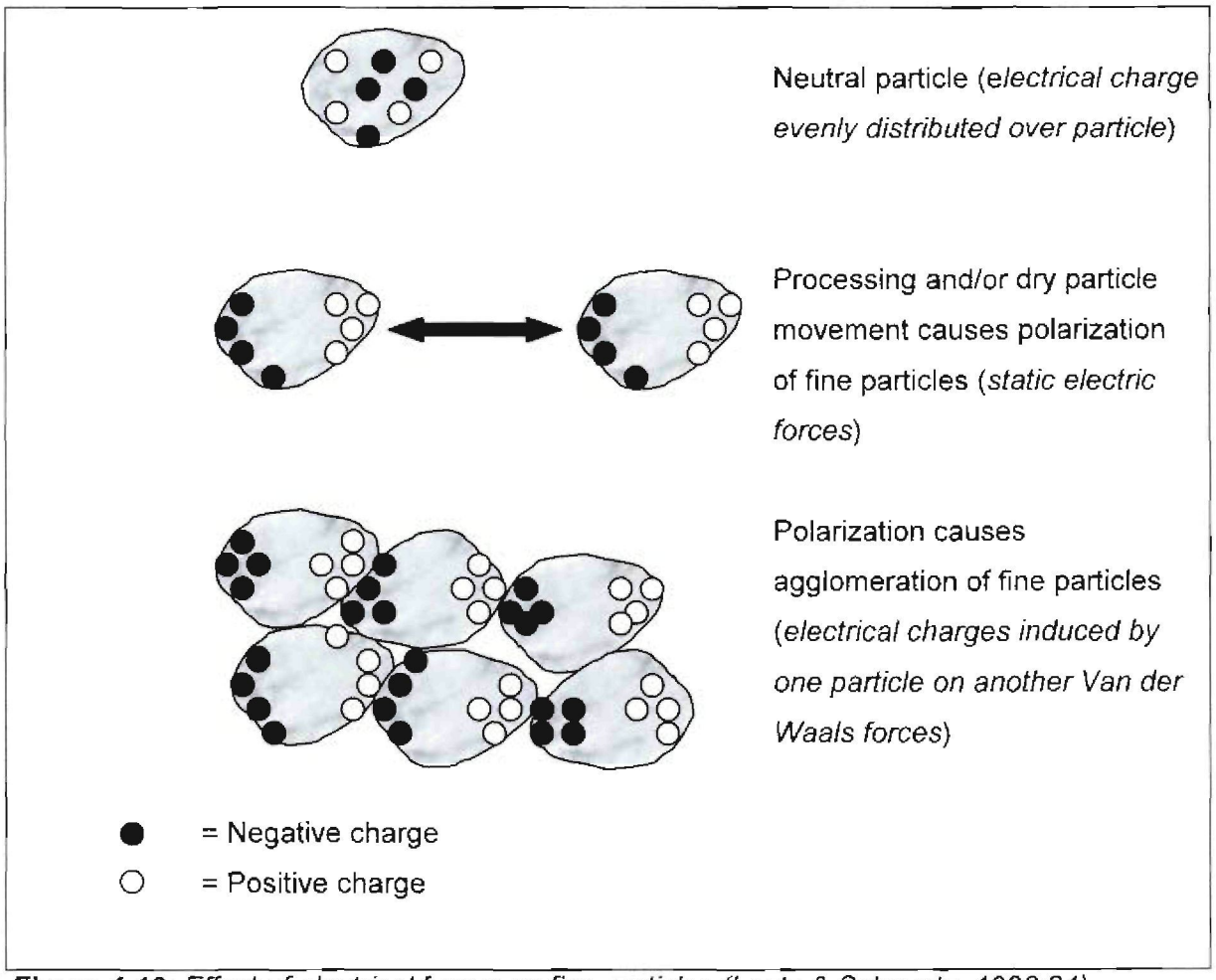


Figure 1.10: *Effect of electrical forces on fine particles (Lantz & Schwartz, 1990:34).*

Size distribution of a powder also has an effect on the packing characteristics, and therefore the bulk density of the powder. This is due to the smaller particles, which occupy interstices between the larger particles, creating a more densely packed powder with flow difficulties.

Different particle shape (figure 1.11) affects powder interparticle friction, and consequently the flow properties of the powder (Lantz & Schwartz, 1990:39). Materials composed of particles with rounded edges, such as (a) and (b) in figure 1.11, will flow more readily than those with sharper edges (c), or two dimensional flat, flake like particles (e). Poor flow is usually encountered with particles having an interlocking shape (d) or fibrous configuration (f).

It is apparent that particle shape affects the angle of repose of a powder, particularly powders with low magnitude surface forces as found with particles greater then 100 μm, and some low free-surface energy-fine powders such as talc (hydrous magnesium silicate) and cornstarch.

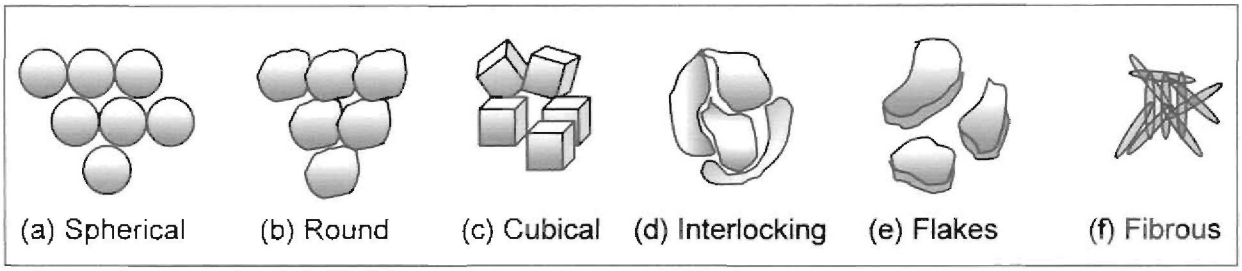


Figure 1.11: *General particle shapes encountered in powder masses (Lantz & Schwartz, 1990:40).*

1.5.2 ASSESSMENT OF GLIDANT EFFECIENCY

Measurement of glidant efficiency is done by means of the following methods.

1.5.2.1 Angle of repose

The angle of repose (α) or the angle of slip is a relative measure of the friction between powder particles but also is a measure, for the most part, of the cohesiveness of fine particles. The angle of repose may be measured in several ways as shown in figure 1.12. Methods 1 and 2 are both dynamic angle of repose measurements. The powder in method 1 flows from a filled powder funnel onto a smooth surface where the angle is measured as illustrated, and in method 2 the powder is moving in a rotating drum while the angle is measured as shown. Method 3 gives the static angle of repose, because the powder container is removed and the powder does not, or is not flowing before the measurement. With care, dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%.

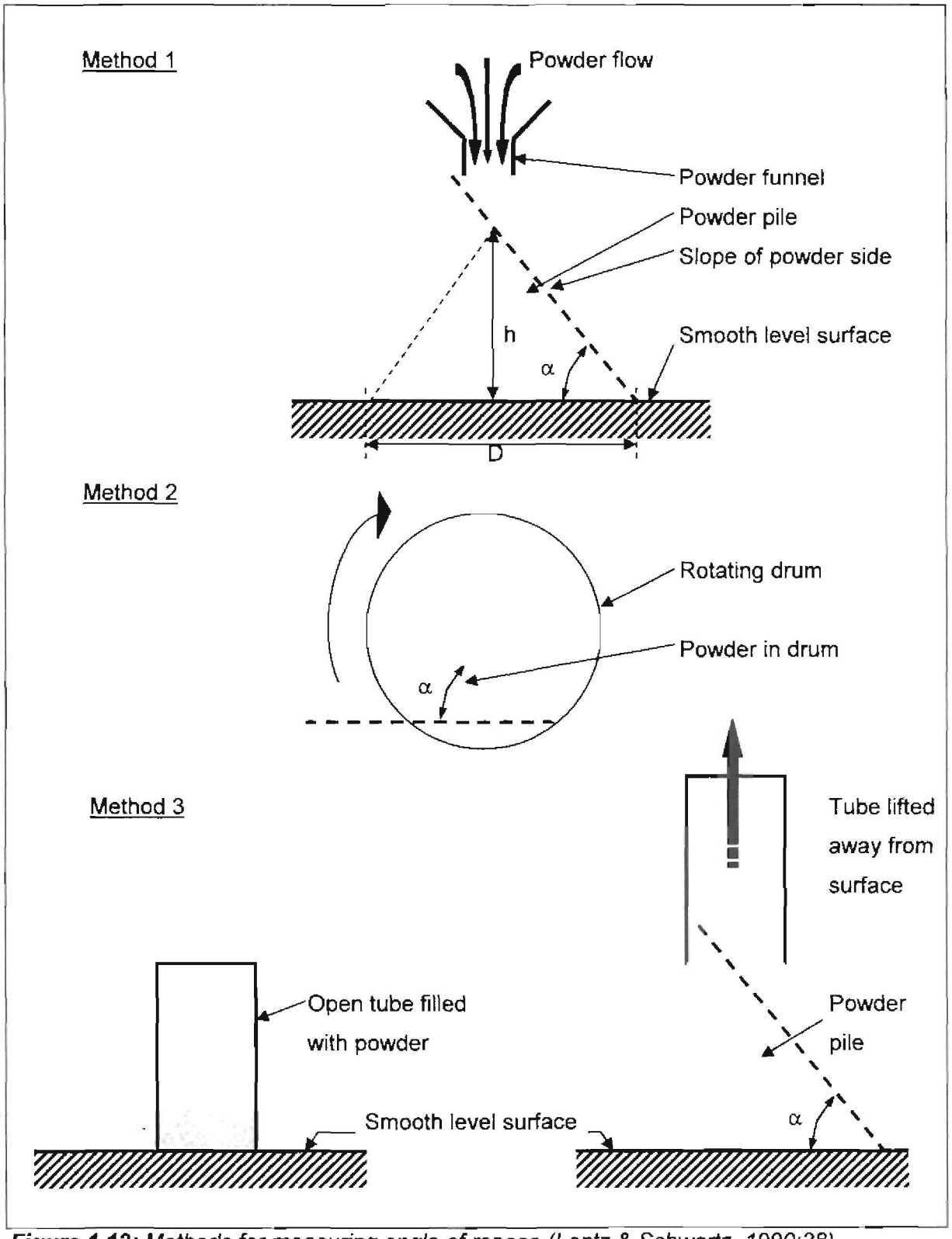


Figure 1.12: *Methods for measuring angle of repose (Lantz & Schwartz, 1990:38).*

Since many factors enter into the angle of repose such as particle size, shape, moisture content, etc., there is some question as to its value in characterizing a powder. However, certain generalizations can be made regarding the angle of repose:

1. α is > 60° for cohesive powders.
2. α is < 25° for non-cohesive particles.
3. High α usually means poor powder flow and the particles are usually less than 75 to 100 μm in size.
4. Low α usually mean good powder flow and the particles are usually greater than 60 mesh or 250 μm in size.

The tangent of the angle of repose (tan α) is termed the "coefficient of friction" of a powder and is preferred by some in referring to the flow properties of a powder. It is evident from this that the smaller the angle of repose, the lower the coefficient of friction and thus the better the flow properties of the powder (Lantz & Schwartz, 1990:35). The coefficient of friction can also be quantified by equation 1.16 (Marshall, 1986:67).

$$\text{Tan}\,\alpha = \frac{2h}{D} \qquad 1.16$$

It must be remembered that all the properties discussed above are intimately interrelated, and, although each one must be considered individually, they must be considered as an entire group of variables when evaluating powder flow properties.

1.5.2.2 Flow rates

Alternatively, resistance to movement of particles, especially for granular powders with little cohesiveness, may be assessed by determining their flow rate (Q) through a circular orifice (a tablet die, for instance, fitted in the base of a cylindrical container).

Flow experiments with mixtures of different size fractions of the same material can be particularly valuable, because in many instances, there exist optimum proportions that lead to a maximum flow rate, as shown in figure 1.13. Note that for this system, when the proportion of fine particles exceeds approximately 40%, there is a dramatic fall in the flow rate (Jones, 1968:2015).

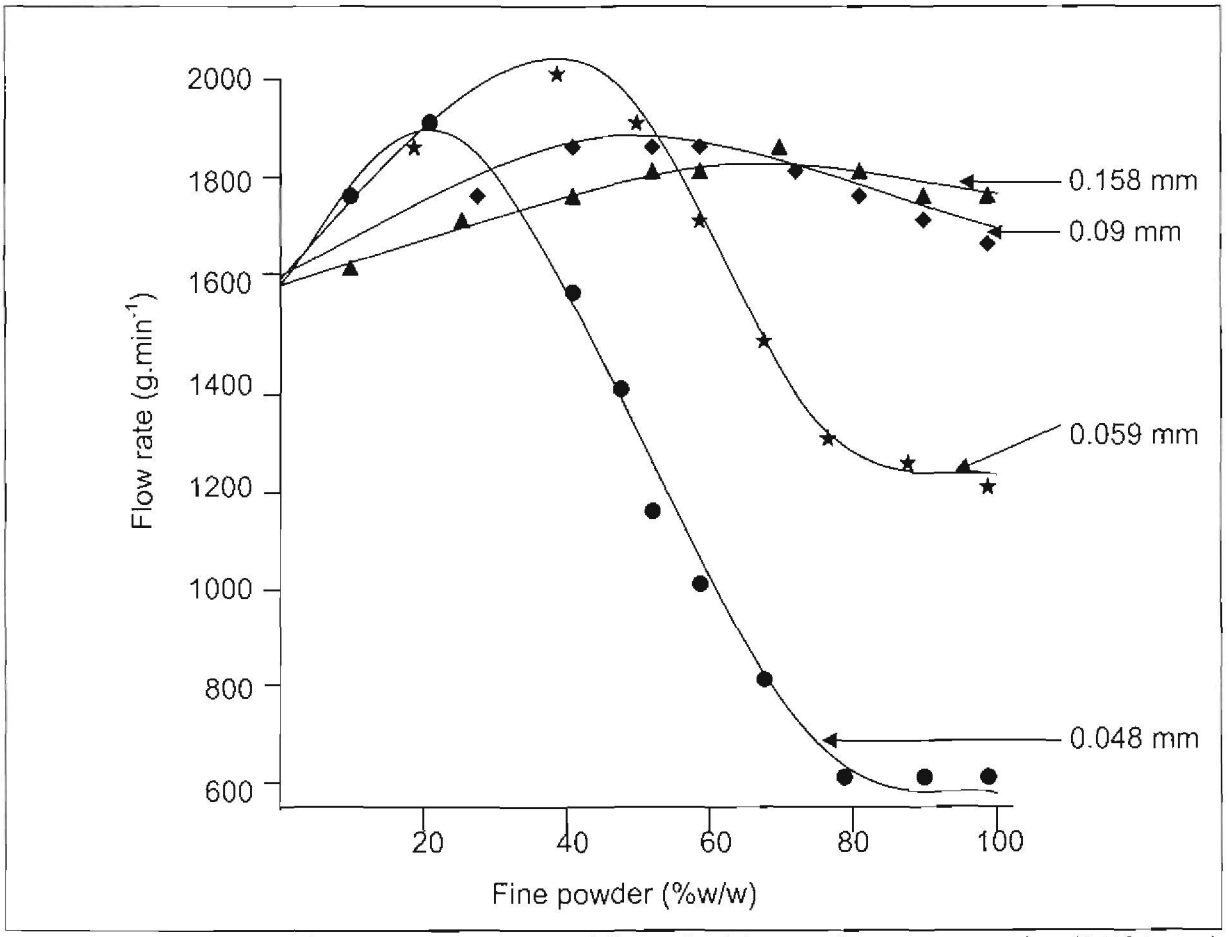


Figure 1.13: *Effect of fineness on the rate of flow of mixtures of coarse granules (0.561 mm) as a function of increasing amounts of fines (Jones, 1968:2015).*

1.6 MIXING OF LUBRICANTS

Since mixing plays such an important role in effective lubrication during tableting, an understanding of the characteristics of the materials being mixed is paramount. Each component in a mixture has distinct physical characteristics, which contribute to, or detract from, the completeness (uniformity) of a mixture. Therefore, it is important to define and characterize the unit particles that make up the direct compression formula.

Powder mixing is an operation to make two or more powder ingredients homogeneous with, if necessary, some amount of liquid, while the latter is not necessary for the direct compression of tablets. The size of powders mixed range widely, and in moisture content the states range from dry to pendular. Being an assemblage of many solid particles subjected to various interactive forces and not being self-diffusive, powders cannot be set in motion without an external force such as mechanical agitation (Miyanami, 1991:595).

The theory of solids mixing has not advanced much beyond the most elementary of concepts and, consequently, is far behind that which has been developed for fluids. This lag

can be attributed primarily to an incomplete understanding of the ways in which particulate variables influence such systems and to the complexity of the problem itself.

When viewed superficially, such multiparticulate solids as pharmaceutical bulk powders are seen to behave somewhat like fluids. That is, to the casual observer, they appear to exhibit fluid-like flow when they are poured from one container to another and seem to occupy a more or less constant bulk volume. Dissimilar powders can, at least in principle, be intimately mixed at the particulate level much like miscible liquids. Contrary to these similarities with fluids, however, the mixing of solids present problems that are quite different from those associated with miscible liquids. The latter, once mixed, do not readily separate and can be poured, pumped, and otherwise subjected to normal handling without concern of undermixing. In addition, they can be perfectly mixed in any standard equipment, with the primary concerns being power efficiency and time required. In contrast, well mixed powders are often observed to undergo substantial segregation during routine handling following the mixing operation. Such segregation of particulate solids can occur during mixing as well and is perhaps the central problem associated with the mixing and handling of these materials (Rippie, 1986:13).

At this stage it is important to note that there is a difference between the mixing order of lubricants, depending on the process of tableting. Wet and dry granulation require for the lubricant to be added after the granulation stage, otherwise the lubricant retard release of the drug from the granules. Direct compression is less dependent of the order of mixing and it could be added at any time, depending on the time of drug-filler mixing times, since overmixing of the lubricant could also lower drug release from directly compressed tablets.

1.6.1 PARTICULATE SOLIDS VARIABLES

Particle size and particle size distribution are important since they largely determine the magnitude of forces, gravitational and inertial, that can cause interparticulate movement relative to surface forces, which resist such motion. As a consequence of high interparticulate forces, as compared to gravitational forces, few powders of less than 100 microns mean particle size are flee-flowing. Most powders, including those encountered in pharmaceutical systems, have a wide range in particle size with the actual distribution determined to some extent by the method of preparation.

Particle density, elasticity, surface roughness, and shape also exert their influence on the bulk properties of powders. Of these, particle shape is perhaps the most difficult variable to describe and is commonly expressed by scalar quantities known as shape factors. When

applied to solids mixing, shape factors provide a number of index to which mixing rate, flow rate, segregation rate, angle of response, and other static or dynamic characteristics can be related. However, the limitations as well as the attributes of shape factors should be understood.

As scalar quantities, shape factors serve as proportionality constants between mean particle diameters and particle surface area and volume. They also serve to relate results of experimental particle size measurements by different methods. In spite of their utility in these ways, shape factors do not describe the shape of the particles they characterize. Thus, a single factor can in no way be considered a unique indication of shape. For example, one cannot differentiate between rods and flat discs by the use of a single shape factor. This limitation somewhat complicates correlations and interpretations of particulate shape effects on mixing.

A large number of shape factors have been defined and used in studies of multiparticulate solids systems. A typical example is that of a surface shape factor, α_s, defined by equation 1.17:

$$\alpha_s = \frac{s}{\sum n_i d_i^{\,2}} \qquad 1.17$$

where:

- s = the total surface area of the powder
- n_i = amount of particles
- d_i = projected diameter of particle n_i

Powders whose particles are highly irregular in shape generally exhibit large values of α_s, which increase substantially as the particles become more angular and deviate from a spherical shape (Rippie, 1986:14).

1.6.2 FORCES ACTING IN MULTIPARTICULATE SOLIDS SYSTEMS

Forces that operate at a particulate level during the mixing process are essentially of two types:

1. Those that tend to result in movement of two adjacent particles or groups of particles relative to each other, and
2. Those that tend to hold neighbouring particles in a fixed relative position.

This division is arbitrary, and often a clear distinction cannot be made, for reasons that will become evident.

In the first category are forces of acceleration produced by the translation and rotational movements of single particles or groups of particles. Such motion can result either from contact with the mixer surfaces or from contact with other particles. In either case, the efficiency of momentum transfer is highly dependent on the elasticity of the collisions. In general, much more rapid and efficient interchange of momentum would be expected if loss by inelasticity were minimal (Rippie, 1986:14).

The shape and surface "roughness" of the particles involved in collision determine, to a large extent, the distribution of the transferred momentum between translational and rotational modes. That is, all other factors being equal, particles with a high coefficient of friction are likely to exchange rotational momentum more readily. This momentum exchange can also be expected to depend more on the "available surface" area than on the density or the mass of the particle. Rotating aggregates experience centrifugal forces that tend to break them into smaller units and aid the mixing process. Gravitational forces also operate and, of course, act on all particles at all times in proportion to their mass (Rippie, 1986:14).

Included in the second category of forces, namely those that resist particulate movement, are interparticulate interactions associated with the size, shape, and surface characteristics of the particles themselves. Powders that have high "cohesive" forces due to interaction of their surfaces can be expected to be more resistant to intimate mixing than those whose surfaces do not interact strongly. Factors that influence this type of interaction are surface polarity, surface charge, and adsorbed substances such as moisture (Rippie, 1986:14).

In moving from one location to another, relative to its neighbours, a particle must surmount certain potential energy barriers. These arise from forces resisting movement insofar as neighbouring particles must be displaced. This effect is a function of both particle size and shape and is most pronounced when high packing densities occur. Particle shape is

important because as the shape of a particle deviates more significantly from a spherical form, the free movement it experiences along its major axes also diverges (Rippie, 1986:14).

Recent studies by several workers, on particulate beds by means of computer simulation, have demonstrated the existence of these barriers. They are manifested by peaks and valleys in the radial location frequency distribution of particles in a bed relative to a reference particle. Figure 1.14 illustrates distributions typical of a bed of particles of relatively uniform size. This diagram shows that moderate bed expansion, short of total fluidization, facilitates interparticulate motion, and hence mixing, by reducing the magnitude of the energy barriers and shortening the distance between preferred locations (Rippie, 1986:14).

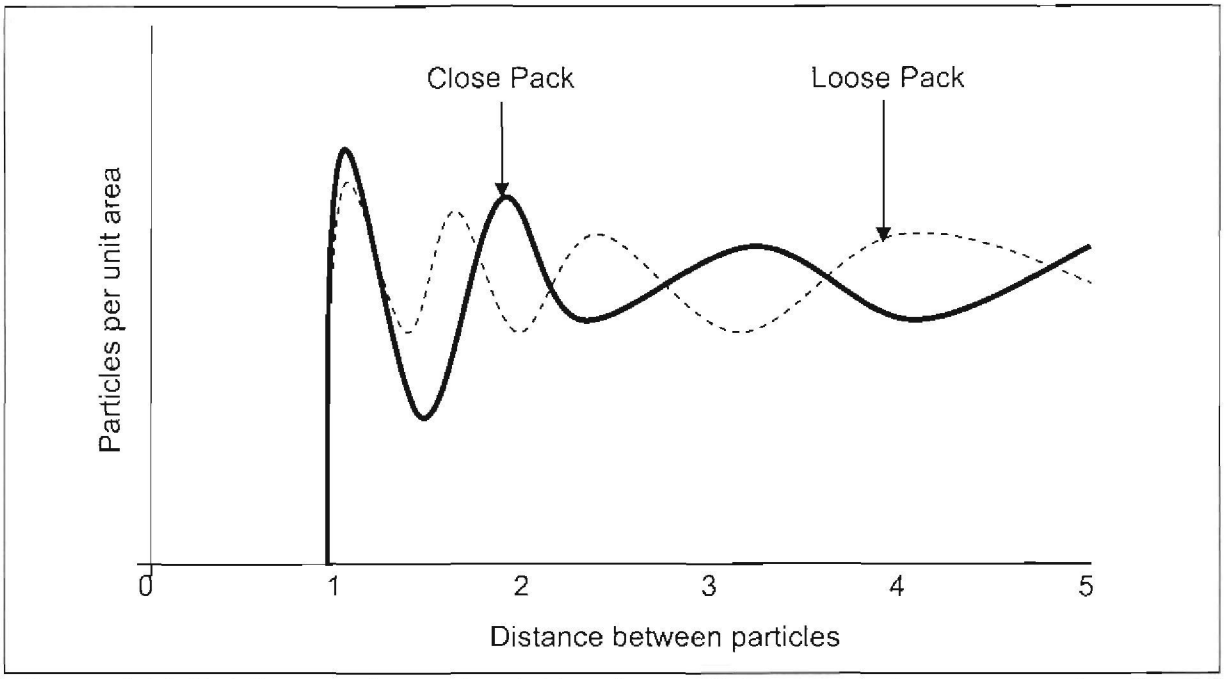


Figure 1.14 *Relative numbers of neighbouring particles per unit area as a function of distance measured in particle diameters from reference particles. Measurements are made center-to-center of relatively spherical particles under both close and loose packing arrangements (Rippie, 1986:15).*

In general, powders and divided solids possess a wide spectrum of particulate properties, which result in an equally wide range of bulk properties. The latter may be classified as being characteristic of either a static or a dynamic state of the system (Rippie, 1986:14).

Attempts to correlate the gross properties of powders with the nature of the individual particles have been somewhat more successful in the systems under static conditions than when the particles are in a state of flow. This is not unexpected since inertial forces become important when the particles are in motion, and the resulting transfer of momentum and kinetic energy is a complex function of the particulate variables (Rippie, 1986:14).

1.6.3 EFFECT OF MIXING INTENSITY AND TIME

The successful mixing together of fine powders is acknowledged to be one of the more difficult unit operations because, unlike the situation with liquids, perfect homogeneity is practically unattainable. All that is possible is to realize a maximum degree of randomness in the arrangement of the individual components of the mix. In practice problems also arise because of the inherent cohesiveness and resistance to movement between the individual particles. The process is further complicated in many systems by the presence of significant segregative influences in the powder mix. These arise due to differences in particle size, shape, and density of the component particles.

Solid lubricants such as magnesium stearate are adsorbed on the granule surface. These lubricants form a uniform surface-adsorbed film in a manner similar to a Langmuir-type adsorption. If it is assumed that during the mixing process lubricant particles first adsorb on the surface and then, upon continued mixing, distribute uniformly upon the granule surface, the breaking of these lubricant particles by delaminating or deagglomeration may take place. Such processes would result in greater coverage of the granule surface by the lubricant, thereby producing a greater interfacial surface between the lubricant and the excipient granule, i.e. surface of separation. Thus, the function of mixing is to enlarge the initial plane of separation between ingredients such as excipients and lubricants, and thereby increasing the amount of surface coverage of carrier particles by lubricant, resulting in less interparticulate binding area and weaker tablets (Hussain *et al.*, 1988:90).

Blender speed may also be a key to mixing efficiency in that the slower the blender, the lower the shear forces. Although higher blending speeds provide more shear, more dusting may be prevalent causing segregation of fines, i.e. as the mixture is tumbling, the fines become airborne and settle on top of the powder bed after blending has ceased.

There is also a critical speed, which, if approached, will diminish blending efficiency of the mixer considerably. As the revolutions per minute (rpm) increase, the centrifugal forces at the extreme points of the mixing chamber will exceed the gravitational force required for blending, and the powder will gravitate to the outer walls of the blender shell, also lowering mixing efficiency (Lantz & Schwartz, 1990:44).

The coating of the formulation with hydrophobic lubricants such as magnesium stearate generally results in decreased mechanical strength, increased disintegration time, and retarded dissolution of the resultant tablets. For laminar lubricants such as magnesium (and calcium) stearate, this effect is also dependent on the duration and intensity of mixing, since

the laminar lubricant particles tend to delaminate on mixing, thereby causing an increased efficiency of coating (coating power) of the formulation particles.

1.6.4 ASSESSMENT OF MIXING EFFECTIVENESS

1.6.4.1 Surface area of lubricants as indicator of lubricant efficiency

There is evidence that different brnads of magnesium stearate dosed by surface area, i.e. using amounts developing equivalent lubricating areas, may produce similar characteristics in the final tablets (Frattini & Simioni, 1984:1117). Thus, magnesium stearate levels could be expressed as a particular weight provided surface area is controlled.

The surface area of magnesium stearate might be the most important parameter to monitor, in terms of lubricant efficiency. A substantial decrease in both ejection forces and tablet hardness is seen for certain brands of magnesium stearate that had higher surface areas. Lubricants with high surface areas might be more sensitive to changes in mixing time than lubricants with low surface areas. Thus, if a particular drug or formulation is deleteriously affected by prolonged mixing of lubricants, adequate characterizations and monitoring of a lubricant surface area should be an integral part of product development and quality control.

Effective surface coverage (equation 1.18) has been estimated by comparing the dissolution rate of unlubricated aspirin tablets to that of lubricated aspirin tablets (Johansson & Nicklasson, 1986:51).

$$\% \text{ Surface coverage} = \left(1 - \frac{\text{Rate}_{\text{lubricated}}}{\text{Rate}_{\text{unlubricated}}}\right) \times 100 \qquad 1.18$$

In a similar manner, estimates of effective surface coverage may be evaluated by comparing initial rates of release from disks with and without lubricants in intrinsic dissolution rate studies (Nicklasson & Brodin, 1982:99).

The surface area of lubricant differ widely, as investigations by Hölzer & Sjögren (1981a:142) had show, where, as indicated in table 1.14, magnesium stearate, sodium stearyl fumarate and Dynasan118® had the largest areas (> 1 $m^2.g^{-1}$); while stearic acid had the smallest area (0.09 $m^2.g^{-1}$).

Table 1.14: *Surface area of some lubricants (Hölzer & Sjögren, 1981a:142).*

Lubricant	Area $m^2.g^{-1}$ (air permeametry, porosity 0.5 - 0.6)
Cutin HR	0.602
Dynasan 118	4.461
Precirol	0.263
Ryoto S-370	0.544
Stearic acid	0.089
Magnesium stearate	6.286
Magnesium lauryl sulphate	0.882
Sodium lauryl sulphate	0.619
Sodium stearyl fumarate	2.720
Teflon P-PFA	0.294

1.6.4.2 Lubricant sensitivity

Lubricant sensitivity is expressed as the lubricant sensitivity ratio (LSR). This is the ratio between the decrease in crushing strength of tablets due to mixing with lubricant and the crushing strength of unlubricated tablets prepared without lubricants (equation 1.19).

$$LSR = \frac{(S_0 - S_{lub})}{S_0} \qquad 1.19$$

Where S_0 and S_{lub} are the crushing strengths prepared without and with lubricant, respectively (Bos *et al.*, 1991:42).

This measurement indicates the effect of increased lubricant concentration, mixing times and intensity, and the interaction between these variables on the crushing strength of tablets, compared with non-mixed, unlubricated tablets.

1.7 MAGNESIUM STEARATE

Magnesium stearate is the most commonly used lubricant and in fact also the most widely used pharmaceutical excipient. This is due to the physical tableting process where lubricants almost always form an integral part of the whole process, especially during the ejection phase of this process.

1.7.1 PHYSICOCHEMICAL PROPERTIES

Magnesium stearate (see table 1.15 for physicochemical properties), also known as magnesium octadecanoate, is a hydrophobic lubricant and may retard the dissolution of a drug from a solid dosage form due to the formation of a hydrophobic film around the excipient particles (Strickland *et al.*, 1956:55; Bolhuis *et al.*, 1975:317). The lowest possible concentration should therefore be used in such formulations, varying from 0.25 – 5.0 % w/w.

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint, characteristic odour and taste. The powder is greasy to the touch and readily adheres to the skin. It is manufactured by either the interaction of aqueous solution of magnesium chloride with sodium or ammonium stearate (see formula below), or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

$$2\ CH_3(CH_2)_{16}COOX + MgCl_2 \rightarrow [CH_3(CH_2)_{16}COO]_2Mg + 2\ XCl$$

where X is a cation such as NH_4^+ or Na^+ (Ertel & Carstensen, 1988a:172).

Table 1.15: *Physicochemical properties of magnesium stearate (Wade & Weller, 1994:280).*

Chemical name	Octadecanoic acid magnesium salt
Empirical formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.27
Structural formula	$CH_3(CH_2)_{16}OOC$ —— Mg —— $COOCH_3(CH_2)_{16}$
Density	1.03 -1.08 $g.cm^{-3}$
Density (tapped)	0.30 $g.cm^{-3}$
Flowability	Poorly flowing, cohesive powder
Specific surface area	2.45 - 16.0 $m^2.g^{-1}$
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%)
Incompatibilities	Strong acids, alkalis and iron salts, avoid mixing with strong oxidizing materials

1.7.2 VARIABILITY

According to Billaney and Richards (1982:497), there may be variation between batches of magnesium stearate. Although the physical properties of different batches of magnesium stearate, such as specific area, have been correlated with lubricant efficacy, it has not been

possible to conclusively correlate the dissolution rate retardation with the observed lubricity (Frattini & Simioni, 1984:1117).

There is evidence to suggest that the hydrophobic nature of magnesium stearate can vary from batch to batch due to the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing very low concentrations of these impurities have been shown to retard the dissolution of a drug to a greater extent than batches containing higher levels of impurities.

High purity magnesium stearate exists either as regular platelike particles in a dihydrate form, or irregular needle shaped particles in a mixture of dihydrate and monohydrate forms (Miller, *et al.*, 1982:42P; Miller & York, 1985:55). Commercial magnesium stearates are mixtures of both forms, along with varying amounts of magnesium palmitate, a known impurity, which also exists in the above two forms, as well as other impurities such as magnesium oxide (*United States Pharmacopoeia* [USP/NF]). Dansereau and Peck (1987:975) evaluated and compared magnesium stearate obtained from 16 domestic and foreign sources, and found significant differences in chemical purity, particle size and surface area.

The USP/NF describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids obtained from fats and consists mainly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The *British Pharmacopoeia* (BP, 2002) describe magnesium stearate as consisting mainly of magnesium stearate with variable proportions of magnesium palmitate and magnesium oleate ($C_{36}H_{66}MgO_4$).

Steffens and Koglin (1993:16) classified magnesium stearates into the following five categories:

1. Type A: amorphous, no crystal water, waxy fragments.
2. Type B: crystalline, dehydrate, mostly platelets.
3. Type C: crystalline, mixture of mono- and trihydrate, often needles.
4. Type D: crystalline, mixture of mono- and trihydrate, mixture of platelets and needles.
5. Type E: crystalline, mixture of all hydrates, mixture of all shapes.

Their investigations showed that specific surface area couldn't be the only parameter influencing the film formation tendencies and the lubricant properties of magnesium stearate. Their studies on identifying the different types of magnesium stearate included comparative measurements of specific surface area, particle size, DSC- and X-ray-measurements.

1.7.3 MIXING VARIABLES AND ITS EFFECT ON TABLET PROPERTIES

An increase in the coefficient of variation of mixing and a decrease in the dissolution rate has been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased, whilst magnesium stearate may also increase tablet friability. Blending times with magnesium stearate should thus be carefully controlled.

The distribution of magnesium stearate in a powder mass upon mixing is shown in figure 1.15. During mixing magnesium stearate is either distributed as a free fraction or deposited as a surface film on the base material. Prolonged mixing time will transfer more lubricant from the free fraction to the surface film. The lubricant film on the die wall is formed from both the free fraction and from the surface film and consequently increased mixing time affects the lubricating properties of magnesium stearate only to a minor extent (Johansson, 1985:343).

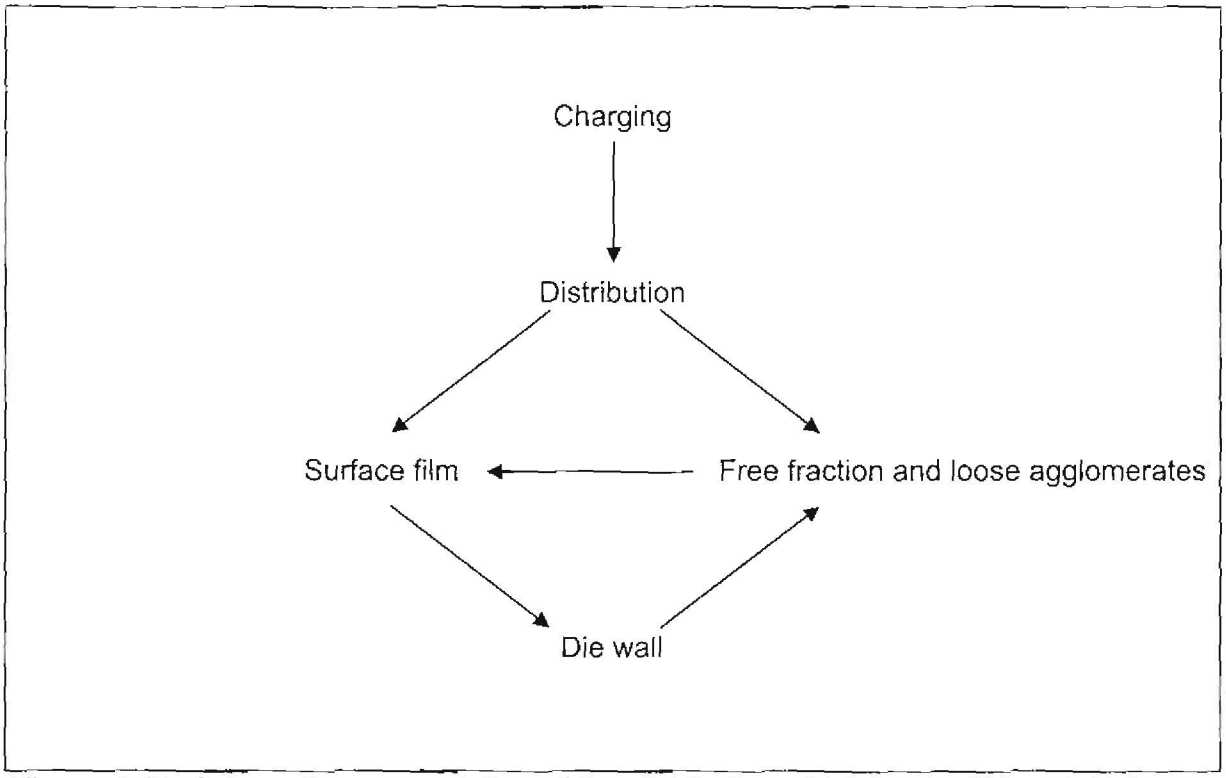


Figure 1.15: *Schematic representation of the distribution of lubricant within a tablet mass (Johansson, 1985:43).*

Khan *et al.* (1983:110) revealed contradictive results for microcrystalline cellulose tablets lubricated with magnesium stearate compared to those of Bolhuis *et al.* (1975:324), which stated that as mixing time increased, disintegration time also increased. Khan and co-workers indicated an initial reduction in disintegration time with increasing mixing time. It

would, therefore, appear that magnesium stearate does not reduce the water penetration of microcrystalline cellulose and they suggested that for a very hydrophilic excipient such as microcrystalline cellulose, the bonding strength and porosity are the dominant factors affecting disintegration.

1.7.4 MECHANISM OF LUBRICATION VIA DISTRIBUTION ON PARTICLE SURFACES

It has been proposed that magnesium stearate reduces the adhesion due to long range Van der Waals forces between the particles of a powder bed (Gold *et al.*, 1968:670). Jones (1968:2016) questioned this on the grounds of the hydrophobic nature of magnesium stearate. However, in the adhesion literature, hydrophobization of materials has been reported to significantly reduce the forces of adhesion (Zimon, 1982:61; Deryaguin *et al.*, 1978:248). An optimal magnesium stearate content, i.e. the concentration which improved powder flow most, can be found when a complete film has been formed surrounding each individual particle. However, above the optimal concentration, i.e. when the film increases in thickness, or when an overshot of fine particles exists, there is a sharp drop in flowability (Jones & Pilpel, 1966:440; Gold *et al.*, 1968:670; Irono & Pilpel, 1982:483). This cannot only be attributed to a weakening of attractive forces between the host particles. During powder flow, particles are in frictional contact with each other. The three basic elements of friction are (i) the area of true contact between the sliding particles, (ii) the type and strength of the attractive forces between the contacting surfaces, and (iii) the shearing and rupture of the materials at the contact points and the surrounding area during sliding (Tabor, 1981:177). For lubricants such as magnesium stearate, which form a film around the particles, the last element is of major importance.

Although the adsorption of magnesium stearate onto particle surfaces often have been thought to result in a monomolecular film (Bolhuis *et al.*, 1975:317), or a monoparticulate layer (Tawashi, 1963:64), recent evidence has suggested a different possibility. Microanalysis of magnesium by scanning electron microscopy (SEM) suggests that the lubricant first lodges preferentially in superficial cavities (Roblot-Treupel & Puisieux, 1986: 131). The cavities apparently are initially partially filled, and then totally filled, after which a peripheral layer of varying density may form (figure 1.16).

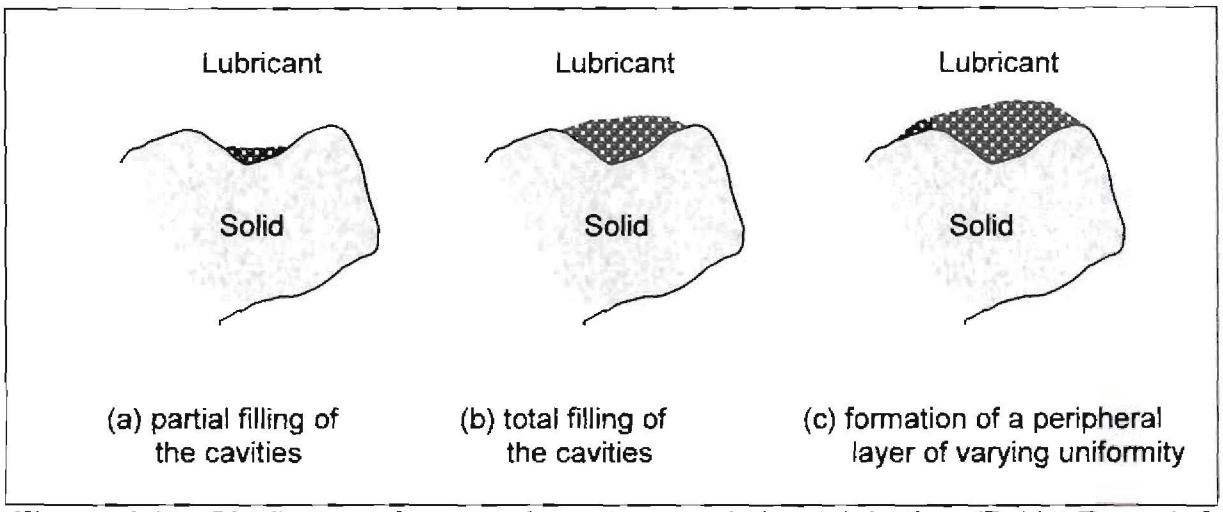


Figure 1.16: *Distribution of magnesium stearate during lubrication (Roblot-Treupel & Puisieux, 1986:135).*

Not all types of tablet excipients are sensitive to lubrication. De Boer *et al.* (1978:80) illustrated that the sensitivity of excipients to magnesium stearate depends on the compression behaviour and on the bonding mechanism of the material. Fragmenting materials (e.g. Emcompress®) are hardly influenced by lubrication. This phenomenon was explained by the assumption that lubricant-free surfaces are created by fragmentation of the particles during consolidation of the particle system.

In a later study, Vromans *et al.* (1988:43) showed that for different types of lactose, the sensitivity to lubrication was related to the bulk density of the powder. Different explanations for this phenomenon were proposed:

1. A low bulk density is an indication of poor flowability of a powder, which might delay or even prevent the formation of lubricant film during the mixing process.
2. A lower bulk density will result in a larger contribution to particle rearrangement and consequently in more friction during consolidation. This could disturb an already formed lubricant film and enhance bond formation.

More recent work by Riepma *et al.* (1993:201) described that the sensitivity of magnesium stearate for brittle materials may not be directly related to the degree of particle fragmentation on compression, but was primarily determined by the degree of coating on the excipient by lubricant from the dry mixing operation.

It is also proposed that the water content in the pseudopolymorphic forms (anhydrous, dehydrate and trihydrate) of magnesium stearate is the main contributing factor to its lubricating action (Pifferi *et al.*, 1999:8).

1.8 SODIUM STEARYL FUMARATE (PRUV®)

Whilst conventional lubricants and especially magnesium stearate usually provide good lubrication, it cannot be used in all cases due to their inherent properties, e.g. lack of solubility, altering effect on drug bio-availability, etc. In particular, their adverse effect on dissolution is well known and a mistake as simple as overmixing can have disastrous consequences. Yet the alternatives available have been complex and imperfect solutions to a difficult problem. Certain materials overcome some of these problems but fall short on the major requirement, i.e. they are poor lubricants and may even be toxic (Mendell, 2002:5).

Sodium stearyl fumarate, commercially available under the propriety name of Pruv® (Mendell, UK), was developed to provide the formulator with a pure material having lubrication properties similar to magnesium stearate, but without its disadvantages. Pruv® is the most effective alternative tablet lubricant and in some instances it has been shown to:

1. surpass magnesium stearate in the reduction of friction coefficients of tableted materials, and
2. reduce the adhesion on tablet punches to the same degree as magnesium stearate.

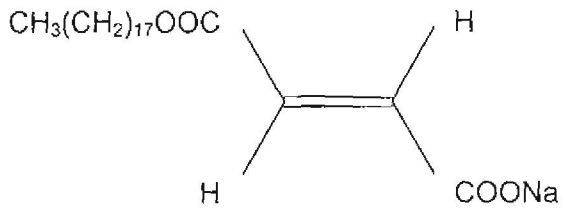
1.8.1 PHYSICOCHEMICAL PROPERTIES

Pruv®, also known as sodium stearyl fumarate, fumaric acid, octadecyl ester, sodium salt or sodium monostearyl fumarate, is supplied in a pure form and is often of value when the less pure stearate-type lubricants are unsuitable due to chemical incompatibility. Pruv® is less hydrophobic than magnesium stearate or stearic acid and has a less altering effect on tablet dissolution than magnesium stearate. It is used in concentrations varying from 0.5 - 2.0 % w/w. A ratio of 10 - 15% of Pruv® are needed to cover granulate surface area, and a concentration of 1.5 – 2.0% w/w Pruv® should achieve this.

Sodium stearyl fumarate (see table 1.16 for physicochemical properties) is a fine, white powder with agglomerates of flat, circular shaped particles (with an average size less than 8 µm). It is manufactured by reacting stearyl alcohol with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate (Wade & Weller, 1994:467).

Pruv® is hydrophilic and this, together with its solubility properties, renders it useful in soluble, dispersible, or effervescent tablet formulations.

Table 1.16: *Physicochemical properties of sodium stearyl fumarate (Wade & Weller, 1994:467).*

Chemical name	2-Butenedioic acid, monooctadecyl ester, sodium salt	
Empirical formula	$C_{22}H_{39}NaO_4$	
Molecular weight	390.5	
Structural formula		
Density	1.12 -1.14 $g.cm^{-3}$ (Beckman air comparison pycnometer 930, air)	
Density (tapped)	0.3 – 0.5 $g.cm^{-3}$	
Specific surface area	1.2 – 2.0 $m^2.g^{-1}$ air permeability method	
Solubility	Solvent	Solubility at 20°C (unless otherwise stated)
	Acetone	Practically insoluble
	Chloroform	Practically insoluble
	Ethanol	Practically insoluble
	Methanol	Slightly soluble
	Water	1 in 20 000 (0.005g/100ml) at 25°C; 1 in 10 (10g/100ml) at 80°C 1 in 5 (20g/100ml) at 90°C
Incompatibilities	Chlorhexidine acetate	

1.9 CONCLUSION

Lubricants are used in tablet formulations in order to ease the ejection of the tablet from the die, to prevent sticking of the tablets to the punches, and to prevent excess wear on dies and punches. Lubricants should be carefully selected for efficiency in compression and according to the specifications of the final tablet, as many studies have shown that there is no universal lubricant. Two of the factors, which are critical to lubricant use, are the particle size of the lubricant and the type and the extent of mixing. Variations in particle size between different lots of the same lubricant will also affect the properties of the tablet formulation.

Lubricants may be broadly divided into two categories, namely (1) the hydrophobic-type lubricants such as fats and oils, which are the most widely used, and (2) the soluble lubricants, which are used largely for tablets meant to be dissolved by effervescence. The

hydrophobic fatty lubricants are the most effective, but excessive use of this type of lubricant will result in rendering the tablet hydrophobic and retarding disintegration of the tablet and drug dissolution. Used in appropriate amounts, and possibly with a surfactant added in the formulation, hydrophobic lubricants do not generally pose problems with their use.

Assessments of lubricity can be done by measurement of the coefficient of lubrication (R-value) to compare efficiency of different lubricants or the dynamic coefficient of friction (μ_W^*) for optimization of lubricant function. Antiadherency can be evaluated through comparison of static (μ_W) and dynamic (μ_W^*) friction coefficients as described in section 1.3.4.2.1 (Hölzer & Sjögren, 1981a:142) or by use of Coulomb's law to determine the adhesive force (C) as outlined in section 1.4.1.3 (Kikuta and Kitamori, 1983:196). Angle of repose (α) or flow rates (I) gives good assessment of glidancy. Mixing efficiency can be measured through lubricant sensitivity ratios (LSR).

Sodium stearyl fumarate (Pruv®) is an effective tablet lubricant and reduces the friction to about the same degree as magnesium stearate. It appears slightly less effective to counter-act the adhesion to the punches. It affects the disintegration time and the tablet strength in a similar way as magnesium stearate when concentrations are increased, but not to the same extent. Prolonged mixing with sodium stearyl fumarate appears to improve the lubricating and the antiadhesive effect with less negative effects on the disintegration than magnesium stearate. Tablet strength increases with mixing time, but may be reduced by prolonged mixing. Thus Pruv® is more sensitive to overmixing then magnesium stearate is (Hölzer & Sjögren, 1979:152). In formulations where magnesium stearate causes problems sodium stearyl fumarate may be a good alternative.

CHAPTER 2

Experimental procedures, apparatus and materials

2.1 INTRODUCTION

The formulation of a solid dosage form often requires precise processing control of the powder mixture to ensure a volumetric delivery of a homogeneous aliquot. Thus, various excipients are gravimetrically added to form the bulk powder with which uniformity is achieved through optimum mixing, appropriate lubrication and good flow of the mixture into the tablet die (Shah & Mlodozeniec, 1977:1377).

This chapter deals with the choice of and motivation for the drug and excipients used in this study. The effects of these excipients on the physical properties of tablets as well as on the dissolution profile of an active ingredient are investigated. The experimental procedures that were employed are explained and the apparatus described.

2.2 MATERIALS

The materials used in the study are presented in table 2.1.

Table 2.1: *Materials, lot numbers and manufacturers used in the study.*

Compound	Lot number	Manufacturer
Furosemide	600	Adcock Ingram Ltd, Wadesville, South Africa
Magnesium stearate	ART 5876	Merck, Darmstadt, Germany
Pruv®	30003103	Penwest Pharmaceuticals Co., Mendell, UK
Avicel® PH-200	M9260	FMC International, Wallingstown, Ireland
Tablettose®	0116	Meggle GmbH, Wasserberg, Germany
Emcompress®	C06D Pallet H	Penwest Pharmaceuticals Co., Mendell, UK

2.2.1 CHOICE OF FUROSEMIDE AS MODEL DRUG

Furosemide, a weak acidic drug (pK_a ~ 3.80), was chosen as model drug tracer during dissolution studies representing a group of drugs, which exhibits poor dissolution due to low water solubility (Boles Ponto & Schoenwald, 1990:305) and poor water wettability. This is probably due to the fact that the drug particles are cohesive and agglomerate spontaneously (De Villiers, 1988:39; De Villiers *et al.*, 1993:160).

The dissolution process limits the absorption of sparingly water-soluble drugs, and the surface area of the drug in contact with the surrounding medium is of primary importance in terms of optimum dissolution. The liberation of the maximum surface-area of the drug exposed to the surrounding medium determines both the rate and extent of drug dissolution, and is to a large extent dependent on the disintegration process (Marais, 2000:60).

Various authors found that disintegration and dissolution of furosemide tablet formulations were dependent on, and could be altered through, formulation excipients (e.g. filler, lubricant, disintegrant, etc.) and processing factors (e.g. mixing variables) (Rubinstein & Price, 1977:5P; Rubinstein & Rughani, 1978:545; Rubinstein, 1980:115; Doherty & York, 1989:228; Akbuğa & Gürsoy, 1987a:2206 and 1987b:2543-2550; Akbuğa, 1991:858; Marais & Van der Watt, 1991:1718; Steyn, 1994:36). The appropriate employment of excipients should, therefore, impart properties to the drug formulations that avert or minimize the challenges that physicochemical properties pose towards dissolution (Shin *et al.*, 1998:18; Boles Ponto & Schoenwald, 1990:385). The relative contributions of each excipient to dissolution could, therefore, be distinguished by evaluation of various formulation and processing variables.

2.2.2 THE CHOICE OF FILLERS/BINDERS IN THE STUDY

The fillers/binders used during this study were each chosen for their respective properties to determine, in part, the mechanism of action (by which both) of the lubricants and to distinguish between the lubricants' individual properties concerning wettability. Avicel® PH-200 is a disintegrating filler which require no lubrication in directly compressible, low drug concentration, formulas. Avicel® PH-200 resembles the "ideal" filler/binder for its popularity in direct compression can be ascribed to its excellent compactibility at low pressures, high dilution potential, superior disintegration properties (Shangraw & Demarest, 1993:32) and most of all its ability to be tableted without lubrication in formulas with low drug concentration (less than 30% w/w of tablet). It should be noted at this stage that any reference to Avicel® made throughout this study actually relates to Avicel® PH-200. Emcompress® does not disintegrate or dissolve without any excipients (disintegrants) being added to improve such characteristics. Its usefulness during direct compression is a result of its low cost and desirable flow and compression characteristics. One of the main advantages of using Emcompress® as a filler/binder is that alkaline lubricants such as magnesium stearate have practically no effect on its binding properties (Bolhuis *et al.*, 1975:320). This insensitivity to lubricants has been attributed to the fact that clean, lubricated surfaces are created by crystal fragmentation during the process of consolidation and compaction. Thus, by addition of lubricants in Emcompress® formulas, compared with the other two fillers/binders, one can

see if there is any disintegration characteristics observed with either of these two lubricants. Tablettose®, on the other hand, slowly dissolves in water, and with the property at hand one can see how these two lubricants affect water wettability.

2.3 PHYSICAL CHARACTERIZATION OF EXCIPIENTS

2.3.1 PHYSICAL PROPERTIES OF POWDERS

The physical properties of powders could influence the tabletability of (the various) formulations. The primary excipient properties of importance are flowability, compactibility and compatibility. The following properties were evaluated in this study: particle size and particle size distribution, particle shape and surface structure of powder particles, powder flow and the applicable characterization procedures are described in the following sections.

2.3.1.1 Particle size and size distribution

Particle size analysis of all materials was conducted by the method of laser diffraction using a Malvern® Mastersizer X (Malvern Instruments Ltd., Worcestershire, UK) fitted with a MSX1 sample suspension unit and a 300 mm lens. A constant velocity setting of 5 was selected to govern the rate of the sample pump, cell stirring, ultrasonic stirring and suspension stirring. This setting was maintained for all evaluations.

Samples were prepared by suspending 1 g Avicel® or 1 g Emcompress® in 15 ml Milli RO® distilled water in MSX1. Due to their poor wettability in water, the two lubricants were prepared by suspending 1 g of each in 15 ml 95% ethanol. Tablettose®, a water soluble binder/filler, had also been suspended in 95% ethanol. The suspended samples were transferred to the sample unit and cycled through the apparatus by addition of 300 ml of a dispersion liquid. The analysis was performed in duplicate.

2.3.1.2 Particle shape and surface structure of particles

The analysis of the physical powder and tablet properties is often the observation of various macroscopic phenomena. An additional means of characterization of the physicochemical properties of powders and tablets is by scanning electron microscopy (SEM), which serves to visualize the shape and surface aspects of particles, and light microscopic analysis, to distinguish between particles of excipients through colouration. Information is gathered on a micro level that might direct a better understanding of the macroscopic phenomenon, e.g. the environment in which excipients exert their actions. Electron and microscope micrographs are included in the result chapters of this study, where applicable.

2.3.1.2.1 Experimental conditions, sample preparation and apparatus for SEM

Avicel®, Tablettose® and Emcompress® were mixed with magnesium stearate or Pruv® for 4 or 8 minutes respectively at 69 rpm in a Tarbula® mixer. The lubricant concentrations used were 0, 0.5, 1, 1.5 and 2% w/w.

Powder samples were affixed on double-sided conductive carbon tape to a sampling tray and dusted with an inert gas. Samples were consequently sputter-coated with a mixture of gold/palladium (80:20) to form a layer of approximately 28 nm on the surface of the samples. An Eiko® ion coater (model IB-2, Eiko Engineering, Japan) was used in all coating procedures and operated under a vacuum higher than 0.06 Torr. Samples were studied using a Philips® XL 30 DX 4i SEM microscope (Eindhoven, The Netherlands).

2.3.1.2.2 Experimental conditions, sample preparation and apparatus for microscopic analysis

Powder samples were mixed with lubricants, which were coloured to see their effect via colour distinction. Crystal violet (gentian violet) were dissolved in ethanol. The lubricant particles were spray dried with the crystal violet - ethanol solution. After drying the powder mass was again sieved through a 69 µm sieve to establish more or less the same particle size as the original lubricant particles. To make sure none of the newly formed coloured lubricant changed its crystal characteristics, SEM photos were taken to confirm. These coloured lubricants were then mixed with fillers/binders to see their effect on the filler/binder as described in the above section. A light microscope was used to view these coloured excipients at 200x magnification and photos were taken with a digital camera through the microscope's lens.

2.3.1.3 Flow properties

Flow behaviour can often be described best by quantification of the process of flow. Numerous methods have been described, either directly, using dynamic or kinetic methods, or indirectly, generally by measurements carried out on static powder beds (Staniforth, 2000:601). These methods include the angle of repose of the powder and weight variation of tablets.

2.3.1.3.1 Angle of repose

The angle of repose (equation 1.17) has been used as an indirect method of quantifying powder fluidity (Staniforth 2000:601). Particles will start to slide when the angle of inclination is large enough to overcome the friction forces between particles.

An amount of powder (100 g) was poured into a Perspex cylinder with a shutter containing an orifice of 10 mm in diameter (the fixed height funnel and free standing cone method) (Lavoie *et al.*, 2002:887-893). The shutter was opened and the powder discharged from a height of 15 cm onto a horizontal glass surface. The flow rate of a powder is proportional to the angle of repose. A large angle is indicative of poor flowability and a small angle of superior flow. The time and mass of the powder discharged from the container was also noted to determine a flow rate through the 10 mm orifice (Staniforth 2000:603).

The experimental conditions and sample preparation for flow characterization were the same for all three filler/binders used as described in section 2.3.1.2.1. Each determination was done in triplicate.

2.3.1.3.2 Static flow index (I_v)

Since flow is not only influenced by particle size and distribution, density and shape, but also the cohesiveness between carrier particles, an assessment of the amount of powder which flowed through an orifice (v) compared to the initial amount of powder (v_0) in the testing tube, were made. A simple indication of the ease with which a material can be induced to flow is given by a static flow index (I_v) as described by equation 2.1:

$$I_v = 100 - \left[1 - \frac{v_o}{v}\right] \times 100 \qquad 2.1$$

The initial amount of powder (v_0) for all the powders tested was 100 g. High I_v values indicate good flow with free-flowing powder particles from the testing tube. Low I_v values represent the opposite.

2.4 PREPARATION AND EVALUATION OF TABLETS

2.4.1 PHYSICAL CHARACTERIZATION OF TABLETS

2.4.1.1 Mixture composition and preparation

One hundred gram (100 g) mixtures of each formulation were prepared in 300 cm^3 glass containers fitted with a screw cap. Parafilm® was used to seal the openings of containers prior to mixing. All mixing procedures employed a Turbula® mixer (model T2C W.A. Bachofen, Basle, Switzerland) and mixing occurred at various mixing times (1; 2; 4 or 8 minutes) and mixing speeds (33; 69 or 97 rpm) unless otherwise stated. In order to assure proper mixing of the lubricant and prevention of it sticking to the container walls or lid, a small indent was made in the surface of the mixture. The lubricant was placed in this hole, which was carefully covered before mixing commenced. Some deviations from the standard mixing variables were also employed in the mixing procedure for binder/filler stability testing. Formulations were constituted of the filler, lubricant and drug (for dissolution studies) as indicated in table 2.2.

Table 2.2: *Composition of formulations that were tableted and evaluated in the study.*

Compound	Function	% w/w
Magnesium stearate	Lubricant	0; 0.5; 1.0; 1.5 or 2.0
Sodium stearyl fumurate (Pruv®)	Lubricant	0; 0.5; 1.0; 1.5 or 2.0
Microcrystalline cellulose (Avicel®)	Filler/binder	Qs to 100
Spray dried α-lactose monohydrate (Tablettose®)	Filler/binder	Qs to 100
Dicalsium phosphate dihydrate (Emcompress®)	Filler/binder	Qs to 100
Furosemide	Model drug for dissolution	0 or 5*

* *Comprising 20 mg per tablet.*

2.4.1.2 Tablet compression

Various compression pressures were used to evaluate filler compressibility (mechanical strength and friability) and to determine the effect of compression force on tablet properties and drug dissolution. Since an instrumented tablet press was not available, compression force was manipulated by changing the depth of movement of the upper punch into the die during compression (using the scale, ranging between 0 and 50, provided on the machine)

and was changed for every binder/filler used as indicated in table 2.3. Reference to compression settings was designated as the term setting(s). The fill volume of the die was maintained at a constant level throughout the study (accept for dissolution studies where a certain drug dose was required) by using the mass, volume and crushing strength of Avicel® mixed with 0.5% w/w magnesium stearate for 4 minutes at 69 rpm, as reference. Since the die fill volume was kept constant during compression, a higher compression setting represented a higher compression force resulting in an increase in the tablet crushing strength (see chapter 4). Therefore, data presented do not indicate compression force, but only a compression setting, which could be related to tablet crushing strength.

Slightly biconcave punches (10 mm in diameter) was utilized to manufacture tablets that presented a slightly biconvex curvature. An eccentric Manesty® F3 press (Manesty Machines Ltd, Liverpool, England) was employed during all tableting procedures. The first twenty tablets of each mixture were disposed of to compensate for sticking of former tableted mixures and machine speed. The tablets were transferred to glass bottles, which was covered with Parafilm® before the screw caps were fitted, and stored in a dark cabinet at room temperature (25°C ± 2 °C) for at least 24 hours to ensure that the tablets underwent the same amount of decay and elastic recovery.

Compression during the lubricant efficiency tests done in chapter 5, were done on an entirely different compression system and is outlined in section 2.4.2.

2.4.1.3 Analysis of physical tablet properties

The following characteristics were determined: weight variation, radial crushing strength, friability, diameter and thickness of tablets and disintegration time.

2.4.1.3.1 Weight variation

The weight variation of each batch of tablets was determined by weighing 20 randomly selected tablets that were lightly dusted. A Precisa® analytical balance (model 240A, PAG OERLIKON AG, Zurich, Switzerland) was used during all weight measurements. The average weight, standard deviation (SD) and percentage relative standard deviation (%RSD) were calculated.

2.4.1.3.2 Crushing strength, diameter and thickness determinations

Evaluation of crushing strength, diameter and thickness was determined for 10 tablets of each formulation using a Pharma Test® (model PTB-311) tablet test unit (Pharma Test, Switzerland).

Whatever variations occur in the structure of the tablet, changes in face curvature, thickness and diameter, will influence the load at which the tablet fractures when subjected to diametral compression. It has been established by Newton *et al.* (1972:503) that under this form of loading convex-faced tablets fracture in tension, i.e. break across the loaded diameter. Even so, without some means of calculating the material strength (i.e. the tensile fracture stress of the material which constitutes the tablet) from the fracture load (crushing strength), an assessment of which of the various tablet shapes has the greatest material strength cannot be made by fracture tests alone.

Tensile strength is calculated in accordance with equation 2.2 for flat-faced punches (Fell & Newton, 1968:658).

$$T = \frac{2P}{\pi Dt} \qquad 2.2$$

where:

T is the tensile strength (MPa), P is the diametrical crushing strength (N), D the diameter (m), t the overall thickness (m)

Since most of the tablets were compressed with convex-faced or bevelled-edge punches, equation 2.3 (Pitt *et al.*, 1988:2728) was used to compensate for this dimensional variable.

$$T = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1} \qquad 2.3$$

where:

W is the central cylinder thickness. The indentation of the top and bottom bevelled-edge punches was 2.17 mm, thus W = D - 2.17.

Equation 2.3 was shown to be valid for convex-faced tablets with W/D in the range 0.1 - 0.3.

2.4.1.3.3 Determination of friability

Ten tablets of each formulation were carefully dusted and weighed on an analytical balance and transferred to a Roche® friabilator. The friabilator was operated at 50 rpm for a duration of 10 minutes (more vigorous test conditions than required by the BP [2002]). This was done to indicate the softening effect lubricants had on the tablets, and since Avicel® tablets had very little friability, a more severe test had to be performed to indicate significant differences. This method had to be applied throughout the study to compare results. After completion of the test, tablets were carefully removed from the friabilator and lightly dusted. The tablets were then weighed again and the weight loss was expressed as a percentage of the original total weight of the tablets (equation 2.4).

$$\%F = 100 \times \frac{W_b - W_a}{W_b} \qquad 2.4$$

where:

%F is the percentage friability, W_a is the total weight of dusted tablets after completion of rotation and W_b is the total weight of dusted tablets before rotation.

2.4.1.3.4 Measurement of disintegration time

The disintegration times of six tablets of each formulation were determined using a Manesty® tablet disintegration test unit (Manesty Machines Ltd, Liverpool, England). The disintegration medium was distilled water and was maintained at a temperature of 37 ± 0.5 °C. Disintegration was determined without discs. The official limit of 15 minutes was employed and all formulations that did not meet the standard were considered non-disintegrating.

2.5 DISSOLUTION STUDIES

2.5.1 APPARATUS AND DISSOLUTION CONDITIONS

Dissolution studies were performed in a six-station dissolution apparatus at 37 °C (model DT6R, Erweka®, Heustenstamm, Germany) using the standard USP paddles, fitted with a thermostat and variable speed synchronous motor.

2.5.2 RATIONAL FOR CHOICE OF THE DISSOLUTION MEDIUM

Since furosemide is a weak acidic drug (pKa of 3.6), its solubility is pH-dependant. Rubinstein and Price (1977:5P) concluded that the pH of the medium played an important role in detecting differences between good and poor formulations. Prasad *et al.* (1982:85)

and Akbuğa and Gürsoy (1987a:2204) showed that as the pH of the dissolution medium was increased away from the pKa of the drug, the differences in dissolution decreased and at pH 7.4 it virtually disappeared. Therefore, the dissolution studies were done in a discriminating medium of 900 cm^3 0.1 M HCl (pH ~ 1.00) at a temperature of 37°C ± 0.5 °C (regulated by the thermostat). The dissolution of drug particles is suppressed by the low pH of the medium and the contributions of the various excipients on dissolution efficiency could, therefore, be determined. A thermostat regulated the temperature of the medium at 37 ± 0.5 °C and the synchronous motor maintained the rotational speed at 50 rpm.

2.5.3 METHOD

The dissolution vessels were filled with the dissolution medium and left to equilibrate at the specified temperature. The rods were pushed down into the vessels (reaching approximately 5 cm from the bottom of the vessel) and lids were secured on each vessel. The motor was started and as soon as the rotational speed reached 50 rpm, the tablets were introduced. The timing sequence was initiated at a starting point of t = 0. The sampling of the analyte (furosemide) from the vessels followed the time schedule of t = 1, 2, 4, 5, 6, 10, 20, 30, 45 and 60 minutes. Samples of approximately 5 cm^3 were withdrawn at equal heights from each vessel and this volume was replaced immediately after sampling with fresh, preheated dissolution medium. The sampling was performed through a filter unit fitted with a 0.3 µm Millipore® prefilter and the samples were transferred to clean 10 cm^3 glass polytops. The samples were subsequently analysed.

Furosemide absorbs ultraviolet light between 275 and 345 nm and fluoresces at 405 to 417 nm. The fluorescence is pH-dependent and quantum yield is maximized in the pH range of 2 to 3 (United States Pharmacopoeia 1990; Chungi *et al.*, 1979:36; Boles Ponto & Schoenwald, 1990:381-383). Therefore, the UV absorbencies of the samples were measured in duplicate at 277 nm against 0.1 M HCl as blank, using a Unicam-spectrophotometer (model Helios α, Unicam Ltd, Cambridge, UK) fitted with a super sipper and a 1 cm^3 flow-through quartz cell. Corrections were made for the amount of drug that was lost during sampling in the calculation of the dissolution data (section 2.5.5.1).

2.5.4 STANDARD CURVE

Standard curves were drawn up each day prior to dissolution testing. Standard solutions with concentrations ranging from 2 to 12 $\mu g.cm^{-3}$ were prepared from a mother solution containing 50 mg of furosemide dissolved in ± 20 cm^3 absolute ethanol and made up with 0.1 M HCl to 250 cm^3. The UV absorbencies of the standard solutions were determined

spectrophotometrically at 277 nm against 0.1 M HCl as blank. The absorbencies were plotted against concentration and the best straight line through the data points was fitted using linear regression. All standard curves exhibited a Beer's law relationship in the concentration range employed, with correlation coefficients (r^2) > 0.9999. The slope (m) and y-axis intercept (c) were used to calculate the furosemide concentration at each sample time (section 2.5.5.1).

2.5.5 CALCULATIONS

All the calculations were done using the Microsoft® Office Excel® XP package for Windows® XP (Microsoft® Corporation, Seattle, Washington, USA).

2.5.5.1 Dissolution data

The amount of furosemide dissolved (µg.cm^{-3}) at each sampling time was calculated using equation 2.5, while equation 2.6 was used to correct for the drug lost through sampling.

$$x = \frac{y^* - c}{1000m} \qquad 2.5$$

where:

y* is the corrected absorbency (from equation 2.5); x is the drug concentration (µg.cm^{-3}) and m and c are the slope and y-axis intercept respectively obtained from the standard curve.

$$y^*_n = y_n + \frac{V_s}{V_m}\Sigma^{n-1}y^* \qquad 2.6$$

where:

y^*_n is the corrected absorbency of n^{th} sample, y_n is the measured absorbency of n^{th} sample; V_s is the sampling volume; V_m is the dissolution medium volume and $\Sigma^{n-1}y^*$ is the sum of all the corrected absorbencies prior to the n^{th} sample.

Dissolution profiles in this study are presented as furosemide dissolved (in µg.cm^{-3}) as function of time (minutes) and are the means of at least four runs of each formulation.

2.5.5.2 Dissolution parameters, DR_i and AUC_n

The initial slope of the dissolution curve between t_0 and t_6 was suggested to be a fair estimate for the initial dissolution rate of furosemide (DR_i) from the various tablet

formulations, while the area under the dissolution profile up to 60 minutes (AUC) would be an indication of the extent of drug dissolution at the end of the dissolution test.

The DR_i ($\mu g.ml^{-3}.min^{-1}$) of furosemide from each tablet formulation (at the specific compaction pressure for that formulation) was determined from the slope of the dissolution curve between t_0 and t_6, while the AUC ($\mu g.min.ml^{-3}$) of the drug between t_0 and t_{60} was determined using the trapezoidal rule, which is given by equation 2.7:

$$AUC = 0.5 \times \sum_{t=n}^{t=0} (t_n - t_{n-1})(c_n + c_{n-1}) \qquad 2.7$$

where:

$(t_n - t_{n-1})$ is the time difference between two consecutive sampling times and c_n and c_{n-1} is the drug concentration ($\mu g.cm^{-3}$) in samples at sampling times corresponding to t_n and t_{n-1}.

The use of the area under the dissolution profile as a method to compare the effects of formulation or processing variables on drug release profiles from tablets is based in the following assumption: If two formulations do not differ much in the rate and extent to which they make the drug available *in vitro*, they will not differ much in their area under the concentration/time curves obtained from dissolution tests (Banakar, 1991:437; Rescigno, 1992:925).

2.5.6 TABLETING METHOD FOR QUANTITATIVE EVALUATION OF THE EFFECTIVENESS OF TABLET LUBRICANTS

In view of obtaining reproducible data, the following operative steps were strictly adopted throughout this part of the study.

2.5.6.1 Sample preparation

Avicel®, Emcompress® and Tablettose® were mixed with magnesium stearate or Pruv® respectively, with concentration ranges as outlined in table 2.2. Mixing occurred at 4 and 8 minutes at 69 rpm under the same conditions described in section 2.4.1.1. The mixtures were removed from the container after the required mixing time and the total mixture were encapsulated in hard gelatin capsules (Gell-U-Cap®, size no. 0, South Africa, Johannesburg). The capsules were used since the binder/filler-lubricant combinations had different densities and thus different mass per volume indexes. It was important to keep the volume more or less constant for each binder/filler to ensure constant contact areas inside the die for measurements.

2.5.6.2 Compression and ejection cycle

From each mixture (section 2.5.4.1), flat-faced tablets with a diameter of 12 mm were compressed at 10 bar (see section 2.5.2.3). The following procedure were followed:

1. A metal polisher and 95% ethanol was used cleaning tools after every mixture analysis.
2. The steel plunger was placed into the die.
3. The powder of three capsules was implied into the die.
4. The top steel plunger was inserted on top of the powder mass embedded in the die.
5. The casing with die and plungers were inserted into the IR press and the plunger screw was adjusted until it made contact with the top plunger.
6. The amplifier was set to compression mode and the current frequency regulator was set at 50 Hz.
7. A compression cycle was initiated on the computer interface. The pressure increased from 0 to 10 bar. Compression continued for 45 seconds to ensure constant maximum radial pressure.
8. After the compression stopped, the bottom steel pallet was removed from the die, but the top plunger was left intact.
9. The die casing was inserted back into IR press and the plunger screw was adjusted again until it made contact with the top plunger.
10. The amplifier was set to ejection mode and the current frequency regulator was set at 8 Hz to slow down movement for the ejection phase.
11. The ejection cycle was initiated on the computer interface. Ejection continued for 30 seconds to ensure the maximum radial pressure for the initial tablet movement was registered, but the tablet had not to leave the die completely.
12. After ejection with the top plunger screw, the tablet was evaluated as described in section 2.4.1.3 for weight variation, dimension and crushing strength.
13. All of the above stages were repeated fifteen times per mixture, with stage one only repeated after every fifteenth mixture was analysed. This was done to measure the affinity of lubricants to the die wall after repeated compressions.

2.5.6.3 Calibration

Since the amount of input pressure had a direct relation to the output radial pressure, the input pressure had to be kept at a constant level. The input pressure was calibrated by use of a non-elastic metal block which was placed on the hydraulic pressurized lift. After the steel block was fastened into the IR press by means of the plunger screw, compression cycle was initiated. The load cell measurement was set to 10 bar by means of the pressure

screw. Hereafter, the newly designed die, filled with plugs of soft rubber, was inserted into the IR press as described in section 2.5.2.2, and compression started. The soft rubber was used since it has elastic properties and acts like a liquid when under compression in the die. Since the input pressure was known, the output signal from radial pressure had to be calibrated. Thus, under perfect elastic conditions, when one exert 10 bar pressure on a closed system like this, the rubber should exert 10 bar pressure throughout the system. So if we insert 10 bar pressure, under perfect elastic conditions, we can interpret the radial output signal as 10 bar pressure. This direct relationship between input and output pressure should be observed for all pressures, but as the pressure increase, the variation on the relationship will also enlarge, due to mechanical failure and extrusion of the die wall. The calibration range was selected on behalf of literature suggesting that 13 bar or less should be used as input pressure (Watt, 1988:289). The calibration was done at 4, 6, 8, 12 and 16 bar. This gave way to results obtained in section 5.3.1, suggesting the no more than 12 bar had to be used, as die wall extrusion started and as the amplifier range was also only between 1 and 12 bar. For the purpose of this study, calibration was done at 7, 8, 9 and 10 bar, since these pressures represented the area were experiments had to be performed.

2.5.6.4 Assimilation of results

Cylindrical pressure vessels carrying powders at high pressures develop both radial and tangential stresses with values that are dependant upon the radius of the element under considerations. In other words, the output signal measured for radial stresses (σ_r) is dependent on the thickness of the die wall, influencing the signal negatively as the wall thickness increases, and the elasticity (E), also known of Young's elastic modulus (E = 190 GPa for stainless steel) of the material used for the construction of the vessel. To compensate for this we make use of equation 2.8 (Shigley & Mischke, 2001:132) to calculate the amount of pressure extruded on the inside of the die wall (p_i).

$$\sigma_r = \frac{p_i r_i^2 - p_0 r_0^2 + r_i^2 r_0^2 (p_0 - p_i)/r^2}{r_0^2 - r_i^2} \qquad 2.8$$

where:

p_0 is the external pressure on the outside wall of the die, p_i the internal pressure, r_0 the outside radius and r_i the inside radius of the die wall.

Since r is the radius were maximum radial stress will occur, $r \approx r_i$. There is also no external pressure on the die wall, thus $p_0 = 0$. Since we measure strain on the outside of the die (ε_r)

with strain gauges, we need to calculate pressure on the inside of the die wall (p_i). Strain is related to stress as a function of elasticity (E), as indicated in equation 2.9.

$$\sigma_r = E\,\varepsilon_r \qquad 2.9$$

Substituting equation 2.9 into 2.8, and compensating for above mentioned variables, result in equation 2.10:

$$p_i = \frac{E.\varepsilon_r(r_0^2 - r_i^2)}{2\,r_i^2} \qquad 2.10$$

The radial force (F_R) can now be calculated by multiplying p_i with the area of contact of the tablet ($2\pi hr_i$) with the die wall (h = thickness of tablet), calculated from tablet dimensions. Axial force (F_A) is calculated from the multiplication of load pressure to surface area (πr_i^2) of compression.

2.6 STATISTICAL EVALUATION OF THE EXPERIMENTAL DATA

Statistical analysis was performed with STATISTICA® 6.1 (StatSoft®, Inc., 2003) data analysis software system. A 95% confidence level ($p < 0.05$) was considered satisfactory for indicating significant differences. Variables influencing this study were compared were relevant for significant differences using one-way and two-way analysis of variance (ANOVA) for factor comparisons.

CHAPTER 3

Physical characterization of excipients

3.1 INTRODUCTION

Successful application of direct compression in pharmaceutical processes depends on the appropriate selection of suitable excipients that are free-flowing, highly compressible, soluble, physiologically inert and chemically compatible with the active ingredient(s). The physicochemical properties of directly compressible filler/binders mainly determine the physical properties of tablets due to their high concentration in the final tablet mass. The physicochemical influence of lubricants on the final tablet product will also be affected by the physiochemical properties of the filler/binder and *vice versa*. Lubricants play an important role in the tableting process and in altering the rate and extend of the release (disintegration) and dissolution of the active ingredient, pending on the lubricant concentration and type. It is furthermore well known that the physical properties of the primary particles may influence the interaction between particles under load. Therefore, it is essential to understand how particle properties, such as size and shape, will affect the flow and the binding properties of a material (and consequently the tablet strength). This chapter deals with the powder properties (i.e. flow, shape, particle size, etc.), compressibility and physical properties of compacts (tablets) of Avicel®, Tablettose® and Emcompress® and the influence of lubricants (magnesium stearate and Pruv®) on their inherent physical properties and their contribution to the physical properties of the tablets. The interpretation of the results obtained from these evaluations provided some insight into the choice of experimental procedures and excipients that were employed in the remainder of the study.

3.2 PARTICLE SIZE AND SIZE DISTRIBUTION

The particle size and size distribution properties of Avicel®, Emcompress® and Tablettose® powder were assessed according to the methods described in section 2.3.1.1. Table 3.1 summarises the average of results obtained in for annexure A.1.

Table 3.1: *Particle size analysis of excipients used in the study.*

Exipient	Average geometric mean particle size (μm)	Density ($g.cm^{-3}$)*	Average specific surface area ($m^2.g^{-1}$)
Avicel®	226.405	1.510	0.049
Emcompress®	192.040	2.390	0.061
Tablettose®	214.665	1.550	0.043
Magnesium stearate	11.955	1.090	1.169
Pruv®	11.405	1.110	0.901

** Densities represent true density values obtained from Kibbe (2000:665)*

Both the mean particle size and the specific surface area of the fillers/binders showed the following rank order: Avicel® > Tablettose® > Emcompress®. The average of all three fillers was, however, in the range of 200 μm, suggesting good flow for all three. The bigger particle size of Avicel® suggests better flow compared to the other two fillers/binders. The size distribution of Avicel® and Tablettose® varied significantly from that of Emcompress® (compare appendix A.1.1.1 and A.1.3.1 with A1.2.1). Whilst the first mentioned fillers both exhibited a rather broad particle size distribution ranging from 10 to 500 μm, Emcompress® showed a rather narrow size distribution between 100 and 500 μm, with a second distict, but small particles range between 3 and 11 μm, with almost no particles between 11 and 100 μm. The high amount of smaller particles gave rise to a bigger surface area for Emcompress® (table 3.1). Although beneficiary, these smaller particles are more or less the same size as that of the lubricants, which might result in competition for contact area on the bigger particles, which will further desensitize the filler/binder against the effect of lubrication and mixing. This higher amount of small particles in the Emcompress® powder could also have a negative impact on its flow. Smaller agglomerates and small crystals could also be detected in all the powders due to a decrease in particle size as seen from the second reading.

The filler densities exhibited the following rank order: Emcompress® > Tablettose® > Avicel®. These densities are an indication of the porosity of the filler, which could have an influence on the compressibility and disintegration of the filler/binder. Different particle size fractions of a material will have different initial packing densities. The packing density of a powder is influenced by the particle size distribution, particle shape, and interparticulate forces (frictional and electrostatic interactions). Generally, smaller particles allow for a higher packing density after the initial particle rearrangement during consolidation and a greater

number of contact points for interparticulate bonding (Katikaneni *et al.*, 1995:13). It is thus expected that the higher density of Emcompress® will give rise to harder tablets compared to the other fillers/binders.

As expected, the mean particle size correlated with the specific surface area of the fillers, with an increase (in this parameter) as the mean particle size decreased. This relationship was also observed by Phadke *et al.* (1991:905). Tablettose® and Avicel® contained only approximately 4% and 5% particles respectively below 25 µm, whilst Emcompress® had about 13% particles below this size. The significant higher specific surface area of Emcompress® compared to the other two fillers, could therefore be attributed to the smaller average particle size of the filler and the presence of a higher percentage of smaller particles. A higher specific surface area of the carrier material provides for more potential contact areas for lubrication and thus less sensitivity for an increase in lubricant concentration or mixing rotations. According to Van der Watt (1986:53) the larger the carrier particles, the larger the shear forces in the mixer, resulting in a faster rate of film formation. From this theory it could be expected that Avicel® will be more sensitive towards increased lubrication and mixing conditions than Tablettose® and Emcompress® during compaction. The higher sensitivity will have a pronounced effect on the hardness, disintegration and dissolution properties of these compacts.

The small particle size of the lubricants compared to the fillers suggested that filler particles would act as a carrier for the lubricant. Due to this size difference between filler and lubricant and the higher concentration of the fillers, its particle size (if shape is not interfering as discussed in section 1.5.1) will be the predominant factor influencing flow. Since both lubricants had particle sizes of about 10 µm, Van der Waals forces or cohesive forces will effect the flow of powders containing these lubricants due to the reduction of adhesion forces between carrier particles (Gold *et al.*, 1968:670). An optimum lubricant content, i.e. the concentration which improved powder flow and decreased friction most, can be found when a complete film has been formed surrounding each individual carrier particle. However, above the optimal concentration, i.e. when the film increases in thickness, or when an overshot of fine particles exists, there is a sharp drop in flowability (Jones & Pilpel, 1966:440; Gold *et al.*, 1968:670; Irono & Pilpel, 1982:483). As a result of the smaller particle size of Pruv®, agglomeration might affect flow properties at a larger extent than magnesium stearate in carrier systems. Contradictory to this theory, magnesium stearate exhibited the biggest particle size and specific surface area, thus suggesting improved flow. It must be mentioned that these mean particle size values for magnesium stearate may be somewhat different from the true values since magnesium stearate particles are not spherical, but exhibit a

platelike structure, depending on the crystal form used. So, it may be concluded that the true mean particle size of magnesium stearate might be smaller than the measured mean particle size.

3.3 PARTICLE SHAPE AND SURFACE STRUCTURE

The particle shape and surface structure of powders are useful in understanding the structure and orientation of particles in mixtures. By the evaluation of different structures and mechanisms of action, certain flow and consolidation phenomena can be explained. Scanning electron microscopy (SEM) and light microscopy are easy and simple methods to evaluate these characteristics as outlined in section 2.3.1.2.

3.3.1 SCANNING ELECTRON MICROSCOPY (SEM)

The photomicrographs illustrate the differences in particle form and structure of the excipients used. Materials to be mixed more often exhibit wide variations in shape, size and surface characteristics. These variations undoubtedly exert a marked effect on flow and transport rate of mixed materials in the mixing chamber.

From figure 3.1a, magnesium stearate can be classified as type D according to the categories defined by Steffens & Koglin (1993:16) as was described in section 2.2.2.2. In a powder bed, the packing arrangement of fibrous material or irregularly shaped particles is quite different from that of spherical particles. In the former, bridging and mechanical interlocking between individual particles greatly reduces free running characteristics. Therefore, the addition of such materials in mixtures, slows their mixing process, and poor dispersion often results. On the other hand, due to their mobility, flat and slippery particles (magnesium stearate) may tend to segregate when included in a mixture. Pruv® (figure 3.1b) seems to be more spherical compared to magnesium stearate. This may lead to less friction between carrier molecules and lubricant during mixing which suggest a better glidant effect for Pruv®.

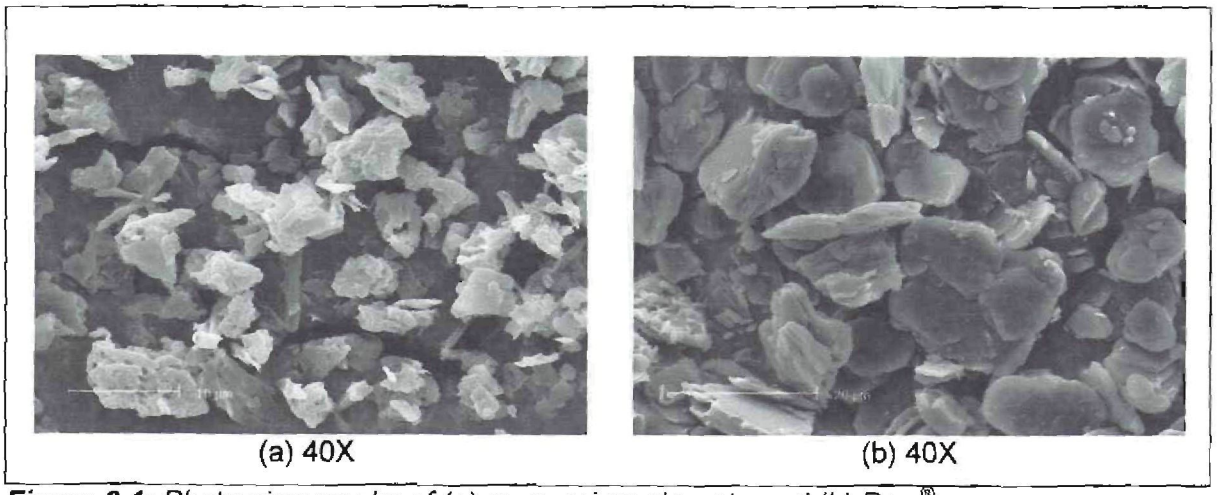


Figure 3.1: *Photomicrographs of (a) magnesium stearate and (b) Pruv®.*

Figure 3.2 shows the SEMs of the fillers/binders used in the flow characterization experiments with no added lubricants. From these photomicrographs it can be seen that Avicel® (figure 3.2 a & b) has the most evenly shaped particles which explains its better flow properties. Emcompress® (figure 3.2 c & d) particles showed surface indentations, which might result in poor flow. Although Tablettose® (figure 3.2 e & f) had the biggest particle size, its unevenly shaped particles might give rise to poor flow.

Another important aspect of the difference in particle shape and size of the various fillers, is its effect on consolidation. Knowledge of the consolidation mechanism of a filler/binder is important to understand the suitability and limitations of the excipient for specific tableting functions. Although tableting theory is not fully developed, it is believed that ductile behaviour of a powder system is an important characteristic for success in tableting. Ductile behaviour, as observed with Avicel® and Tablettose® particles, establishes regions of permanent interparticulate contact and bonding that produce mechanical strength in the resultant tablet (Katikaneni *et al.*, 1995:13).

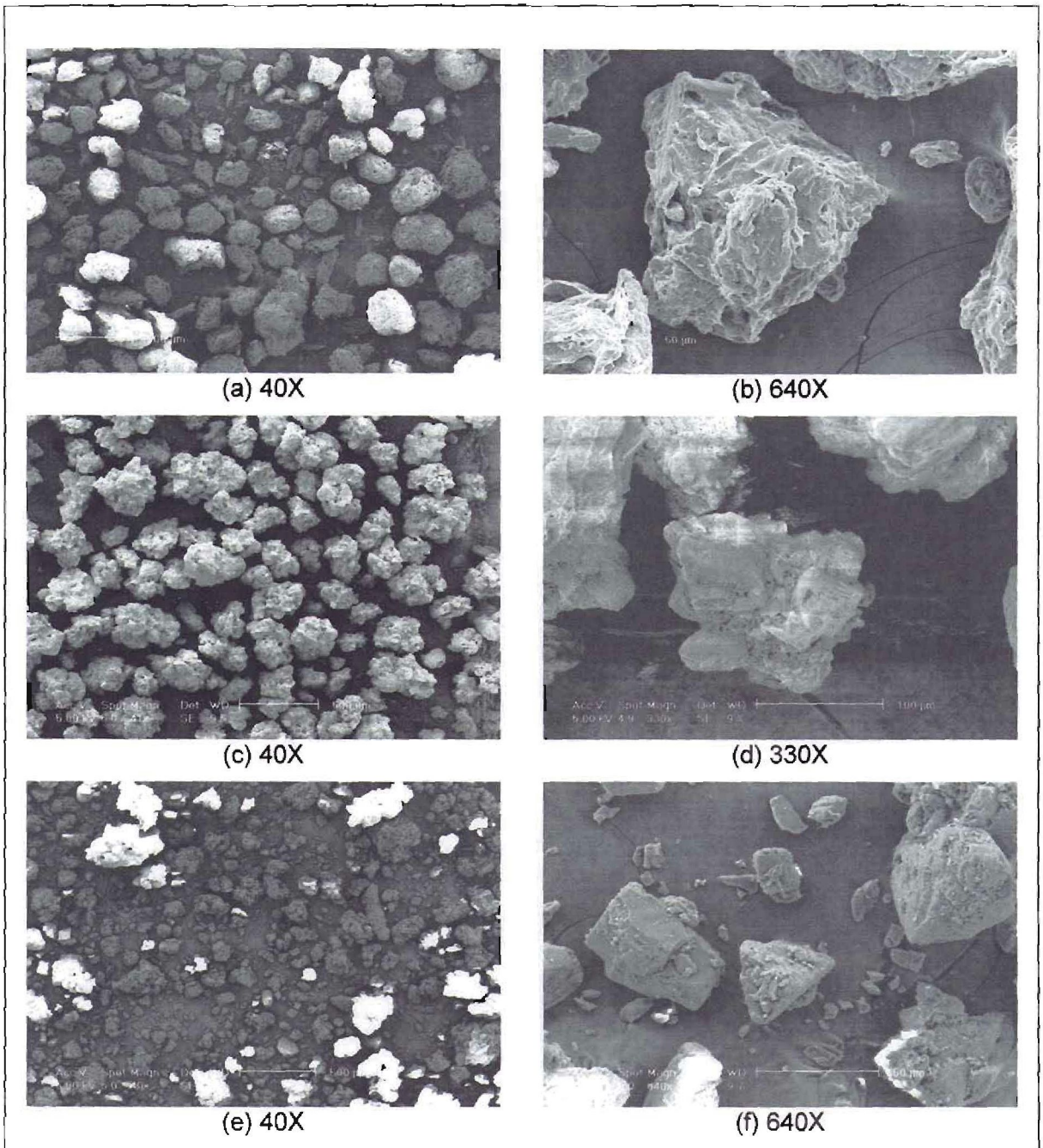


Figure 3.2: *Photomicrographs of Avicel® PH-200 (a and b), Emcompress® (c and d) and Tablettose® (e and f) at different magnification.*

Particle shape and roughness could also influence the true contact area between solid particles and forces of adhesion. Surface properties of particles play an important role during mixing, with lubricants, since the lubricant usually fills the gaps on the carrier particle surfaces and might even scratch off rough edges with proper mixing. This could lead to

more evenly, spherical shaped particles, which in turn may result in better flow. SEM of mixtures of the fillers with the lubricants are shown in figure 3.3.

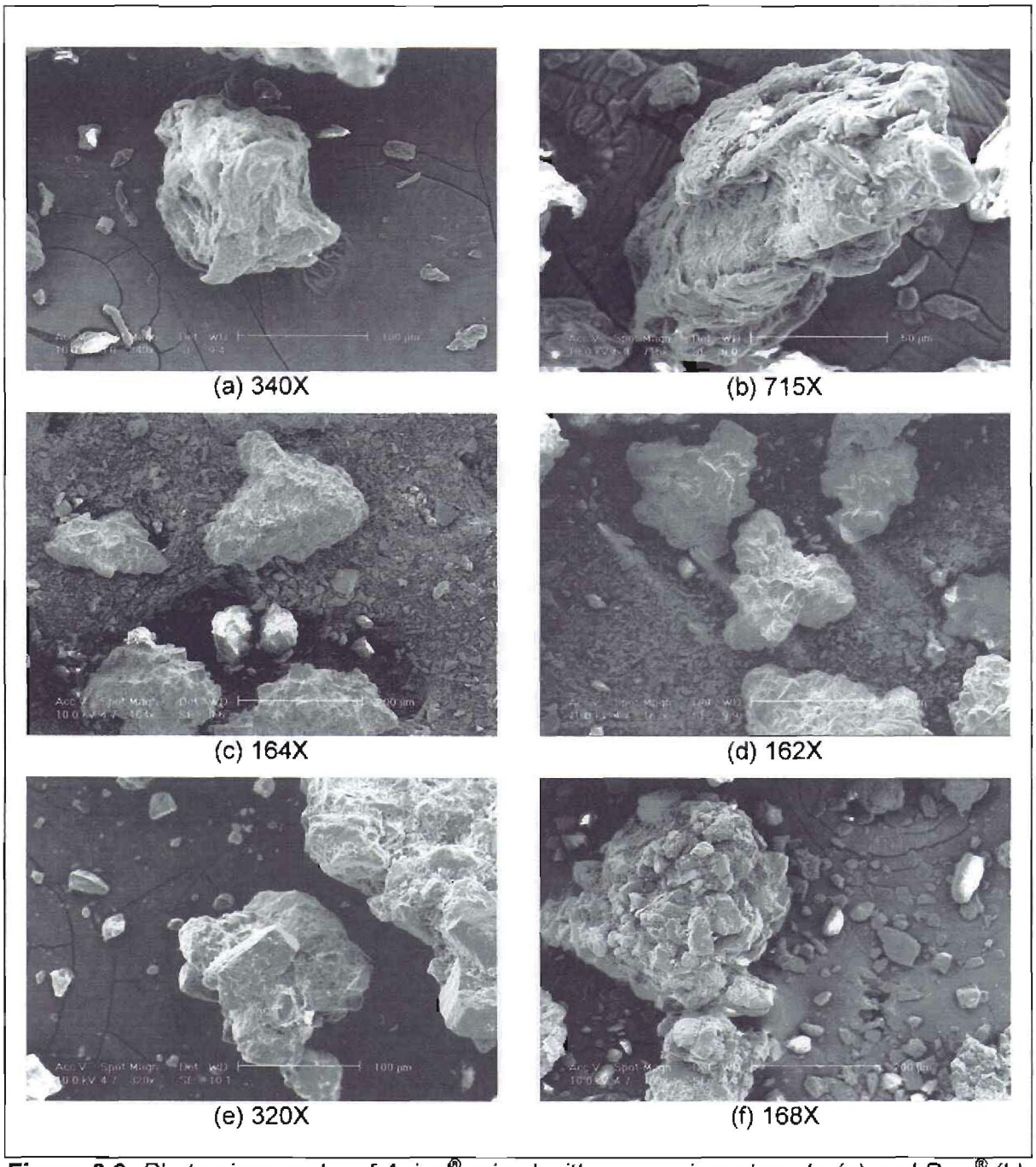


Figure 3.3: *Photomicrographs of Avicel® mixed with magnesium stearate (a) and Pruv® (b), Emcompress® mixed with magnesium stearate (c) and Pruv® (d) and Tablettose® mixed with magnesium stearate (e) and Pruv® (f). All mixtures contained 2% w/w lubricant, mixed 8 minutes at 97 rpm.*

Comparison of the photomicrographs in figure 3.2 and 3.3 exhibit the smoother surfaces of the fillers/binders containing the lubricants (figure 3.2). From figures 3.3(c) and 3.3(d) it is

obvious that lubrication had a more profound effect on the Emcompress® particles, due to the brittle nature of the particles. This is due to indentation filling or surface scraping on the carrier particles. The flatter particle shape of magnesium stearate also tend to lay disks of lubricant particles over the carrier particle instead of filling gaps as exhibited by Pruv®. This characteristic, along with the bigger specific surface area of magnesium stearate, suggest that magnesium stearate will cover the carrier particles more efficiently. This may lead to lower optimum lubrication concentrations and more mixing sensitivity than Pruv® might have. Although not seen in the photomicrographs (figure 3.3), filler/binder would be more sensitive to magnesium stearate than to Pruv®. The larger particles of magnesium stearate suggest that carrier particle surfaces will be covered to a larger extent as mixing prolonged.

Lubricants in tablet formulations may decrease tablet strength. The mechanism of such decrease is thought to be due to the finer lubricant particles coating the larger excipient particles and interrupting interparticulate bonding. Fragmentation of brittle particles (Emcompress® particles) results in large areas of new unexposed surfaces reducing the detrimental effect of a lubricant on tablet strength. Ductile deformation (Avicel® and Tablettose® particles) does not produce the same extent of new particle surfaces and the tablet strength of ductile materials is typically more sensitive to lubricants.

3.3.2 MICROSCOPIC ANALYSIS

Due to the inadequacy of SEM to distinguish clearly between different particles, another method had to be found to observe this effect. The need to distinguish between lubricant and carrier particles was necessary to observe effective lubricant coverage of carrier surfaces. A light microscope was ideal for this, since it could distinguish between colours. After colouration of the lubricants, as described in section 2.3.1.2.2, the lubricant were mixed and viewed under the light microscope.

Figures 3.4 – 3.6 indicate the difference between powder mixtures of coloured lubricant (purple spots) added in low (0.5% w/w) and high (2% w/w) concentrations and that of Avicel® (figure 3.4), Emcompress® (figure 3.5) and Tablettose® (figure 3.6). Only the two extreme mixing conditions (4 minutes at 69 rpm and 8 minutes at 97 rpm) were photographed, since the mixing conditions between these two extremes revealed little optical variance. For all filler/lubricant combinations an increase in particle coverage was observed with an increase in both lubricant concentration and mixing time. This confirmed that both lubricants are boundary lubricants, which acted on the surface of the carrier particles as indicated by Roblot-Treupel and Puisieux (1986:131). It is evident from figure 3.4 (a & b) that magnesium stearate covers carrier particles better than Pruv® (figure 3.4 c & d) at the same

concentration and mixing conditions. This is due to its bigger surface area and platelike particle shape.

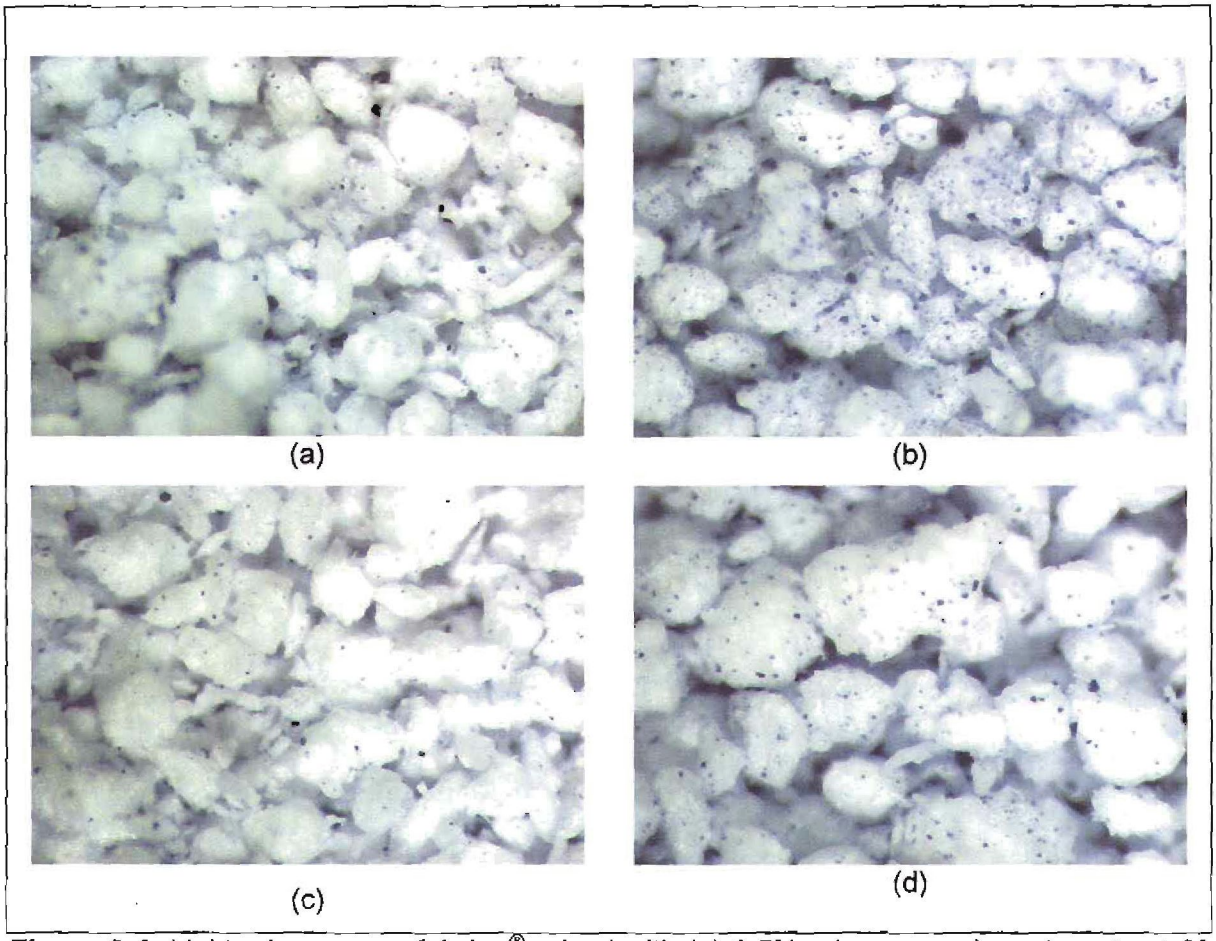


Figure 3.4: *Light microscopy of Avicel® mixed with (a) 0.5% w/w magnesium stearate at 69 rpm for 4 minutes, (b) 2% w/w magnesium stearate at 69 rpm for 8 minutes, (c) 0.5% w/w Pruv® at 69 rpm for 4 minutes and (c) 2% w/w Pruv® at 69 rpm for 8 minutes.*

It was interesting to note the high amount of lubricant on the Emcompress® particles (figure 3.5), since these particles had more surface area for lubricant coverage. It is thus expected that less lubricant would adhere to these particles. But, due to indentation filling or surface scraping on the Emcompress® carrier particles, smoother particles were observed with less lubricant between particles than for Avicel® or Tablettose®.

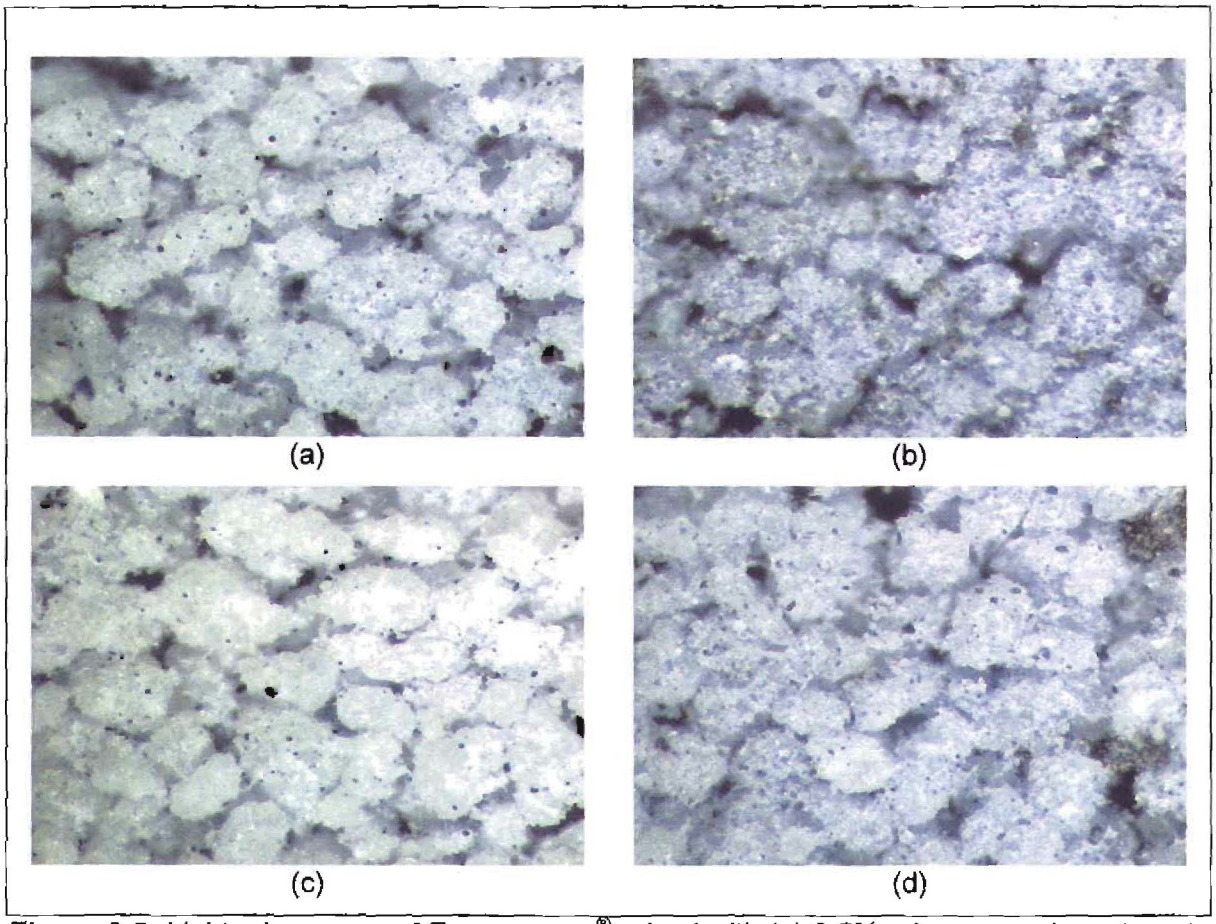


Figure 3.5: *Light microscopy of Emcompress® mixed with (a) 0.5% w/w magnesium stearate at 69 rpm for 4 minutes, (b) 2% w/w magnesium stearate at 69 rpm for 8 minutes, (c) 0.5% w/w Pruv® at 69 rpm for 4 minutes and (d) 2% w/w Pruv® at 69 rpm for 8 minutes.*

Tablettose® (figure 3.6) had the least amount on lubricant on its surfaces, suggesting that more lubricant had to be between the carrier particles. This poor adhesion of lubricant to the carrier particles could be attributed to less electrostatic adhesion forces between the carrier and lubricant particles. Due to the high amount and poor flow of these lubricants between the Tablettose® particles, poor flow is suggested for the mixture as well. Capping might also be a big problem during compression, since there are too many lubricant between particles. From figure 3.6 (d) the poor lubrication coverage effect of Pruv® is visible, suggesting poorer performance than magnesium stearate will have as lubricant during compression.

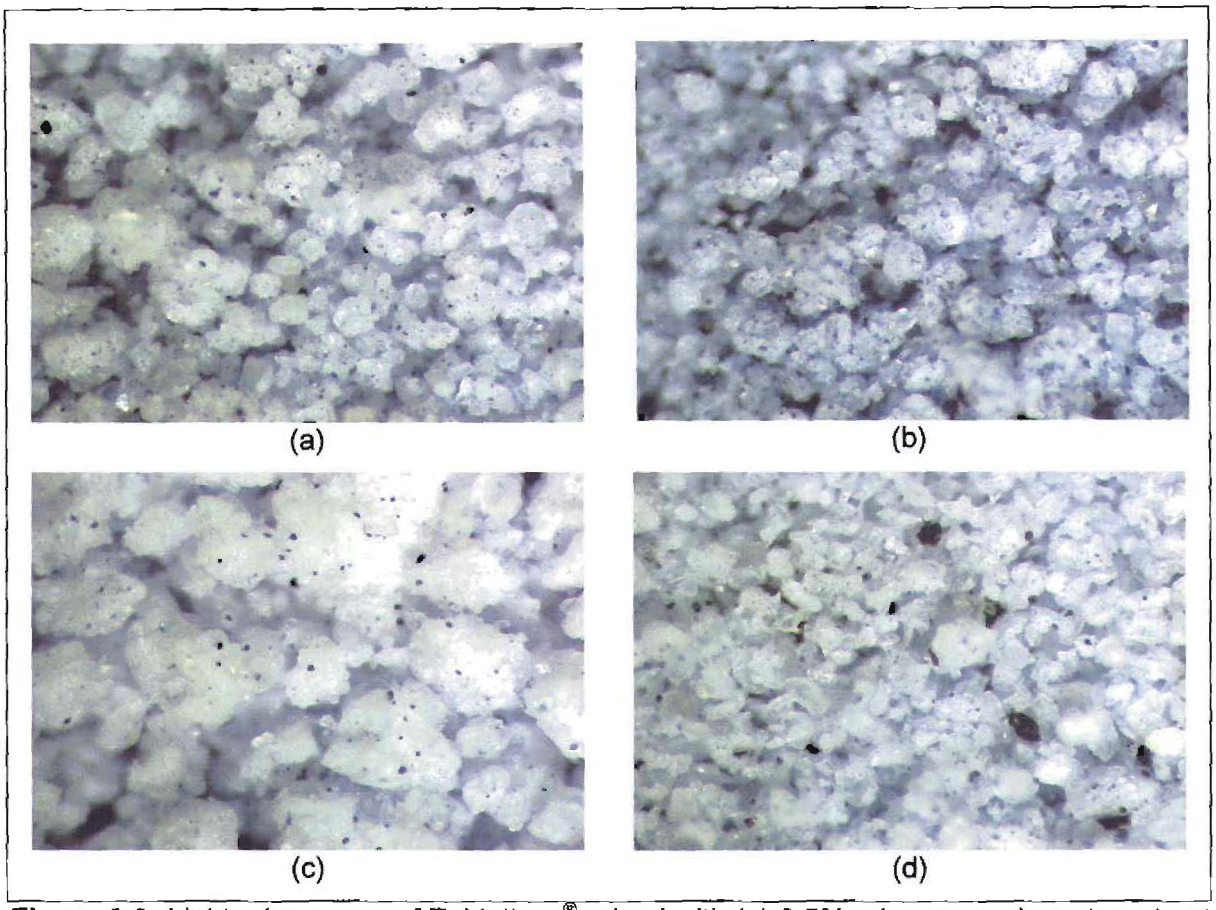


Figure 3.6: *Light microscopy of Tablettose® mixed with (a) 0.5% w/w magnesium stearate at 69 rpm for 4 minutes, (b) 2% w/w magnesium stearate at 69 rpm for 8 minutes, (c) 0.5% w/w Pruv® at 69 rpm for 4 minutes and (d) 2% w/w Pruv® at 69 rpm for 8 minutes.*

The mechanism of action by which lubricants work during the tableting process can be observed in figure 3.7. The purple coloured lubricants were mixed with fillers/binders and compressed as described in section 2.3.1.2.2. From the figure it is clear that both lubricants acted on the surface of the tablet, between the tablet surface and the die wall. The darker purple marks on the topside of the vertical surfaces indicate a higher amount of lubricant which shows that the concentration decreased downwards as the tablet was ejected. Thus the conclusion that the lubricant's mechanism of action is during the ejection phase of the tableting process.

Figure 3.7: *Light microscopy of tablet compressed with (a) Avicel® mixed with 2% w/w magnesium stearate at 69 rpm for 8 minutes and (b) Tablettose® mixed with 2% w/w Pruv® at 69 rpm for 8 minutes.*

3.4 FLOW PROPERTIES

The formulation of a solid dosage form often requires precise processing control of the mixture to ensure a volumetric delivery of a homogeneous aliquot. Thus, various adjuvants are gravimetrically added to form the bulk mix to achieve uniform mixing and flow of the powders as in tablet die filling. Lubricancy in solid particles improves the fluidity and packing characteristics of a blended mix and permits a homogeneous mix to be transferred compositionally intact to a target volume such as a compressing die. Agents that reduce such interparticulate friction also alter the particle packing characteristics by modifying the particle size and shape factors and have been termed glidants.

Most lubricants used in direct compression, also possess glidant properties beside lubricant and antiadherent actions. This is due to a reduction or alteration of electrostatic interactions and filling of the unevenness of particle surfaces (Bolhuis *et al.*, 1975:324). Flow properties of powders can be evaluated through the determination of the angle of repose, flow rate of the powder through an orifice and to a lesser extend, the weight variation of compressed tablets. An increase in crystal shape or more uniform particle surface characteristics (i.e. surface roughness) will lead to a smaller angle of repose indicating better flow of the powder. The flow properties Avicel®, Tablettose® and Emcompress® mixed with different aliquots of magnesium stearate or Pruv® were determined as described in section 2.3.1.3 Table 3.2 summarises the results obtained for these experiments and annexure A.2 provides the data obtained for each determination. The weight variation of different filler-lubricant compacts was obtained from annexure B.

Table 3.2: *Flow properties of fillers mixed for 4 or 8 minutes with different concentrations of magnesium stearate or Pruv®.*

Lubricant	Mixing time (min)	% w/w Lubricant	Avicel® PH-200				Emcompress®				Tablettose®			
			α (°)[a]	Flow rate ($g.s^{-1}$)	I_v (%)[b]	Tablet weight variation (% RSD)	α (°)[a]	Flow rate ($g.s^{-1}$)	I_v (%)[b]	Tablet weight variation (% RSD)	α (°)[a]	Flow rate ($g.s^{-1}$)	I_v (%)[b]	Tablet weight variation (% RSD)
		0.0	28.863	3.283	64.572	n/d	33.398	2.076	43.600	n/d	34.236	2.808	64.578	n/d
Magnesium stearate	4	0.5	28.840	3.900	98.806	1.514	32.179	2.149	42.270	0.411	27.867	4.545	93.938	0.820
		1.0	33.429	3.738	97.181	1.523	35.754	1.907	41.325	0.315	30.174	4.051	91.825	1.066
		1.5	33.558	3.603	96.083	0.310	36.497	1.900	41.174	0.288	30.865	4.047	91.741	0.609
		2.0	34.732	3.468	92.489	0.919	37.992	1.797	40.723	0.260	32.658	3.409	82.950	0.798
	8	0.5	30.413	4.736	93.145	2.332	33.394	2.061	44.651	0.213	29.572	4.408	95.514	0.383
		1.0	32.225	4.293	91.574	0.927	35.142	2.079	42.962	0.272	30.865	3.984	87.641	0.969
		1.5	33.193	3.313	90.562	0.772	38.739	1.781	42.747	0.245	31.759	3.571	84.520	1.042
		2.0	36.248	2.863	89.712	1.074	40.433	1.765	38.244	0.213	33.434	3.473	83.361	0.647
Pruv®	4	0.5	24.961	3.799	60.784	0.461	35.377	2.114	40.167	0.218	n/d	n/d	n/d	0.358
		1.0	28.923	3.475	57.921	0.449	35.700	1.900	38.341	0.188	n/d	n/d	n/d	0.631
		1.5	39.958	3.061	57.146	0.613	38.234	1.879	37.914	0.308	n/d	n/d	n/d	0.746
		2.0	43.919	1.135	22.331	0.437	39.497	1.753	36.029	0.404	n/d	n/d	n/d	0.454
	8	0.5	26.972	4.914	42.585	0.278	37.442	1.899	39.738	0.219	n/d	n/d	n/d	1.803
		1.0	27.783	3.791	35.385	0.420	38.172	1.651	31.469	0.285	n/d	n/d	n/d	0.441
		1.5	33.060	2.271	34.826	0.413	38.496	1.413	29.563	0.244	n/d	n/d	n/d	0.628
		2.0	43.912	1.612	32.232	0.329	40.956	1.211	24.892	0.194	n/d	n/d	n/d	1.165

[a] *Φ is the calculated angle of repose;* [b] *I_v is the static flow index; n/d – no date could be obtained*

Comparison of the flow properties of the unlubricated fillers, indicated superior free-flowing characteristics for Avicel®, compared to the other two fillers as indicated by the smaller angle of repose (28.8°) and higher flow rate (3.3 $g.s^{-1}$). Although Tablettose® exhibited the largest angle of repose (34.2°), its flow rate (2.8 $g.s^{-1}$) was higher than that of Emcompress® (2.1 $g.s^{-1}$). These results suggested that the use of the angle of repose alone as indicator of powder flow might not be appropriate to evaluate the flow properties of powders. This observation will be examined and discussed more extensively later.

The better flow of Avicel® could be attributed to less interparticulate friction due to the spherical nature of the Avicel® particles (figure 3.2 b) compared to the rough and unevenly shaped particles of Tablettose® (figure 3.2 f) and Emcompress® (figure 3.2 d), thus implying that particle shape was more influential on powder flow than the size of the particles. The poor flow of Emcompress® could also be related to its smaller average particle size (204 µm) and higher percentage of small particles present in the powder bed (13% particles below 25 µm).

These results correlated with the findings of Staniforth (2000:604), who suggested that the larger the particle size (only to some extent where large size results in poor flow due to particle shape) and more uniform particle shape, the better the fluidity of the excipient. However, it is contradictory to the findings of Podczeck and Miah (1996:187) who found that for unlubricated powders the angle of internal friction was found to depend both on particle size and shape in a nonlinear manner, whereas the flow factor depends only on particle shape. While the flow factor depends only on particle shape, the corresponding optimal lubricant concentration was found to depend only on the particle size. This theory was congruent with the results obtained in the SEM and particle size analysis.

The addition of a lubricant had varying effects on the flow properties of the three fillers, and both the type and concentration of the lubricant and the mixing time played a role. In the case of Avicel® the initial addition of lubricant (0.5% w/w) and mixing for 4 minutes had little effect on the angle of repose (figure 3.8), but slightly increased (19%) the flow rate (figure 3.9) in the presence of magnesium stearate, whilst Pruv® reduced the angle of repose (by 15%), but also slightly increased the flow rate (19%). After 8 minutes, however, the angle of repose increased slightly (5%) in the presence of magnesium stearate (suggesting poorer flow), but the flow rate increased significantly (45%). For Pruv, the same tendency was observed, with a slight increase in the angle of repose (compared to 4 minutes), but a 50% increase in flow rate.

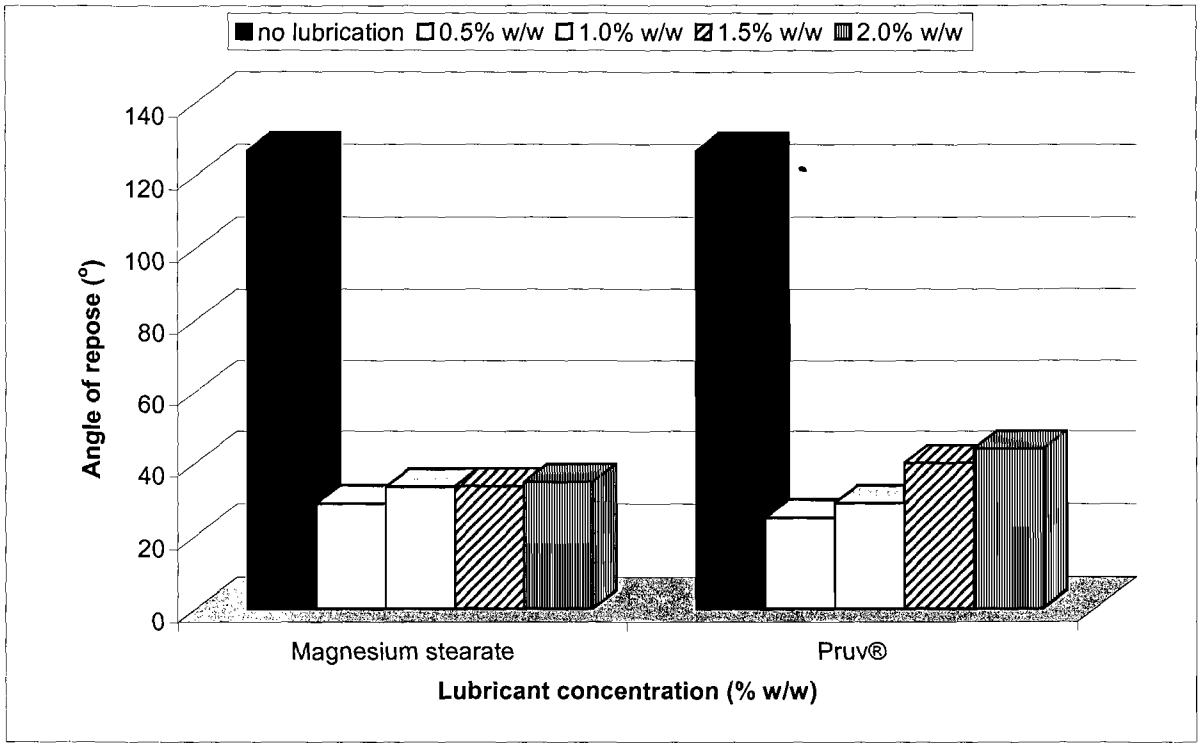


Figure 3.8. *The influence of lubricants on the angle of repose (α) of different fillers/binders.*

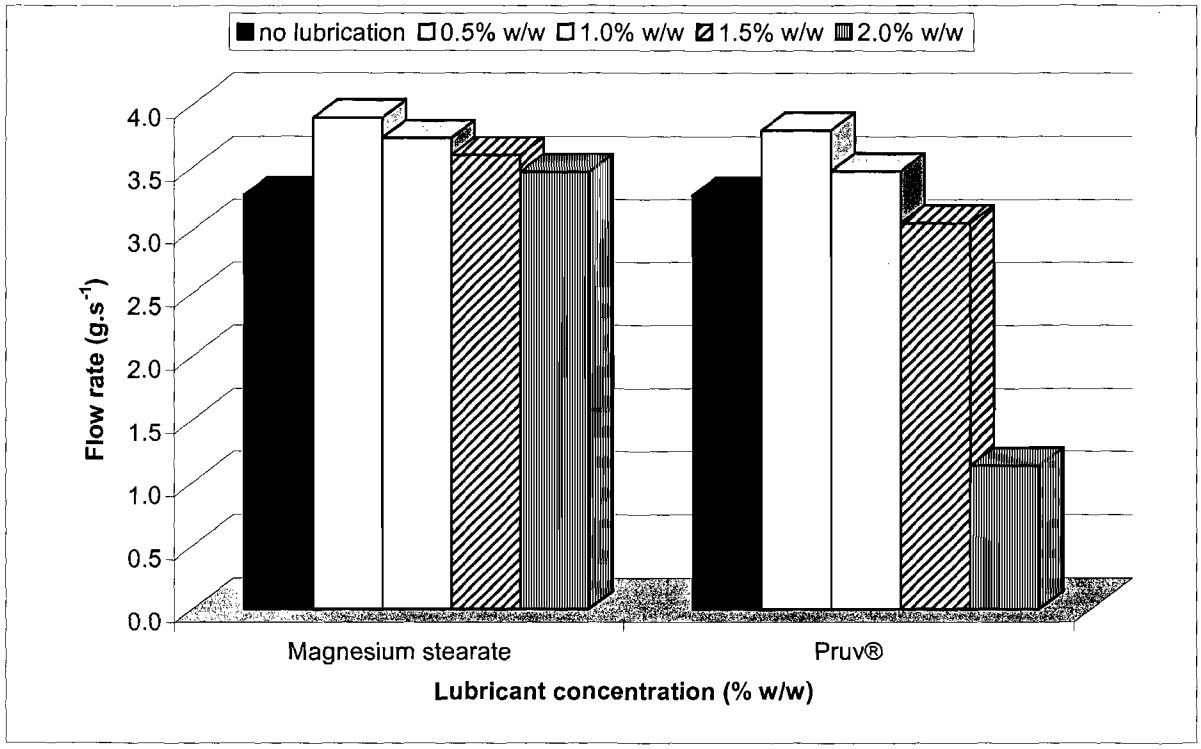


Figure 3.9: *The influence of lubricants on the flow rate of different fillers/binders.*

These results, once again, suggested contradictory results from the two flow parameters. Whilst the angle of repose indicated a negative effect of the lubricants on the powder flow, the flow rate clearly demonstrated the opposite. At higher concentrations of both lubricants, however, the angle of repose increased and the flow rate declined, with Pruv® being more detrimental to flow compared to magnesium stearate. Also, for both lubricants, longer mixing times (8 minutes) aggravated the negative effect of the lubricants on flow.

In the case of Emcompress®, the addition of 0.5% w/w magnesium stearate had no significant effect on either the angle of repose or on the flow rate (at 4 and 8 minutes), whilst Pruv® reduced flow (observed in an increase in the angle of repose and a reduction in the flow rate). With an increase in the lubricant concentration the flow further deteriorated, with Pruv® having a more pronounced effect than magnesium stearate. For both lubricants, 8 minutes mixing time resulted in poorer flow than at 4 minutes.

The difference in lubricant effect was best demonstrated from the results obtained for Tablettose®. Magnesium stearate reduced the angle of repose by 19% (at 4 minutes) and increased the flow rate by 62%. Although an increase in the concentration of magnesium stearate reduced flow, it never declined to the level of the unlubricated filler. Once again, optimum flow was obtained at 0.5% w/w magnesium stearate and mixtures prepared at 4 minutes surpassed those prepared at 8 minutes. The poor glidant and antiadherent properties of Pruv® were demonstrated clearly, since no data could be generated with Tablettose®. During determination of the flow rate of Tablettose®, the filler generated static forces in the Perspex tube, resulting in poor flow. However, magnesium stearate was able to overcome these negative forces and still impart acceptable flow, whilst Pruv® was unable to do so. This difference in lubricant properties had to be attributed to the hydrophobic or hydrophilic nature of each, since hydrophilic powder would be more prone in generating and conducting electrostatic forces.

Although some correlation existed between the angle of repose and the flow rate, quite a number of instances occurred where these parameters suggested opposite effects, i.e. the angle of repose decreased suggesting better flow, whilst the flow rate indicated poorer flow, and *vice versa*. These observations, once again, raise the question of the suitability of the angle of repose as a single indicator of powder flow. Both these parameters did not represent the actual flow observed for the mixtures in magnitude or value. There was also no direct correlation between the uniformity of flow and an increase in lubricant concentration. Longer mixing times also had no effect on the uniformity of flow. Another parameter, the static flow index (I_v), was a better indication of flow and represented the

observed flow characteristics to the same extent as it happened. I_v values were calculated using equation 2.1 as described in section 2.3.1.3.2.

Very high I_v values were obtained for free-flowing fillers without lubrication and Avicel® and Tablettose® (approximately 65% for both) revealed superior flow compared to Emcompress® (44%) as was experienced during experiments and as was expected from the difference in particle shape. The static flow index increased with the addition of magnesium stearate (0.5% w/w) as a result of the improved glidant effect (figure 3.10). Although higher concentrations decreased the I_v value, it was still larger than for formulation without lubrication and slight differences (< 10%) occurred between various concentrations and mixing ranges. According to Sadek *et al.* (1982:43), the optimum concentration for flowability is generally less than 1% and is typically 0.25 - 0.5% w/w. This optimum concentration may be related to the amount needed to coat the host particles and was reached at 0.5% w/w for all three fillers. Exceeding this concentration had resulted in either no further improvement in flow and, even worsening of flow as cohesive forces strengthen between lubricant particles. This was, however, not the case for Emcompress® as a result of surface indentations and the addition of lubricant (at any concentration and mixing level) gave rise to poorer flow.

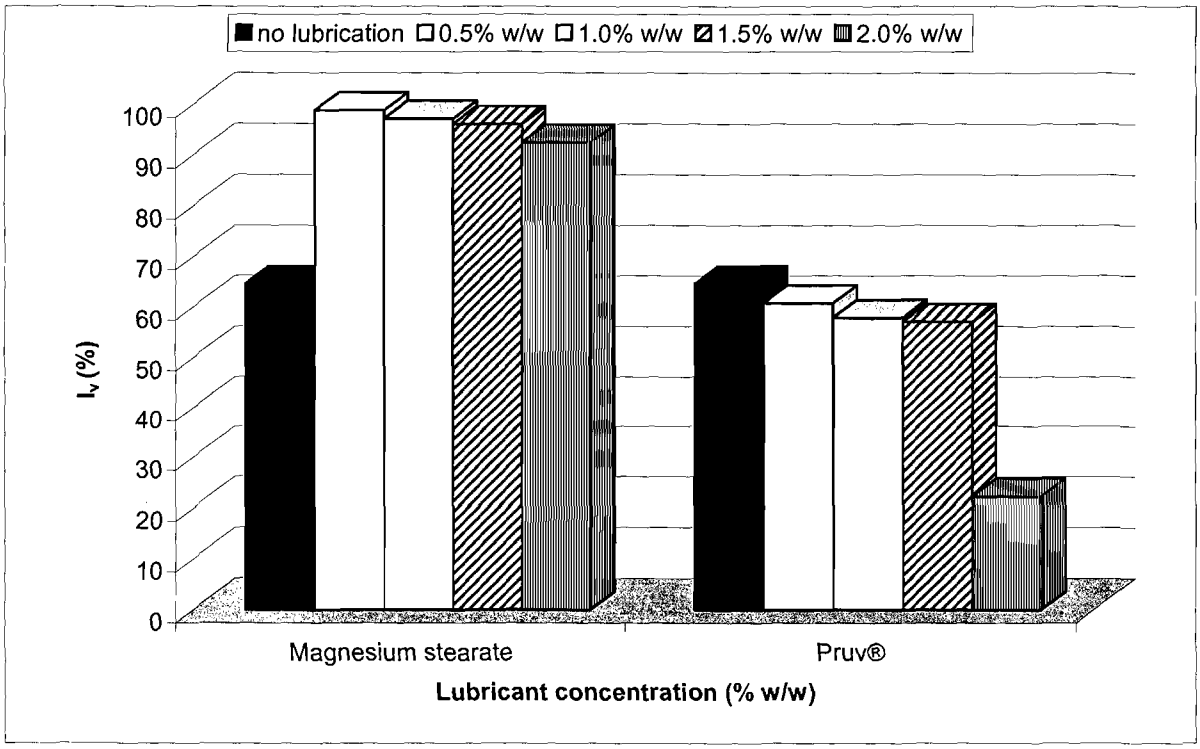


Figure 3.10: *The influence of lubricants on the static flow index (I_v) of different fillers/binders.*

Pruv® had no glidant effect of fillers and no initial increase in I_v values was observed. The decrease with the addition of lubricant was a result of Van der Waals forces or cohesive forces, which affected the flow due to the increase of adhesion forces between carrier particles (Gold *et al.*, 1968:670) with Pruv® generating the strongest forces and decreased I_v values by nearly 100% when very a high concentration of Pruv® (2.0% w/w) was added at prolonged mixing times (8 minutes). This effect was clearly illustrated with Tablettose® since no data were generated to obtain I_v values as a result of no or very poor flow. Mixing gave rise to bigger surface of separation and thus reduced the glidant effect of lubricants.

According to Velasco *et al.* (1995:2390) the flow rate of powder mixtures decreased with an increase in the angle of repose. The static flow index also decreased with an increase in the angle of repose, which indicated a decrease in flow and an increase in cohesive forces between lubricant particles. Poor flow was experienced with all of the Avicel®/Pruv® combinations, which gave I_v values of lower than 61%. From this evidence it can be concluded that the I_v index is a better indication to measure flow than the angle of repose.

The problem of weight uniformity in tablets is attributed mainly to irregular filling and the failure to attain random mixing of the powder. Data obtained from tablet compression studies indicated that the uniformity of weight was positively affected by the addition of lubricants. These opposing results suggested better flow for Emcompress® compared to Avicel® or Tablettose® and was probably a result of the presence of a larger percentage of small particles (or agglomerates) in Emcompress®, which effectively filled the voids between larger particles, thereby creating a more even compact weight with less variation. As lubricant was added to Emcompress® it followed the same tendency toward poorer flow as was observed with the other two fillers.

3.5 CONCLUSION

Knowledge of the characteristics of a tablet filler/binder is important to understand the suitability and limitations of the excipient for specific tableting functions. It can be concluded that particle size, and in particular particle shape, influence the friction and flow properties of powder. The particle shape of the fillers/binders used had the most pronounced effect on flow, since these carrier particles were larger in size and volume. Larger and more evenly shaped (spherical) particles gave better flow properties. As the lubricant concentration increased, an optimal concentration for flow was observed for both magnesium stearate and Pruv® at 0.5% w/w concentrations. This optimum was observed when the surface area of the filler/binder was covered with lubricant. Above this optimum concentration the cohesive forces between the lubricant increased to the extent of no improved flow or even a decrease

in flow. For compacts the optimum concentration was observed when friction between the tablet and die wall decreased to ease ejection. Mixing time aggrevated the effect the lubricant had on the filler/binder properties and 4 minutes seemed to be an effective mixing time.

An increase in lubricant concentration and mixing time gave rise to an increase in angle of repose, decrease in flow rate, decrease in static flow index (I_v) and decrease in the weight variation of compacts. The static flow index (I_v) gave the most realistic presentation of flow properties, indicating that as the lubricant concentration increased, cohesive forces between lubricant particles became more apparent.

Magnesium stearate was a more effective glidant at all concentration levels than Pruv®, for all the fillers/binders used. This could be attributed to the larger specific surface area and flatter shape of magnesium stearate particles which was more effective in covering surface area of carrier particles with lubricant. Pruv®, however, was more sensitive to mixing time. It should be stressed, however, that smaller lubricant interval ranges might actually be more precise for establishing the optimum concentration, since most lubricants' optimum glidant effect is in the region of 0.2 - 0.5% w/w. Mixing effectiveness also need a smaller index (between 4-8 minutes for this study) to establish optimum conditions. Although the glidant characteristics of lubricants is important, their main purpose is for lubrication and thus it would be inappropriate to establish optimum concentration ranges at this point, based only on flow efficiency.

Larger carrier particles were also more sensitive to an increase in mixing time due to an increase in shear forces in the mixer, resulting in a faster rate of film formation and larger surface of separation. This was true for the fillers/binders used, since Tablettose® was most sensitive to lubrication, followed by Avicel®. Emcompress® were not sensitive to any lubrication, due to the indentations on its surface and smaller particle size.

The evaluation of Avicel®, Emcompress® and Tablettose® fillers/binders revealed their suitability for direct compression based on their acceptable flowability (pending the amout and type of lubrication system under certain mixing conditions), measured for different powder samples. This property reflected in the weight variation of tablets that could not be produced without appropriate lubrication. The characterization of the powder material and tablets provides the stepping stone from which modification of the undesirable properties of the filler can now commence. A systematic evaluation of excipients is conducted to evaluate their effects on the filler as well as on each other to ultimately identify optimized drug-carrier systems.

CHAPTER 4

Effect of lubricants and mixing variables on the physical properties of tablets composed of different fillers/binders

4.1 INTRODUCTION

In tablet formulation, a lubricant usually permits resolution of several production problems related to compression. As an essential unit operation in the production of a compressed tablet, lubrication facilitates glidancy of the powders during material flow, eliminates binding of the compact to the die, and minimizes sticking to and picking onto the punch surfaces in contact with the compressed tablet. But these properties come at a price, since lubricants also have a negative impact on disintegration times and tablet hardness and overlubrication may affect both properties negatively. A change in mixing properties may also influence the effect the lubricant has on the overall performance of formulations. However, the duration and intensity of mixing not only affect the properties of the compact but also the properties of the blended mixture by altering the apparent bulk volume, the compression force required to make a prescribed compact, and the hydrophobic nature of the mixture. A tablet formulator may be faced with competing objectives. It is important to establish an optimum concentration and mixing condition where these advantages overstay the disadvantages from a practical outlook. Properties of the compact critical to its performance include the ejection force, tablet hardness, disintegration, and dissolution. It is generally recognized that a lubricant modifies these properties. The extent to which the lubricant modifies these properties is a function of type and concentration of the lubricant, other excipients present in formulation and mixing variables.

4.2 THE EFFECT OF LUBRICATION AND MIXING ON TABLET HARDNESS

Mixtures containing Avicel®, Tablettose® or Emcompress® as fillers and magnesium stearate or Pruv® as lubricants (0 – 2.5% w/w) were prepared in a Turbula® mixer at various mixing times (1-16 minutes) at different mixing speeds (33, 69 and 97 rpm) as described in section 2.4.1.1, and tablets were produced on a Manesty® F3 single punch tablet press described in section 2.4.1.2. Tablet properties, namely hardness, thickness, diameter and friability were determined as described in section 2.4.1.3. Selected data points for magnesium stearate and Pruv® are tabulated for hardness (table 4.1) and friability (table 4.2). Annexure B contains the data for tablet diameter and thickness.

Table 4.1: *Crushing strength (N) of tablets from different fillers/binders mixed with different lubricants at various concentrations and mixing conditions. Values for unlubricated tablets are indicated in parentheses.*

Lubricant	Mixing speed (rpm)	Mixing time (min)	**Avicel®** (218.040)				**Emcompress®** (n/d)				**Tablettose®** (n/d)			
			0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Magnesium stearate	33	2	128.920	113.090	93.480	83.150	106.610	107.350	103.960	103.830	99.030	88.430	87.280	80.170
		4	127.970	106.970	82.840	72.280	110.500	108.860	104.560	103.350	101.000	85.320	81.930	76.610
		8	121.960	86.030	69.210	64.270	117.320	107.590	103.710	103.820	85.530	85.530	75.600	74.930
	69	2	117.180	84.130	67.990	62.640	118.570	113.640	113.800	108.700	97.740	87.850	77.510	74.950
		4	100.320	76.280	64.710	58.400	115.960	110.330	111.470	108.600	104.660	95.490	91.170	68.400
		8	77.160	68.220	54.670	54.670	105.220	108.620	108.360	109.260	101.590	88.670	88.300	64.680
	97	2	82.410	60.810	49.230	47.720	126.090	113.740	111.840	109.100	87.600	80.810	79.070	66.610
		4	67.110	52.520	47.970	43.110	116.320	109.710	108.450	108.250	95.350	78.780	79.150	55.930
		8	56.500	48.460	44.050	40.620	105.460	107.880	103.660	109.860	89.090	81.020	79.030	n/d
Pruv®	33	2	140.350	120.860	117.973	108.070	123.160	119.490	114.730	112.120	n/d	100.690	98.300	93.090
		4	132.190	135.750	123.000	107.100	123.680	115.590	114.530	111.790	n/d	94.010	96.960	93.770
		8	132.350	137.910	124.410	122.730	123.110	121.180	115.600	109.100	n/d	83.600	84.870	82.070
	69	2	134.650	128.550	119.230	108.200	106.080	100.610	112.650	112.840	n/d	93.070	83.880	88.260
		4	153.720	134.890	122.170	109.240	112.400	107.590	105.220	106.480	113.140	116.700	107.050	89.650
		8	148.050	143.010	131.500	109.310	106.670	91.030	96.180	100.110	112.570	114.820	101.480	86.310
	97	2	135.740	125.320	111.550	100.720	105.760	109.710	100.440	99.990	n/d	87.450	87.370	88.360
		4	151.010	134.610	120.050	95.660	113.010	101.020	97.320	95.630	n/d	110.820	106.410	85.030
		8	164.580	139.010	118.250	107.090	106.030	92.550	91.850	92.260	n/d	104.180	99.330	78.000

n/d – no data available

Table 4.2: *Friability(%) of tablets from different fillers/binders mixed with different lubricants at various concentrations and mixing conditions. Values for unlubricated tablets are indicated in parentheses.*

Lubricant	Mixing speed (rpm)	Mixing time (min)	**Avicel®** (0.048)				**Emcompress®** (n/d)				**Tablettose®** (n/d)			
			0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Magnesium stearate	33	2	0.022	0.134	0.253	0.245	2.801	2.983	2.947	3.066	1.447	1.733	1.874	2.095
		4	0.028	0.149	0.275	0.294	2.639	2.891	2.991	2.997	1.507	1.759	1.907	1.985
		8	0.033	0.166	0.314	0.377	2.568	2.742	2.886	2.799	1.569	1.925	2.066	2.185
	69	2	0.066	0.242	0.389	0.557	2.560	2.903	2.192	2.779	1.430	1.815	1.911	2.055
		4	0.039	0.248	0.442	0.749	2.672	2.827	2.816	2.640	1.311	1.573	1.734	2.198
		8	0.056	0.274	0.539	0.709	2.904	2.753	2.817	2.720	1.409	1.723	1.775	2.638
	97	2	0.031	0.196	0.371	0.688	2.167	2.472	2.622	2.638	1.600	2.110	2.197	2.571
		4	0.087	0.317	0.498	0.539	2.469	2.581	2.687	2.579	1.594	1.913	3.628	6.962
		8	0.098	0.395	0.600	0.720	2.836	2.678	2.723	2.680	3.068	4.371	2.049	n/d
Pruv®	33	2	0.067	0.360	0.682	0.659	2.368	2.856	3.126	3.341	n/d	1.387	1.649	1.653
		4	0.072	0.432	0.740	0.793	2.469	2.861	3.073	3.325	n/d	1.495	1.579	1.618
		8	0.089	0.448	0.845	1.017	2.580	2.710	3.114	3.081	n/d	1.776	1.932	2.105
	69	2	0.177	0.652	1.049	1.499	2.901	3.581	3.009	3.141	n/d	1.638	1.892	1.976
		4	0.106	0.667	1.191	2.018	2.805	3.472	3.694	3.286	1.581	1.638	1.745	1.848
		8	0.150	0.738	1.452	1.910	3.033	3.683	3.427	3.689	1.526	1.551	1.760	2.078
	97	2	0.085	0.529	0.999	1.853	3.077	3.315	3.491	3.559	n/d	7.847	1.861	1.897
		4	0.235	0.854	1.341	1.453	2.856	3.418	3.766	3.631	n/d	1.504	1.726	2.032
		8	0.265	1.064	1.616	1.940	3.188	3.692	3.870	3.715	n/d	1.702	1.804	3.377

n/d – no data available

Comparison of the consolidation properties of the fillers, indicated superior hardness for Avicel® compacts, compared to the other two fillers as indicated by the higher crushing strength and lower friability. Although Avicel® exhibited the highest crushing strength (145.38N) and lowest friability (0.21%) for best performing lubricated formulas, the variation between lower and higher parameter limits was higher than that of Emcompress®, with Tablettose® performing the worst under the influence of lubrication and mixing. These results suggested that lubricants and mixing conditions had a more pronounced effect on Avicel® and specifically Tablettose®, than on Emcompress® compacts. Although crushing strength and friability indicated the hardness of tablets, comparison of tablets from different fillers had to be examined with tablet dimension as contributing factor. This observation will be examined and discussed more extensively later.

The addition of magnesium stearate had varying effects on the hardness of tablets from the three fillers, and both the type and concentration of the lubricant and the mixing time played a role. In the case of Avicel® the initial addition of lubricant (0.5% w/w) and mixing for 1 minute significantly decreased the crushing strength (35% compared to no lubrication), but decreased (57%) the friability in the presence of magnesium stearate, whilst Pruv® increased the friability (by 15%), but also slightly decreased the crushing strength (33%). After 2 minutes, however, the crushing strength decrease declined to a 10% decrease and thereafter narrowed to only 3% decrease (when mixing was prolonged from 8-16 minutes) in the presence of magnesium stearate (suggesting less decrease in crushing strength as mixing prolonged as a result of an increase in surface of separation), but the friability increased significantly (65%) as mixing time changed from the 1 to 16 minute interval. For Pruv®, the opposite was observed, with a slight increase (12%) in crushing strength (when mixing increased to 16 minutes), but a 65% increase in friability rate. This suggests that Pruv® particles did not absorb onto carrier particles to the same extent as its counterpart magnesium stearate, causing better interparticulate bonding as a result of less lubricant between carrier particles and bigger surface of separation. The excess lubricant on the tablet surface, however, had a negative impact on the friability.

At higher concentrations of magnesium stearate (2.5% w/w) there was a 33% increase in crushing strength when compared to the lower levels (0.5% w/w). This was especially true for formulas mixed at high mixing times and revolutions (8 - 16 minutes at 97 rpm). These phenomena could be explained according to the mechanisms of boundary lubricants put forward by Strickland *et al.* (1956:51). Higher concentrations of magnesium stearate decrease the amount of binding sites between carrier particles, thus decreasing hardness and increasing friability. This theory explains why tablets became harder upon continual

mixing at high energy levels, and due to the decrease in the weakening effect of magnesium stearate after the 2% w/w concentration, the larger surface of separation might even further decrease interparticulate bonding strength. This also explains why upon continual mixing, the change in friability decreased as more lubricant was distributed from the tablet surface towards the particle surfaces.

Pruv® decreased the hardness of the tablets (table 4.1) in a similar manner that magnesium stearate did. The same indirect relationship was observed for mixing. Mixing time and speed also had a negative influence on the hardness of tablets containing Pruv®, as a result of film formation around the filler/binder particles. Formulations containing Pruv® gave harder tablets as a result of poorer lubricant coverage on carrier particles. There was no relationship between crushing strength and friability (r^2 = 0.577) of tablets containing Pruv® as was experienced with magnesium stearate.

Again surface of separation had an effect on the crushing strength at high mixing conditions, the effect of which was not as profound as was observed with magnesium stearate. The increase in crushing strength at higher lubricant concentrations was also not observed for Pruv®, although there was a decrease in the % change in crushing strength towards higher lubricant levels.

Although Avicel® was the only filler/binder capable of compression in the absence of lubrication, Emcompress® was least effected by magnesium stearate lubrication due to fragmentation of brittle particles which resulted in large areas of new unexposed surfaces reducing the detrimental effect of a lubricant on tablet strength. Ductile deformation does not produce the same extent of new particle surfaces and the tablet strength of ductile materials (e.g. Avicel®) is typically more sensitive to lubricants (Katikaneni *et al.*, 1995:14). Emcompress® was also least effected by Pruv® lubrication, but Tablettose® showed high sensitivity towards Pruv® compared to magnesium stearate. At low concentrations of Pruv® (0.5% w/w) it was impossible to compress Tablettose® due to capping and poor lubrication as suggested by friction noise and heat energy inside the die. Thus the conclusion that magnesium stearate had superior lubrication properties compared to Pruv®. At higher lubricant levels lamination was observed indicating too much lubricant between carrier particles. This suggested that due to its particle shape, Pruv® covered carrier particles to a larger extent than magnesium stearate did.

The higher friability observed with tablets containing Pruv® was proof that less sensitivity toward mixing was experienced when compared to magnesium stearate. The higher amount of lubricant on tablet surface explained the higher friability, which suggested less lubricant on

carrier particle surfaces, leading to stronger interparticulate binding forces. This was observed in table 4.1 and 4.2 as tablets containing Pruv® gave overall harder tablets with more friability compared to magnesium stearate.

The need for a parameter detailing the tablet dimentions as a function of its hardness was previously mentioned, since tablet dimensions will influence the load at which the tablet fractures when subjected to diametral compression, and thus it has been established that tensile strength is a more accurate parameter than crushing strength in the evaluation of tablet strength. Tensile strength is furthermore a good parameter for comparison between different filler/binder systems since it takes into consideration the difference in tablet thickness due to density differences between carrier systems. The tensile strengths of the data obtained were calculated (equation 2.2) for formulations containing magnesium stearate and Pruv®. The hardness of tablets as a function of tablet tensile strength and friability was then expressed as a tensile strength friability index (TFI). High TFI values indicated high tensile strength and/or low friability parameters, which are both associated with harder tablets and low TFI values represented the opposite. TFI_{Avg} represents the average TFI values of a specified parameter range. Baseline values represent tablets with only filler/binder, without any lubricant present and no mixing.

The high TFI_{Avg} values obtained for Avicel® (figure 4.1) was due to the low friability these tablets showed compared to the other two fillers/binders. Tablets with magnesium stearate had higher TFI_{Avg} values due to the higher crushing strength and lower friability compared to the tablet containing Pruv®. When lubricant concentrations surpaseed the 1.0% w/w concentration range the TFI_{Avg} values, for all the fillers/binders used, decreased slightly, indicating that the optimum lubrication concentration was already reached at 0.5% w/w and that all the carrier particles were covered with lubricant. Pruv® decreased the hardness of the tablets in a similar manner magnesium stearate did and again the high TFI_{Avg} values obtained for Avicel® was due to the lower friability compared to the other two fillers/binders. The lower TFI_{Avg} values obtained for formulations containing Pruv® instead of its counterpart, served as evidence of poor surface coverage of Pruv®. When more than 1.0% w/w Pruv® was added the TFI_{Avg} values did not decrease that much further, which indicated that the optimum lubrication concentration was already reached at 0.5% w/w. There was an average reduction of 80% in TFI_{Avg} values when the 0.5% w/w lubricant level for both lubricants was exceeded. Magnesium stearate gave tablets with double the strength of those containing Pruv® when lubrication was kept at 0.5% w/w as a result of lower friability for formulations containing magnesium stearate, thereafter both gave more or less the same amount of decay in tablet hardness (TFI_{Avg}).

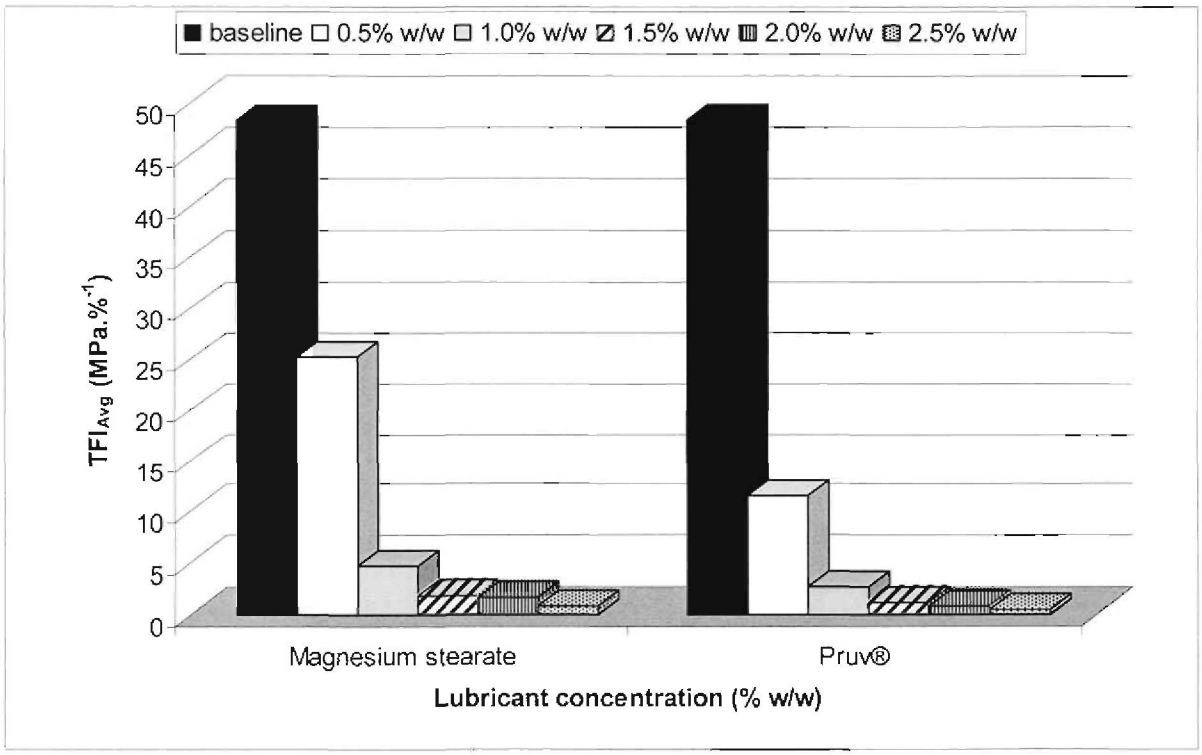


Figure 4.1: *Effect of different lubricant concentrations (magnesium stearate or Pruv®) on the hardness of Avicel® tablets.*

A significant decrease in TFI_{Avg} values (78-91%) was observed as mixing time prolonged (from 0 to 16 minutes) for magnesium stearate (figure 4.2). This decrease was experienced due to a decrease in crushing strength, indicating less lubricant on the tablet surface and more on particle surfaces. Mixing time had little effect (11%) on TFI_{Avg} values for Pruv® beneath the 8 minute mixing period. Thereafter a decrease in TFI_{Avg} (43%) was observed as a result of high friability values and a decrease in crushing strength, thus indicating less sensitivity for Pruv® towards mixing. At comparative lubricant concentrations, the TFI_{Avg} of the tablets with Pruv® was almost 60% lower compared to magnesium stearate tablets. This indicated less sensitivity for Pruv® towards mixing than magnesium stearate.

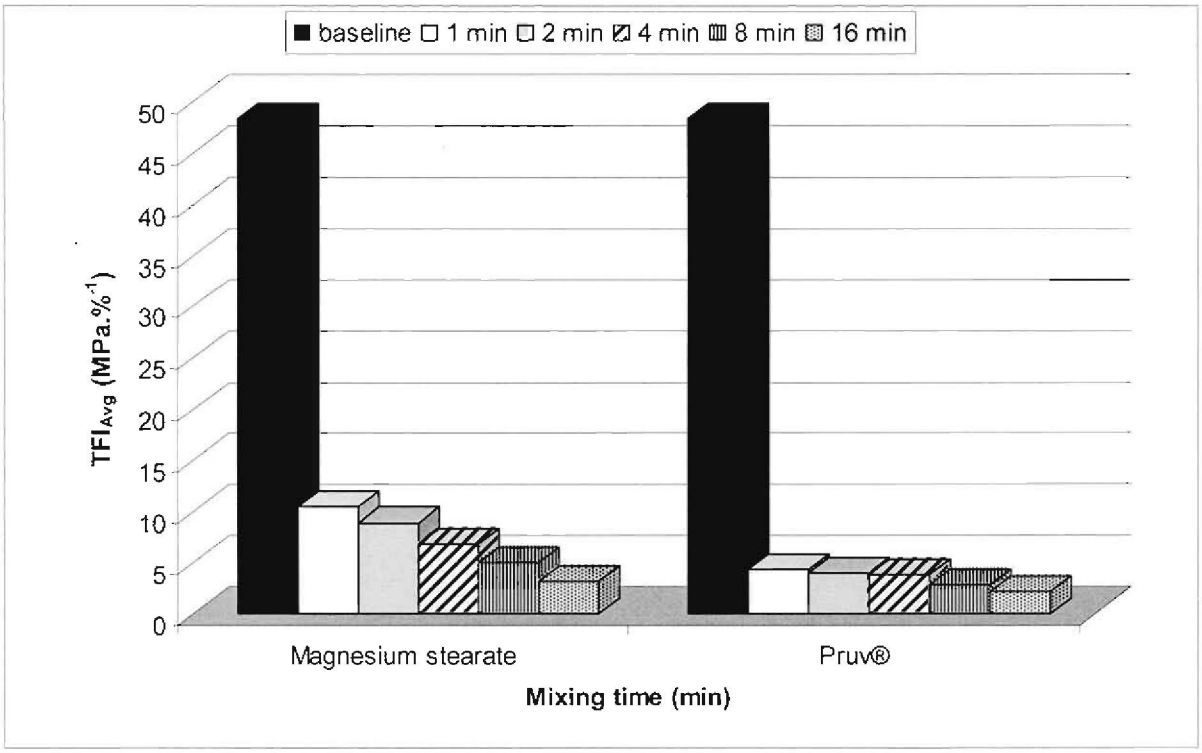


Figure 4.2: *Effect mixing duration has on the hardness of Avicel® tablets in the presence of different lubricants (magnesium stearate or Pruv®).*

Mixing speed decreased TFI_{Avg} with an average of 80% when mixing started (0 - 33 rpm) and this decrease declined to 55% when mixing speed was increased to 69 rpm (figure 4.3). Above the 69 rpm speed no significant change in TFI_{Avg} was observed, thus indicating no improved mixing or need for futher speed increases. A mixing speed of 69 rpm delivered sufficient mixing energy towards this carrier system.

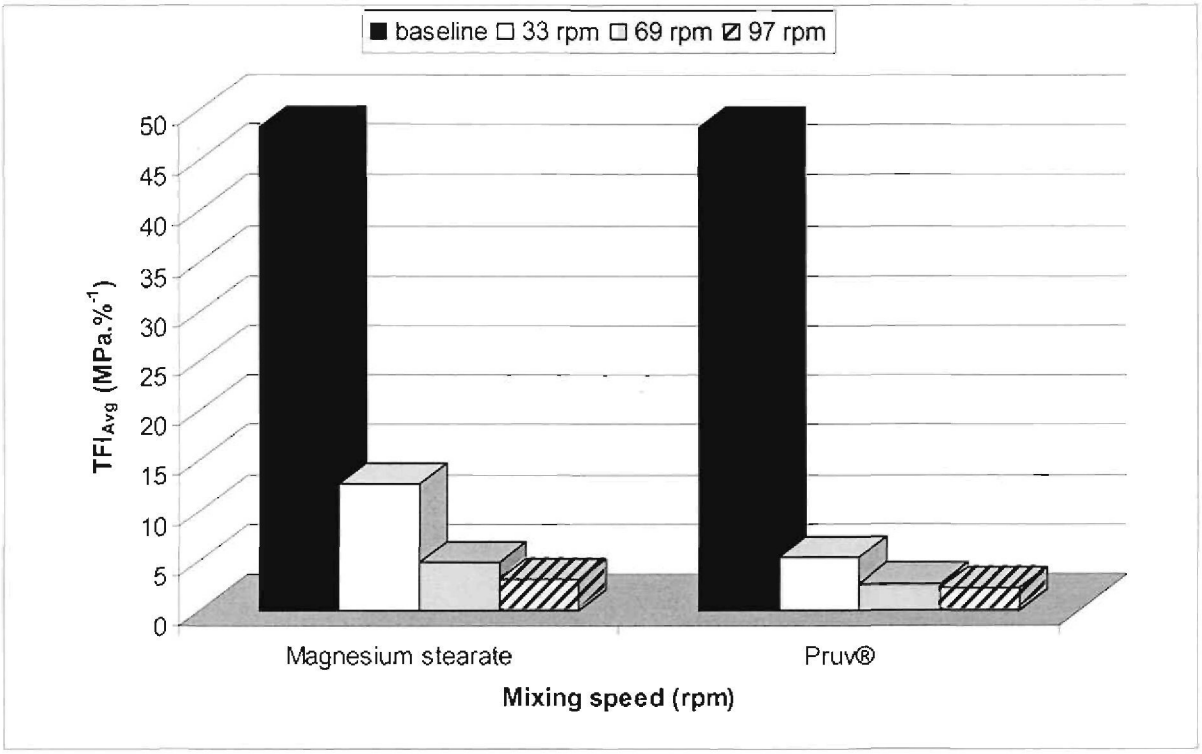


Figure 4.3: *Effect mixing speed has on the hardness of Avicel® tablets in the presence of different lubricants (magnesium stearate or Pruv®).*

From the data obtained for Avicel® tablets, the lubricant levels were limited to 2% w/w, since the data revealed that no significant changes in TFI_{Avg} values occurred above these levels. Mixing time was also minimized to 2 minutes due to poor flow at these mixing times, and maximized to 8 minutes due to overmixing problems, which occurred at the 16 minute interval.

The TFI_{Avg} values for Emcompress® and Tablettose® showed the same bar chart profiles as those obtained for Avicel®. Magnesium stearate had no significant effect on the TFI_{Avg} values obtained for Emcompress® (< 10% over the 0 - 2% w/w magnesium stearate concentration range), which agrees with results of Bolhuis *et al.* (1975:325). All the TFI_{Avg} values varied between 0.22 and 0.55, which were not significant changes. This lower sensitivity to magnesium stearate is considered primarily to be due to the large surface area and deformation behaviour of the compacted material. Due to the much larger specific surface area, the total lubricant formation is less than for Avicel® and Tablettose®. It was observed that at 33 rpm, the lubrication was too poor, since the tablets increased in hardness as the mixing time prolonged, indicating friction in the die. Emcompress® was more sensitive towards Pruv® as lubricant, which is a result of the poor surface coverage of Pruv® upon mixing compared to magnesium stearate. Tablettose® was very sensitive towards Pruv® and mixing conditions played a mayor role in the efficiency of this lubricant.

The 1% lubricant level were the smallest amount of lubricant required to produce tablets under all mixing conditions, thus acting as optimum concentration. Since tablets were only obtainable when Pruv® was mixed at 69 rpm for 4 - 8 minutes, these mixing times seemed to be the optimum. Due to the higher amount of lubricant needed to obtain optimum lubrication, it is conclusive that magnesium stearate is a better lubricant than Pruv®.

An interesting observation was made from figure 4.4 where it was seen that magnesium stearate strengthens tablets when added to Avicel®. This was, however, only seen at low concentrations of magnesium stearate (0.5% w/w) and up until the 4 minute mixing time range. This increase in TFI was due to less friction between the tablet and die wall during ejection with the addition of magnesium stearate. Above 0.5% magnesium stearate, the lubricant covered the carrier particles to such an extent that no interparticulate binding between carrier particles was possible. This phenomenon also occurred at mixing times exceeding 4 minutes and as the mixing time prolonged, the tablet hardness decreased.

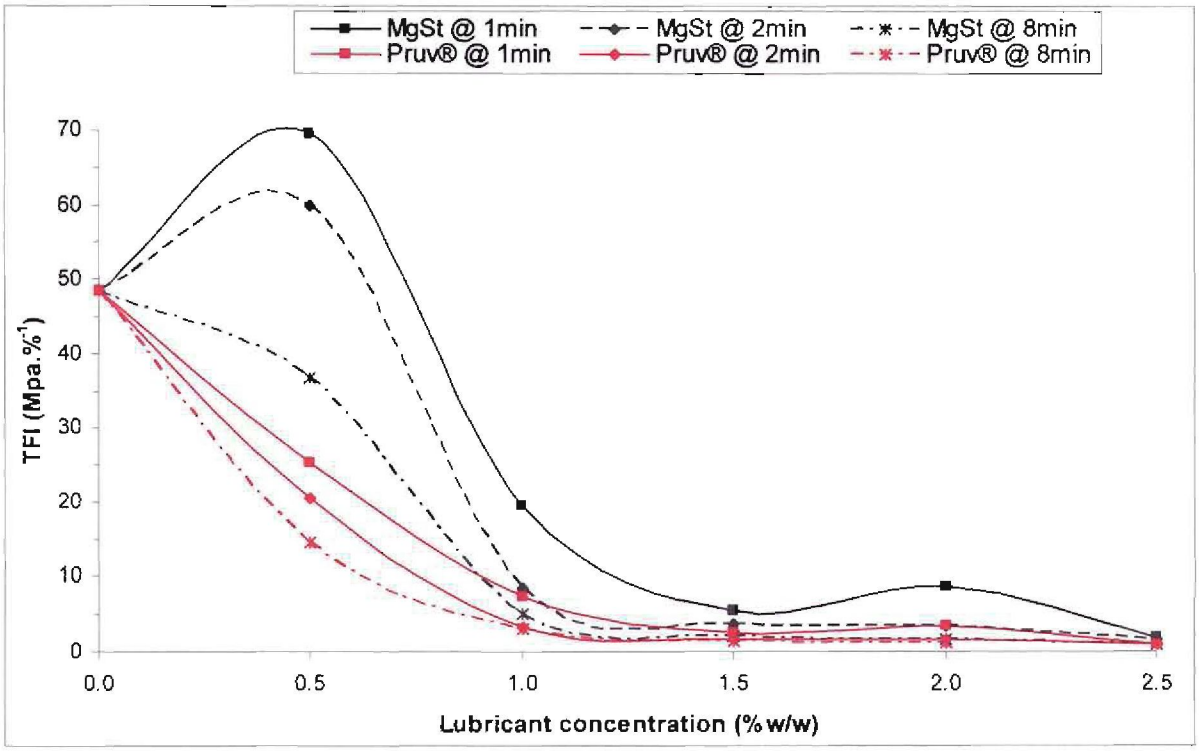


Figure 4.4: *Effect of different lubricant concentrations (magnesium stearate [MgSt] or Pruv®) on the hardness of Avicel® tablets. Mixing occurred at 33 rpm at various mixing times.*

The extent whereto lubricant absorbs onto carrier particles as a function of crushing strength may be expressed as a lubricant sensitivity ratio (LSR) according to equation 1.19. This is the ratio between the decrease in crushing strength of tablets due to mixing with lubricant and the crushing strength of unlubricated tablets prepared without lubricants. When mixing

progressed from 1 to 16 minutes there was an 13% increase in LSR for magnesium stearate, but no significant change (4%) for Pruv®, due to the poorer adsorbtion of Pruv® onto Avicel® particles (figure 4.5). The lower sensitivity of Pruv® towards mixing was also evident from the magnitude of the bar charts compared to its counterpart. These results were contradictory to findings of Shah *et al.* (1986:1329) who suggested more sensitivity toward mixing time for Pruv® than for magnesium stearate.

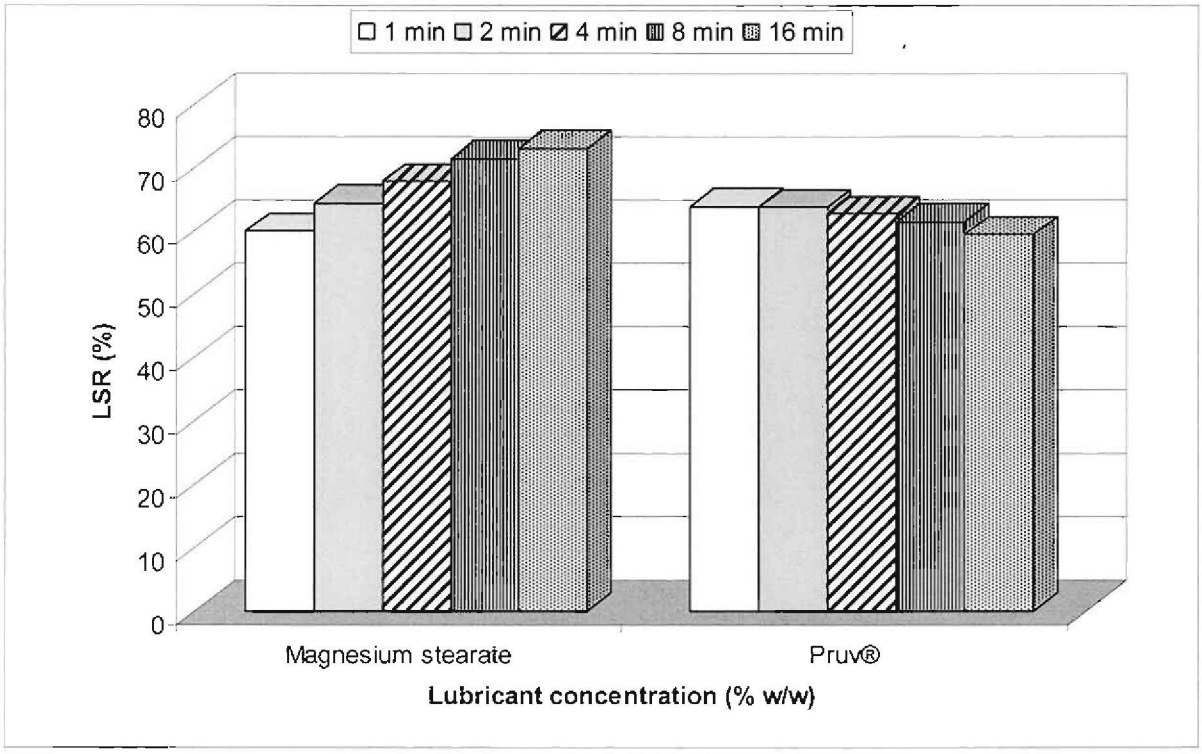


Figure 4.5: *Effect mixing duration has on the lubricant sensitivity of Avicel® tablets in the presence of different lubricants (magnesium stearate or Pruv®).*

An increase in mixing energy (33 – 97 rpm) again resulted in an increase (of nearly 18%) in LSR for magnesium stearate, but LSR decreased for Pruv® when mixing speed was adjusted from 33 to 69 rpm (figure 4.6). Thereafter, there was no change in LSR as mixing speed was increased (from 69 to 97 rpm), indicating less sensitivity for Pruv® towards mixing speed. Due to the poor lubrication properties of Emcompress® and Tablettose®, no unlubricated tablets were compressed and thus no LSR values could be calculated.

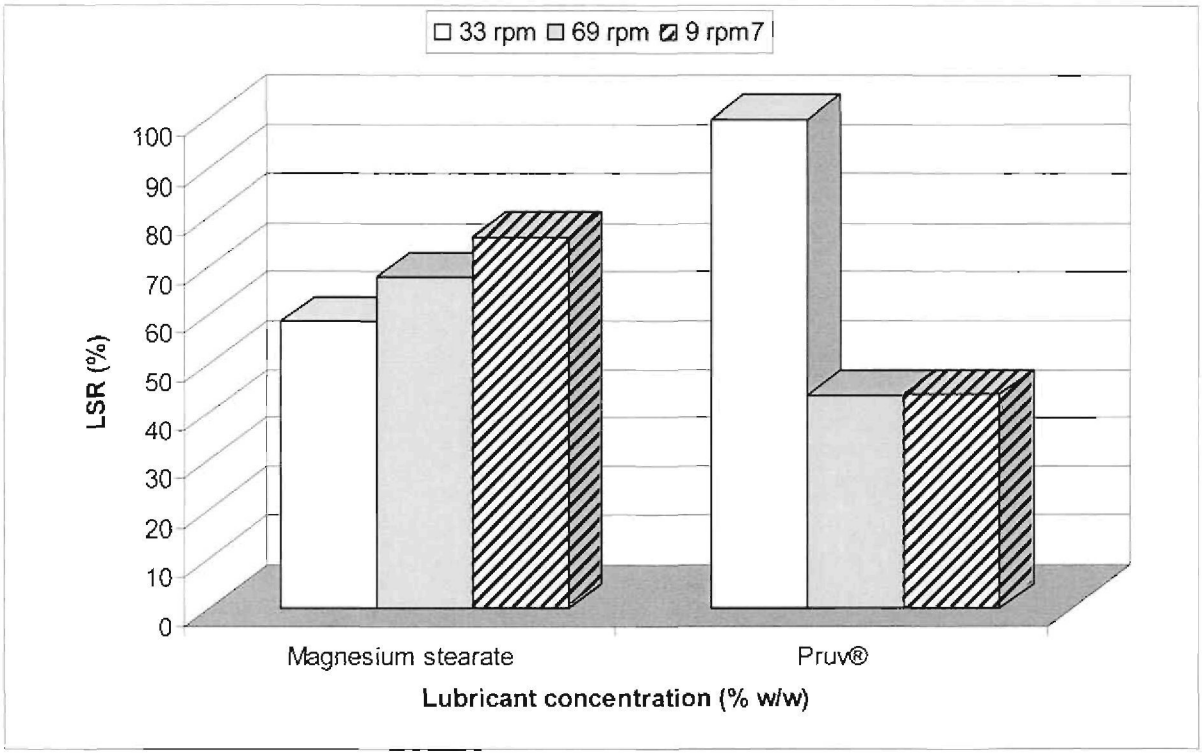


Figure 4.6: *Effect mixing speed has on the lubricant sensitivity of Avicel® tablets in the presence of different lubricants (magnesium stearate or Pruv®).*

Statistical evaluation (95% confidence interval) of the TFI data indicated significant differences ($p < 0.05$) between friability and tensile strength for magnesium stearate and Pruv® than with Avicel®. There was an interaction between type of lubricant and lubricant concentration, but not for mixing speed and time. The amount of decay of Avicel® tablets over the whole lubricant concentration range remained relatively unchanged. TFI values decreased between 98 - 99% irrespective of the mixing time, speed or lubricant used. This led to the conclusion that mixing energy did not potentiate the effect of lubrication. In tablets containing Emcompress® mixing time and lubricant concentration did not influence one another to potentiate the effect of lubrication on TFI. Tablettose® was most effected by the addition of lubricants and mixing conditions, but none of the mixture variables had any significant effect on friability ($p > 0.05$). Mixing time and speed did not potentiate the effect lubrication had on the TFI for Tablettose® tablets.

4.2.1 CONCLUSION

The weakening effect lubricants had on tablets was observed for all the binders/fillers and tablet strength deteriorated as magnesium stearate or Pruv® concentration increased. The same indirect relationship was observed for magnesium stearate as mixing prolonged, but mixing improved the crushing strength of tablets containing Pruv®. This was a result of less

lubricant sensitivity for Pruv®, which increased when mixing decreased as a result of an increase in surface of separation to leave carrier particles with less lubrication on surface areas and thereby increasing crushing strength. It therefore appears that, as mixing time and speed proceeded, particle bonding was weakened or strengthened as a function of the lubricant sensitivity ratio (LSR) of the lubricant used.

Friability increased when lubricant concentration and mixing time and speed increased for both lubricants in all carrier systems as a result of better surface coverage of lubricant. Since Pruv® has less lubricant sensitivity, less lubricant particles are adsorbed onto carrier particles to leave more lubricant onto the tablet surface, which explains the higher friability observed for Pruv® than for magnesium stearate. There was no direct correlation between crushing strength and friability (r^2 = 0.554), but harder tablets was characterized with higher crushing strengths and lower friability.

The optimum level of concentration for magnesium stearate was found at 0.5% w/w and for Pruv® at 1.0% w/w, thus indicating the first as superior to the last as lubricant. Mixing also reached an optimum when sufficient lubrication ensures good homogeneity, flow and lubrication in the powder mixture. It was seen that the 1 minute mixing time was insufficient due to poor flow, and that the 16 minute mixing period resulted in overmixing. The 4 minute mixing period was found to be the best optimum time for both lubricants, since it gave in most cases the hardest tablets with the best weight uniformity. For all the fillers used, 69 rpm proved to be the optimum mixing speed, with 33 rpm and 97 rpm resulting in poor lubrication due to either slower coverage of carrier particle surfaces or centripetal forces weakening the mixing process. Although Avicel® was the only filler/binder which could be compressed without lubrication, it was most sensitive to increasing lubrication levels due to ductile deformation, with Emcompress® the least affected.

4.3 THE EFFECT OF LUBRICATION AND MIXING ON TABLET DISINTEGRATION

The nature and extent of surface coverage of the lubricant achieved by mixing often predetermine the strength or weakness of the consolidating forces. Ultimately, of course, the bonding forces must be designed to fail in cohesion and/or adhesion when the tablet performs, i.e. disintegrates and dissolves. The duration of mixing exerts not only a statistical effect on randomizing the location of the lubricant within the compact but also affects surface characteristics of the powder and interparticular bond strength in the compact. The degree of mixing, both in duration and shearing energy, may affect the porosity, air permeability, and liquid penetration rate of a tablet (Khan & Rhodes, 1976:943).

Mixtures containing Avicel®, Tablettose® or Emcompress® as fillers and magnesium stearate or Pruv® as lubricants (0 – 2.5% w/w) were prepared at various mixing times (1-16 minutes) at different mixing speeds (33, 69 and 97 rpm) as described in section 2.4.1.1, and tablet disintegration properties were determined as described in section 2.4.1.3.4. Selected data points for magnesium stearate and Pruv® are tabulated for disintegration (table 4.3).

Lubrication with magnesium stearate resulted in an increase in disintegration time which further prolonged as the lubricant concentration was increased (table 4.3). This was especially observed for concentrations above 1.0% w/w where an average of 100% increase in disintegration time was observed. This was due to saturated interparticular spaces being filled with more hydrophobic lubricant. The decrease in disintegration time with mixing time at low mixing speeds and concentration ranges was due to either poor lubrication resulting in weak tablets and/or could be attributed to the weakening effect lubricants had on crushing strength. The increase in disintegration times at higher concentration and mixing conditions acted as proof that lubricants delayed water penetration due to the filling of interparticulate spaces since mixing distributed more lubricant on particle surfaces with less on the tablet surface. At high energy mixing (97 rpm) the effect weakened due to poor mixing as a result of centripetal forces acting inside the mixing container.

Table 4.3: *Disintegration (seconds) of tablets from different fillers/binders mixed with different lubricants at various concentrations and mixing conditions. Values for unlubricated tablets are indicated in parentheses.*

Lubricant	Mixing speed (rpm)	Mixing time (min)	**Avicel®** (45.000)				**Emcompress®** (n/d)				**Tablettose®** (n/d)			
			0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Magnesium stearate	33	2	40.000	28.333	25.000	31.167	900.000	900.000	900.000	900.000	221.667	900.000	900.000	900.000
		4	34.167	53.667	20.500	78.333	900.000	900.000	900.000	900.000	607.500	900.000	900.000	900.000
		8	16.500	16.000	36.500	242.500	900.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000
	69	2	11.000	13.667	49.500	588.333	900.000	900.000	900.000	900.000	636.667	900.000	900.000	900.000
		4	11.000	24.667	130.500	1630.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000
		8	8.833	57.333	480.500	1551.667	900.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000
	97	2	10.500	35.833	332.000	971.667	900.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000
		4	11.167	95.833	624.167	874.167	900.000	900.000	900.000	900.000	900.000	900.000	900.000	900.000
		8	19.167	136.667	1440.833	1105.833	900.000	900.000	900.000	900.000	900.000	900.000	900.000	n/d
Pruv®	33	2	143.333	83.333	94.167	62.333	900.000	900.000	900.000	900.000	n/d	155.000	168.000	173.000
		4	102.500	105.000	80.833	54.167	900.000	900.000	900.000	900.000	n/d	161.167	186.500	202.500
		8	105.000	85.000	62.500	55.000	900.000	900.000	900.000	900.000	n/d	183.333	205.000	232.500
	69	2	123.833	91.167	51.167	43.833	900.000	900.000	900.000	900.000	n/d	172.500	199.167	234.000
		4	27.500	92.500	40.333	30.000	900.000	900.000	900.000	900.000	158.333	190.833	205.833	257.500
		8	95.833	72.500	29.500	20.500	900.000	900.000	900.000	900.000	223.333	205.000	230.833	279.333
	97	2	120.000	81.167	45.000	17.500	900.000	900.000	900.000	900.000	n/d	207.500	223.833	259.333
		4	100.833	38.167	17.333	37.500	900.000	900.000	900.000	900.000	n/d	237.500	259.167	275.000
		8	48.500	16.000	11.667	14.167	900.000	900.000	900.000	900.000	n/d	262.500	277.500	291.667

n/d – no data available

Pruv® showed the same tendency towards mixing and prolonged and aggravated mixing conditions increased the disintegration process. Another difference was seen with added Pruv® concentrations which had a positive impact on disintegration properties of tablets. The reason being that as concentration and mixing time increased, more lubricant was adsorbed onto carrier particles and its hydrophilic nature decreased disintegration time. These properties were only observed for disintegrating filler (Avicel®) use, as the opposite was seen for non-disintegrating water-soluble carrier systems (Tablettose®). Pruv® had no effect on the poor disintegrating and poor water-soluble system (Emcompress®).

Disintegration is dependent of the amount of hydrophilic sites on the tablet surface, but among other, also of the hardness and porosity of the tablets. There is, however, no direct correlation between friability and disintegration ($r^2 < 3.8$). To compensate for density variations between filler/binders used and variable lubrication levels, a tensile strength-disintegration index (TDI) seemed to be the most appropriate measurement for water wettability evaluation of tablets. High TDI values indicated good disintegration as a result of hydrophilic lubricant properties and/or harder tablets, and low TDI values represented the opposite. TDI_{Avg} represents the average TDI values of a specified parameter range.

TDI_{Avg} values for formulations containing magnesium stearate indicated that as lubricant concentration increased, the tablets disintegrated slower, lowering the TDI_{Avg} values (figure 4.7). This negative effect is due to the hydrophobic nature of magnesium stearate. This was especially true for formulations where the magnesium stearate concentration exceeded 0.5% w/w and TDI_{Avg} values dropped more than 30%. Pruv®, however, increased TDI_{Avg} values as concentration increased in Avicel® formulations. The opposite effect was observed when Tablettose® was used as filler/binder as a result of the decrease in tensile strength and a small increase in disintegration compared to Avicel®. After the 1.5% w/w concentration level, TDI_{Avg} values remained constant as a result of less change in disintegration among concentration levels. This could be attributed to saturated interparticulate spaces and optimum particle surface coverage by Pruv®. The increase in TDI_{Avg} value from 0 - 0.5% magnesium stearate was a result of harder tablets as was seen in figure 4.4, whereas the sharp decrease in TDI_{Avg} when Pruv® was added was due to the decrease in crushing strength.

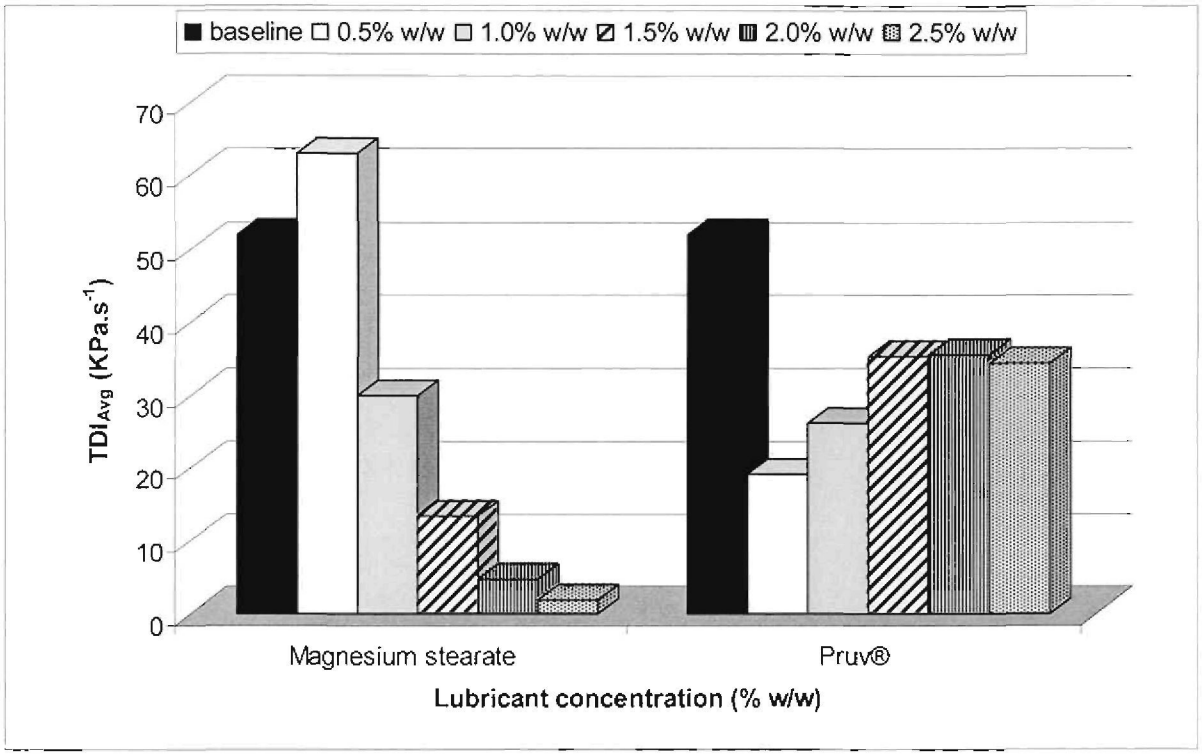


Figure 4.7: *Effect of different lubricant concentrations (magnesium stearate or Pruv®) on the disintegration of Avicel® tablets.*

Prolonged mixing times (figure 4.8) and faster rotational speed increased disintegration of tablets containing magnesium stearate. However, unlike the results reported by Lerk *et al.* (1977:33) who showed that as mixing time increased, disintegration time also increased, Khan *et al.* (1983:111) found that there was a reduction in disintegration with increased mixing. This was seen as there was a small decrease (1%) in TDI_{Avg} values as the lubricant mixing time changed from 1 to 2 minutes. Thereafter the TDI_{Avg} values decreased significantly (± 10%) as mixing prolonged above the 4 minute period. This could be attributed to less lubricant on the surface of the tablets, since mixing spreads the lubricant more uniformly around the rest of the carrier particles, being beneficiary to the wettability of the tablet surfaces.

Again, opposing disintegration results were obtained for formulations containing Pruv® rather than magnesium stearate. The increase in TDI_{Avg} values was due to better disintegration as a result of the hydrophilic nature of Pruv® as suggested by literature, opposed to the hydrophilic nature of magnesium stearate. The increase in TDI_{Avg} values as mixing time prolonged was the result of the uniformity of Pruv® content throughout the mixture and was improved upon continuous mixing.

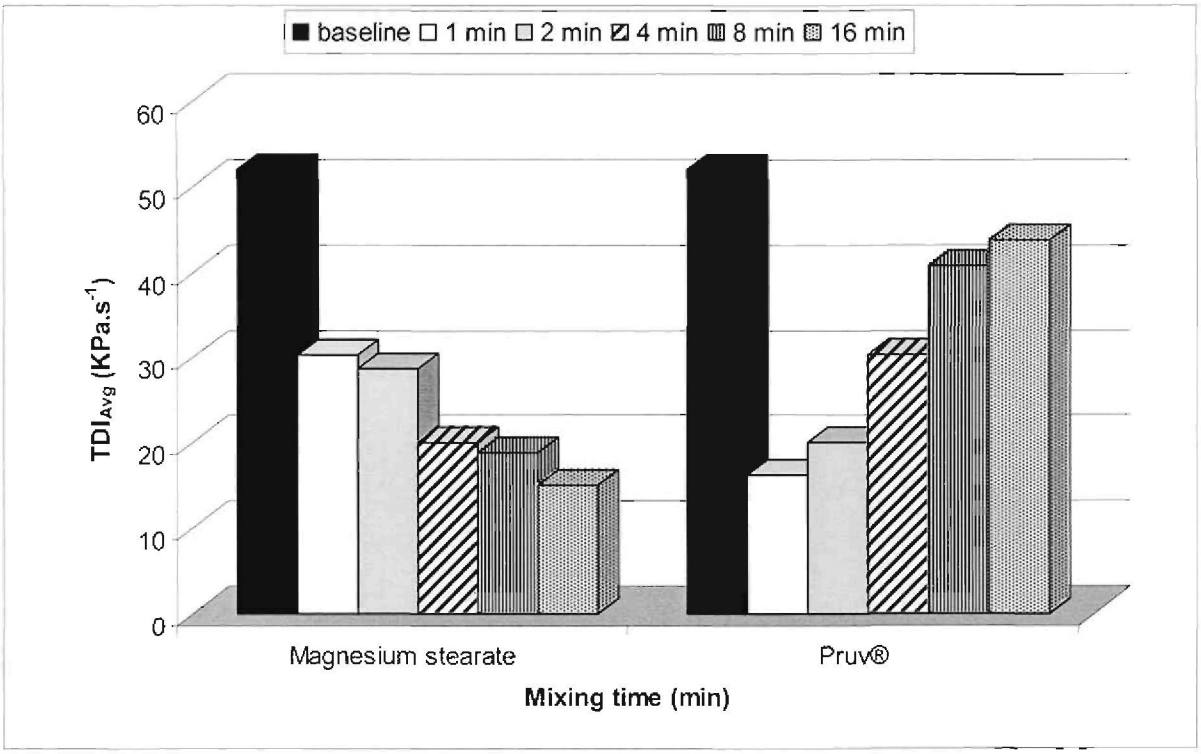


Figure 4.8: *Effect mixing duration has on the disintegration of Avicel® tablets in the presence of different lubricants (magnesium stearate or Pruv®).*

Emcompress® tablets were again insensitive toward lubrication. When placed in water, Emcompress® tablets are rapidly and completely penetrated by the liquid. This rapid penetration is caused by the hydrophilic nature of the material (Caramella *et al.*, 1986:1765) and the high porosity of the tablets. Despite the fast and complete water penetration, Emcompress® tablets do not disintegrate because the excipient is relatively insoluble in water and no disintegration force is developed (Khan & Rhodes, 1976:943), leading to disintegration times above 15 minutes and thus not complying with BP 2002 standards for disintegration. Therefore, it is important to include a disintegrant with an active mechanism such as swelling to induce the disintegration forces necessary to break up the tablet. Disintegrants will influence the effect magnesium stearate will have on the disintegration properties of Emcompress®. Evaluation of disintegrants falls beyond the scope of this study and any evaluation of the TDI values obtained without disintegrants will be unnecessary, as this will only indicate the effect of the hardness of the tablets as discussed in section 4.2.2.

Although most of the disintegration times obtained for Tablettose® were above 15 minutes when magnesium stearate was added, as were the case with Emcompress®, this was only due to the hydrophobic nature of magnesium stearate, since Tablettose® dissolves in water. Again the evaluation of TDI values will only indicate the effect lubrication had on tablet hardness.

The lubricant levels were again limited to 2% w/w, since the data obtained showed that no significant changes in TFI_{Avg} values occurred above these levels. Mixing time was also minimized to 2 minutes due to poor flow at these mixing times, and maximized to 8 minutes due to overmixing problem, which occurred at the 16 minute interval.

Since no tablets were obtained when no Pruv® was present for formulations containing Tablettose® as filler/binder, the inclusion of this lubricant was essential (figure 4.9). Even at low Pruv® concentrations (0.5% w/w) the tableting process seemed impossible and at the 0.5% w/w Pruv® level, tablets were compressed only for mixtures mixed at 69 rpm for longer than 2 minutes. This immediately indicated this mixing speed as the most effective and cancelling 2 minutes as the optimum mixing period. Since harder, faster disintegrating tablets were obtained at the 4 minute time interval than for the 8 minute interval, 4 minutes were the most prominent mixing period. Poor performance of slower mixing conditions was an indication of the low surface coverage with Pruv®, thus resulting in friction problems.

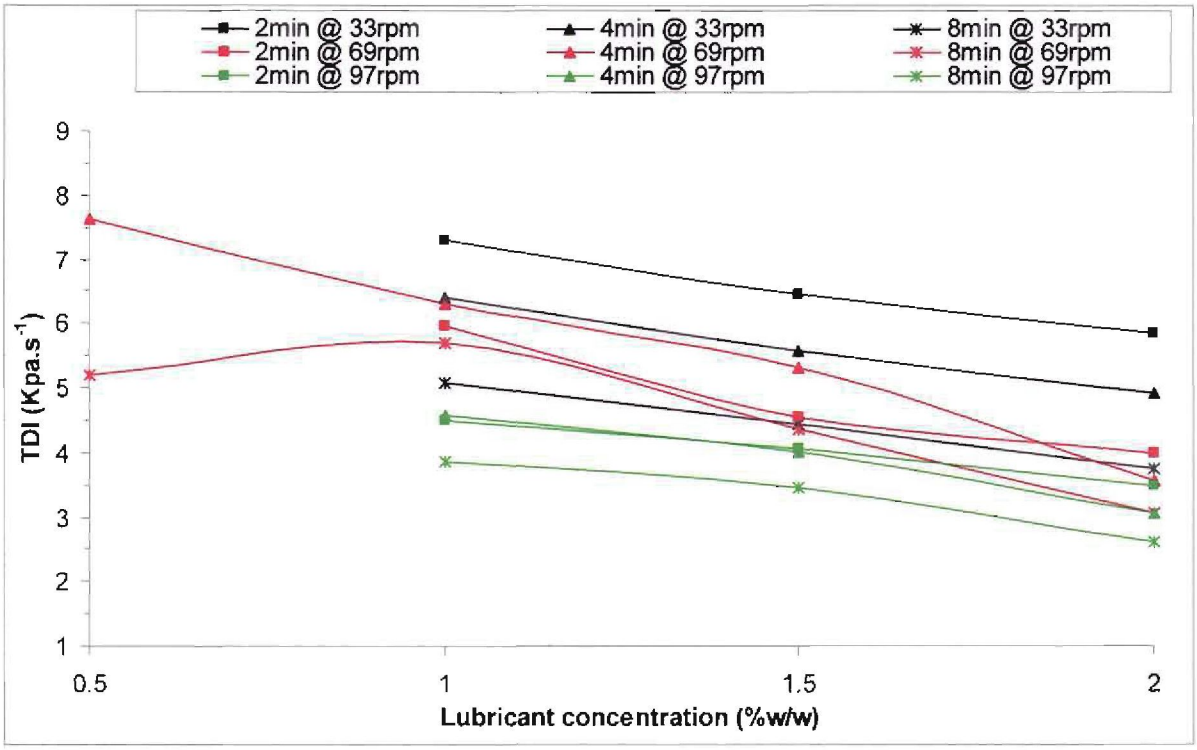


Figure 4.9: *Effect of different concentrations Pruv® on the TDI of Tablettose® tablets. Mixing occurred at various mixing times and speeds.*

When higher concentrations of Pruv® were added to Tablettose®, the friction (capping) problem stopped, indicating better lubrication at this level (1.0% w/w), but with declining TDI values. This decline was due to weaker tablets and longer disintegration times. These opposing results, compared to Avicel®, was related to the poor wettability of the Tablettose®

compared to the fast disintegration properties observed with Avicel® tablets. As Pruv® concentrations increase and mixing rotation prolonged, there was a decline in TDI values as a result of the increasing water wettability effect of Pruv®, which only worsens the water retardation of Tablettose®. The interesting observation was the almost straight lines obtained for each of these mixing conditions as concentration increased, indicating a direct relationship between the hardness and disintegration properties of Tablettose® tablets when lubricated with Pruv®.

Statistical evaluation (95% confidence interval) of the data indicated significant differences ($p < 0.05$) between friability and tensile strength parameters for magnesium stearate and Pruv®, at different concentrations, when mixed for different times. Mixing speed had no statistically significant effect on disintegration time. There was no interaction between the variables, except between the lubricant concentration, the lubricant used and the mixing speed, but mixing speed and time did not potentiate the altering effect lubrication had on disintegration. The above statistical evaluation on the effect lubrication has on tablet disintegration was true for all the fillers/binders used.

4.3.1 CONCLUSION

As the amount of magnesium stearate increased the disintegration time increased. This was due to the lipophilic nature of the magnesium stearate and the weakening effect it had on carrier particles. The importance of a disintegrant to improve and/or initiate disintegration was also observed as only fillers with disintegrant properties, e.g. Avicel®, disintegrated with the addition of magnesium stearate. Emcompress® and Tablettose® had little to no disintegration with/without the addition of magnesium stearate. Interestingly enough, prolonged and aggravated mixing improved the disintegration process. These results are concurrent with the results obtained by Khan *et al.* (1983:110) indicating that an initial reduction in disintegration time with increasing mixing time was due to less magnesium stearate between interparticular spaces and more on the surface area of carrier particles. It therefore appears conclusive that, as mixing time proceeds, particle bonding is considerably weakened as a result of the build-up of a film of magnesium stearate around the drug and carrier particles. This weakening is manifested as a decrease in tablet strength and as a decrease in disintegration time. The slight increase in TDI values as was observed with Avicel® for 0.5 % w/w magnesium stearate was due to harder tablets at prolonged mixing due to less friction in the die.

Pruv® had the opposite effect on hydrophilic substrates (Avicel®) than magnesium stearate did. The addition of more hydrophilic Pruv® had a positive impact on Avicel® tablets.

Prolonged mixing with Pruv® appears to improve the lubricating effect with less positive effects on the disintegration. This was due to less lubricant between Avicel® particles improving wettability. Poor wettable and soluble fillers/binders such as Tablettose®, experienced the same negative effect to the addition of Pruv® and mixing rotations than with magnesium stearate, but to a much lesser extent. In fact, there was nearly an 80% increase in disintegration when Pruv® was added to Tablettose® compared to the same aliquots of magnesium stearate. Emcompress® was yet again, as was seen with magnesium stearate, unsensitive to Pruv® since disintegration fell beyond the 15 minute limit disintegration time.

For both of these lubricants the optimum mixing conditions to produce tablets with relative good disintegration properties, with the allowance of good flow properties and harder tablets, was mixing for 4 minutes at 69 rpm for all the fillers/binders being used. The optimum lubricant concentration differed with magnesium stearate performing optimally at 0.5% w/w and Pruv® between 0.5% w/w and 1.0% w/w pending on the filler system used.

4.4 THE EFFECT OF LUBRICATION AND MIXING ON DRUG DELIVERY SYSTEMS

Due to their hydrophobic properties, tablet lubricants are known to interfere with the release of active drug substances. It is generally assumed that the lubricant will form a film around drug particles during mixing. The lubricant decreases the effective drug/solvent interfacial area and thereby decreases the release of the drug.

If lubricant concentration in a tablet is sufficiently high, penetration of water into the tablet is prevented. At lower concentrations, its less extreme effects are lengthening of tablet disintegration time (Strickland *et al.*, 1956:55) and decrease in the rate of dissolution of tablet constituents (Levy & Gumtow, 1963:1144). The mechanism by which this is achieved is complex. Contamination of surfaces by lubricants will modify the mechanisms of bonding during compression and, therefore, the break-up of a tablet in water. Changes in the shape and size distribution of the capillaries, which conduct water into the tablet, may result from the volumetric contribution of a lubricant, which compacts with ease, or the reduction of interparticulate friction, which it produces. It is probable, however, that the major mechanism lies in the inhibition of penetration due to the high contact angle of lubricants with water.

Mixing will play an important part in the distribution of a lubricant. The problems of dispersing a small proportion of a highly cohesive powder through a mass, which is probably of quite different particle size, are obvious enough. When a limit is imposed on the mixing energy which can be expended in order to avoid the break-up of granules, the dangers of

misdistribution become severe and a gross variation in the aqueous penetration of tablets subsequently prepared becomes possible.

4.4.1 PHYSICAL TABLET PROPERTIES

The protocol described in section 2.4.1.1 was followed to produce and evaluate tracer tablets. Furosemide was mixed (4 or 8 minutes at 69 rpm) with Avicel® and Tablettose® powder in the absence/presence of different lubricants at varying concentration. Mixing conditions were concluded from preceding sections to be at optimum at 69 rpm for 4 minutes. The 8 minute interval was included to demonstrate the effect of prolonged mixing on drug release. Since dissolution is dependent of the contact area produced through disintegration, poor disintegrating formulas like those with Emcompress® as filler/binder, were of little use during this part of the study.

The incorporation of a troublesome drug substance, like furosemide, could influence the physicochemical properties of the tablets produced, compared with those with no furosemide as was previously evaluated. Therefore, the main characteristics of these tablets had to be evaluated. As satisfactory flow was established at the mixing conditions used, only the hardness and disintegration properties had to be evaluated, since these two properties also had the most pronounced effect on drug release.

The physical properties of tracer tablets (table 4.4) indicated that when disintegrating fillers systems (Avicel®) was used, lubricant weakens the tablets as concentrations increase and mixing conditions prolong. The Avicel® tablets react the same towards both hydrophilic (Pruv®) and hydrophobic (magnesium stearate) lubricants. The weaker tablets' disintegration time decreased, but the addition of lubricant had a negative impact on disintegration. Thus the observation that when the lubricant concentration was the same and mixing time increased to 8 minutes, the disintegration time decreased as a result of less lubricant between carrier particles.

Water-soluble fillers (Tablettose®) react the same towards prolonged mixing and increased lubrication as was seen with Avicel®, but hydrophilic lubricants (Pruv®) had a negative impact on disintegration even at prolonged mixing. This indicated poor adhesion of Pruv® towards carrier particles as a result of electrostatic forces generated between Tablettose® and Pruv® particles as more energy was added to the mixture during prolonged mixing. The poor water wettability of Tablettose® also played a major role in the increase in disintegration time as an increase of Pruv® between Tablettose® particles, due to higher concentration or mixing, caused worse wettability properties, thus lengthening disintegration.

Table 4.5: *Physical tablet properties of tracer tablet formulations. %RSD is indicated in parentheses.*

Filler/binder			**Avicel® tablets**			**Tablettose® tablets**		
Lubricant	Mixing time (min)	Lubricant concentration (% w/w)	Average crushing strength (N)	Average disintegration (s)	HDI ($N.s^{-1}$)	Average crushing strength (N)	Average disintegration (s)	HDI ($N.s^{-1}$)
Magnesium stearate	4	0.5	97.880 (7.1658)	22.500 (8.315)	4.350	86.870 (8.034)	359.167 (17.464)	0.242
		1.0	90.020 (6.366)	22.167 (7.227)	4.061	84.900 (8.744)	900.000 (0.000)	0.094
		1.5	82.470 (3.501)	25.333 (6.446)	3.255	85.300 (4.188)	900.000 (0.000)	0.095
		2.0	70.910 (6.404)	23.333 (9.258)	3.039	81.100 (5.051)	900.000 (0.000)	0.090
	8	0.5	114.160 (6.974)	10.5000 (5.216)	10.872	83.810 (6.812)	804.667 (11.336)	0.104
		1.0	80.410 (7.640)	15.500 (12.070)	5.188	74.470 (6.429)	900.000 (0.000)	0.083
		1.5	67.090 (8.886)	13.167 (14.740)	5.095	77.380 (7.223)	900.000 (0.000)	0.086
		2.0	59.4040 (8.935)	36.667 (44.536)	1.610	74.110 (7.774)	900.000 (0.000)	0.082
Pruv®	4	0.5	105.550 (4.443)	25.333 (17.055)	4.166	83.960 (4.481)	119.500 (3.029)	0.703
		1.0	95.960 (4.459)	26.000 (11.666)	3.691	86.630 (3.093)	147.500 (6.121)	0.587
		1.5	89.460 (5.816)	26.500 (20.634)	3.376	86.380 (4.575)	167.000 (3.123)	0.517
		2.0	80.540 (8.684)	22.500 (8.315)	3.580	82.810 (8.204)	196.667 (9.048)	0.421
	8	0.5	105.290 (4.743)	23.833 (6.176)	4.418	84.690 (3.210)	132.500 (5.395)	0.639
		1.0	86.010 (7.777)	24.667 (12.207)	3.487	86.990 (6.197)	166.833 (3.204)	0.521
		1.5	80.380 (10.112)	24.000 (10.865)	3.349	86.060 (6.731)	203.167 (4.418)	0.424
		2.0	78.500 (9.270)	26.833 (13.2110)	2.925	86.700 (5.620)	249.167 (7.553)	0.348

It can be concluded that the addition of furosemide in small concentrations (20 mg per 400 mg tablet) had no significant change in the physical properties of tablets compared to those without furosemide. Thus the former data obtained with formulations without any furosemide is also relevant for those with furosemide and any conclusion formerly made are also applicable for the tracer tablet formulations.

4.4.2 DISSOLUTION STUDIES

The physical properties of the tracer tablets seemed adequate and meet most of the prerequisites of direct compression. The dissolution behaviour of the tracer should reveal properties imparted to the formulations by excipients that could finally determine their suitability.

The protocol described in section 2.5 was followed to produce and evaluate tracer tablets. Furosemide was mixed (4 and 8 minutes) with Avicel® and Tablettose® with different lubricant concentrations (0 - 2% w/w). Baseline values represent tablets with furosemide mixed (4 or 8 minutes) with filler, without any lubricant present. All formulations were tableted as was described in section 2.4.1.2, with baseline formulations for Tablettose® compressed with pre-compression lubrication of the die. Detailed presentations of the dissolution data, determined as described in section 2.5, are given in annexure C.

Two parameters are noted that were normalized. Normalization of data allows comparison of the AUCs (extent of dissolution) and DR_is (initial rate of dissolution from $t_0 - t_b$) of the various formulations. These normalizations abstract the three basic constituents of the tracer formulations (furosemide, lubricant and filler/binder) from the dissolution parameters and allow evaluation of the contribution that auxiliaries made to these parameters. This method is an adaptation of the method utilized to compare AUCs of various formulations to that of a suspension of an analyte (Vadas *et al.*, 1984:782). Calculations of these values made it possible to rank AUC and the respective DR_i values to determine the dissolution efficiency of the formulations. Equations 4.1 and 4.2 are utilized to normalize the dissolution parameters which are presented in table 4.5.

$$(AUC)_n = \frac{(AUC)_{formula}}{(AUC)_{baseline}} \qquad 4.1$$

where:

$(AUC)_n$ = normalized AUC, $AUC_{formula}$ = AUC of formulation and $AUC_{baseline}$ = AUC of reference.

$$(DR_i)_n = \frac{(DR_i)_{formula}}{(DR_i)_{baseline}} \qquad 4.2$$

where:

$(DR_i)_n$ = normalized DR_i, $(DR_i)_{formula}$ = DR_i of formulation and $(DR_i)_{baseline}$ = DR_i of reference.

Table 4.5: *Dissolution parameters of tracer tablet formulations.*

Filler/binder			**Avicel® tablets**		**Tablettose® tablets**	
Lubricant	Mixing time (min)	Lubricant concentration (% w/w)	$(DR_i)_n$	$(AUC)_n$	$(DR_i)_n$	$(AUC)_n$
No lubrication (baseline)			1.000	1.000	1.000	1.000
Magnesium stearate	4	0.5	0.778	0.966	1.157	0.873
		1.0	0.688	0.944	1.050	0.508
		1.5	0.516	0.836	0.904	0.182
		2.0	0.310	0.644	0.527	0.096
	8	0.5	0.918	1.014	0.510	0.771
		1.0	0.765	1.015	0.076	0.275
		1.5	0.520	0.840	0.024	0.142
		2.0	0.496	0.784	0.024	0.073
Pruv®	4	0.5	0.830	0.920	0.317	0.831
		1.0	0.711	0.878	0.016	0.706
		1.5	0.701	0.807	0.030	0.578
		2.0	0.609	0.826	0.026	0.587
	8	0.5	0.783	0.920	0.610	0.812
		1.0	0.749	0.886	0.360	0.691
		1.5	0.704	0.854	0.462	0.564
		2.0	0.741	0.888	0.171	0.465

Both normalized parameters showed a decrease as magnesium stearate concentrations and mixing time were increased. Baseline formulations, although impossible to compress due to poor lubrication properties of filler, were compressed by first lubricating die wall surfaces before tableting. This was essential since reference tablets were required in the comparison of dissolution profiles. Pruv® showed the same phenomena but with less variation between concentration levels. Mixing however, had a positive effect on the dissolution rate as $(DR_i)_n$

values increased from 4 to 8 minute mixing times. This observation unmistakably illustrated the difference between the effect hydrophilic and hydrophobic lubricants have on the dissolution of the analyte in the medium. The biggest difference was observed at prolonged mixing times (8 minutes), and at high lubricant concentrations (2.0% w/w). The large decrease in $(DR_i)_n$ of Tablettose® tablets observed between 0.5% w/w and 1.0% w/w lubrication for magnesium stearate at 8 minute mixing time and Pruv® at 4 minutes, was an indication of optimum lubrication at 0.5% w/w for both lubricants. This also indicated the higher sensitivity of Pruv® towards mixing conditions. From the decrease in $(AUC)_n$ and $(DR_i)_n$ values for formulas with lubrication compared to unlubricated formulas, it was obvious that lubrication, no matter the hydrophilic/hydrophobic nature, decreased the rate and extent of dissolution.

The force driving a liquid into a tablet is dependent of the surface tension of the penetrating liquid and the contact angle between the penetrating liquid and the capillary surface. The contact angle of water on magnesium stearate is large enough so that water will not enter a tablet composed of this material (Ganderton, 1969:10S). Pruv® has better water wettability characteristics compared to magnesium stearate and thus the difference in dissolution parameter when compared to water-soluble Tablettose® formulas with magnesium stearate. An intermediate effect will be found when lubricants is mixed and compressed with a powder which is freely wetted by water. This could explain the small differences between magnesium stearate and Pruv® formulas with Avicel® as filler. Capillaries with surfaces composed of some proportion of lubricant will not then transmit water and the proportion of capillaries so affected will depend upon the distribution of lubricant through the tablet matrix. For given samples of lubricant and powder base, the three major factors which will affect this property are the concentration of lubricant, the processes of tablet manufacture and the intensity of mixing operations (Ganderton, 1969:10S). The effect of concentration was relatively straightforward. Higher proportions of lubricant yielded an increase in the non-wetting internal surface and the number of capillaries not contributing to the transport of water. The increase in surface of separation with prolonged mixing contributed positively towards the non-wetting internal surface, thereby decreasing the transport of water.

The large $(AUC)_n$ and $(DR_i)_n$ values for 0.5% w/w magnesium stearate when mixed with Avicel® for 8 minutes indicated this level as optimum for the amount and rate of drug released. The same amount of magnesium stearate gave optimum levels in Tablettose® formulations, but after 4 minute mixing.

Optimum drug release with efficient lubrication was found with 0.5% Pruv®. Mixing had opposing effects on carrier systems compared to magnesium stearate with 4 minute and 8 minute mixing times acting optimally to Avicel® and Tablettose®, respectively, when lubricated with Pruv®.

4.4.2.1 Disintegrating carrier systems (Avicel® tablets)

The behaviour of the disintegrating Avicel® tablets provided the basis from which certain effects could be described, even for the non-disintegrating tablets (figure 4.10). Baseline formulations demonstrated that furosemide was released to a larger extent than when lubricant was added. The dissolution of furosemide was determined by the amount of drug which dissolved on the surface of the carrier particles, since the tablets disintegrated. Furthermore, at the lowest concentration of the lubricants, magnesium stearate proved superior to Pruv® for disintegrating carrier systems. This discrepancy could be attributed to the higher $(DR_i)_n$ of the magnesium stearate formulations. The negative impact of the hydrophobic magnesium stearate was, however, observed at higher concentration levels (2.0% w/w). The lower variation between different Pruv® concentration levels was the result of the hydrophilic nature of this lubricant.

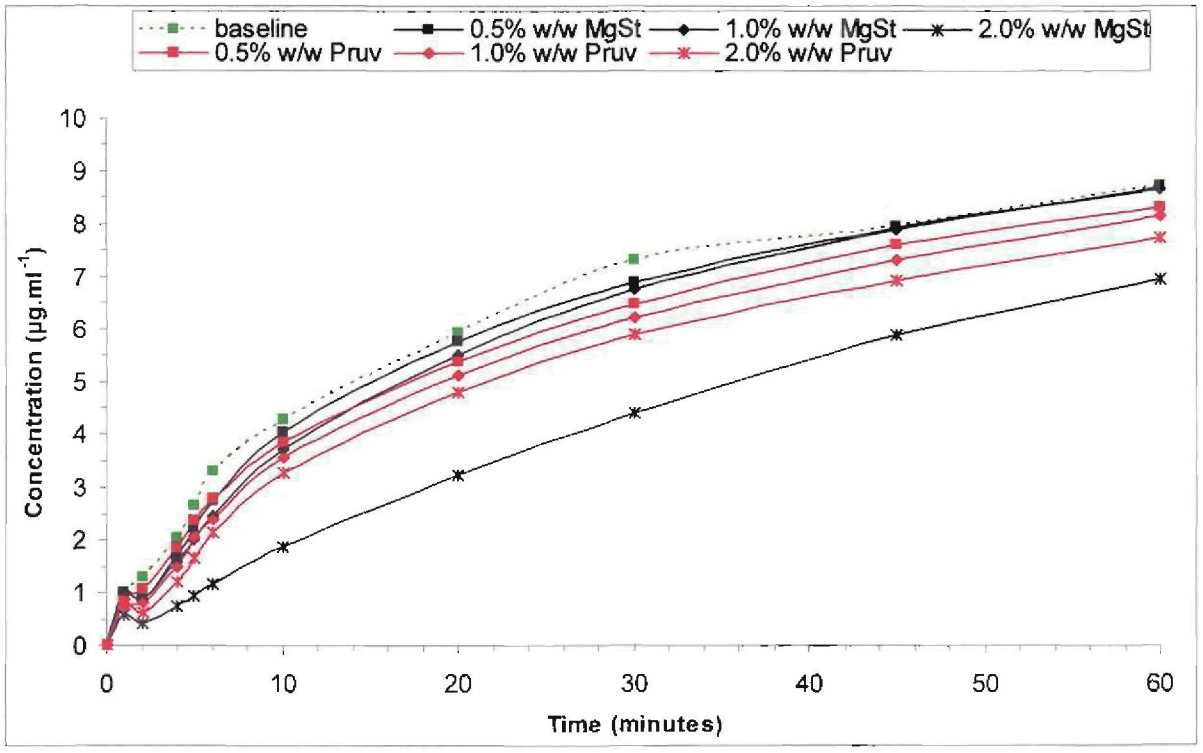


Figure 4.10: *Reference dissolution profiles for Avicel® tablets. Disintegrating formulations comprise of different lubricant (magnesium stearate [MgSt] or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

It should be noted that the initial improvement in drug release was due to drug particles on the tablet surface and not disintegrating properties. An increase in mixing time resulted in the same dissolution profile, but with less variation between Pruv® concentration and more variation among different levels of magnesium stearate. This stemmed from the better surface coverage of magnesium stearate upon carrier particles with increased mixing.

Both the lubricants showed erratic dependencies of DR_i on disintegration time. Therefore, rapid disintegration could not be seen as the sole determinant of DR_i and therefore, neither of AUC. Due to the prodigious disintegration of all formulations the exposed surface area of tracer particles were maximized and surface area played a lesser role in dissolution efficiency than did DR_i. However, two continuances regarding the dependence of $(AUC)_n$ on $(DR_i)_n$ were found – one for magnesium stearate formulations, the other for Pruv® (figure 4.11). Neither magnesium stearate nor Pruv® formulations illustrated a significant linear dependence ($r^2 < 0.9$) of $(AUC)_n$ on $(DR_i)_n$. On closer inspection, the slope of both formulations corresponded closely to one another (~ 0.5), indicating the same tendency that a decrease in AUC resulted from a decrease in DR_i.

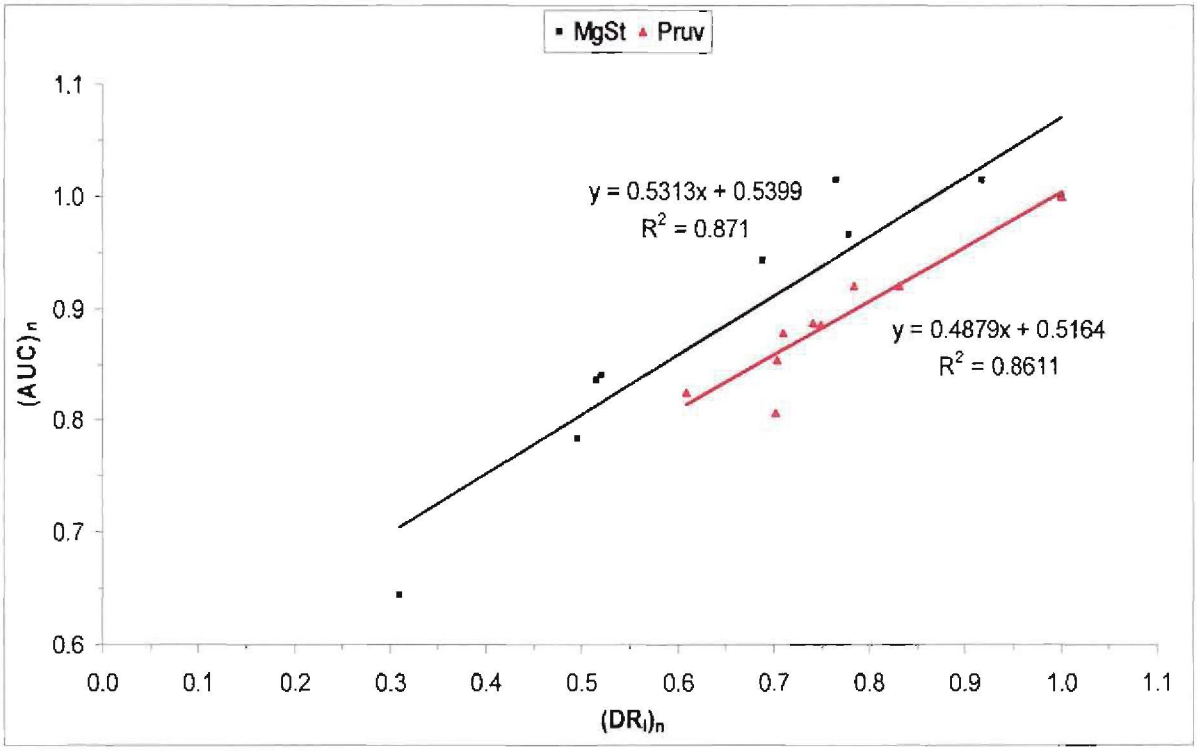


Figure 4.11: *The dependence of the extent of dissolution $(AUC)_n$ on the initial rate of dissolution $(DR_i)_n$ for Avicel® tablets with different lubricant (magnesium stearate [MgSt] or Pruv®) concentration levels mixed for 4 minutes at 69 rpm. Real data points were utilized to construct linear regression trendlines.*

Some conclusions were made regarding figure 4.11. The decline seen in the extent of dissolution for the magnesium stearate formulations could primarily be attributed to the decrease in the DR_i. Various factors could affect DR_i and will be discussed in some detail. The gradient of the curve could be described as a system constant indicating the sensitivity of change in $(AUC)_n$ to change in $(DR_i)_n$. The constant could most probably be a lubricant disintegration dependent constant. The mere presence of lubricants implicated a constant dependence of $(AUC)_n$ on $(DR_i)_n$ and the magnitude of this dependency was altered by modifications in $(DR_i)_n$. In turn the changes in $(DR_i)_n$ could most likely be attributed to formulation variables. Since only the first 6 minutes ($t_0 - t_6$) of the dissolution profile was used to calculate the DR_i (section 2.5.5.2), it might prove a phenomenal timesaving measure to predict the success of a lubrication formulation regarding its dissolution altering.

The addition of magnesium stearate resulted in a significant alteration in the $(AUC)_n$ (figure 4.12). The $(DR_i)_n$ parameter followed the same pattern compared to the reference rate (figure 4.13). Two important conclusions could be made regarding this observation. The $(AUC)_n$ did correspond linearly to the $(DR_i)_n$ and lubricants decreased the solubility of the tracer in a disintegrating carrier system. The decrease in $(DR_i)_n$ could be attributed to an increase in viscosity of the microenvironment and the decrease in $(AUC)_n$ due to the solubilization effect.

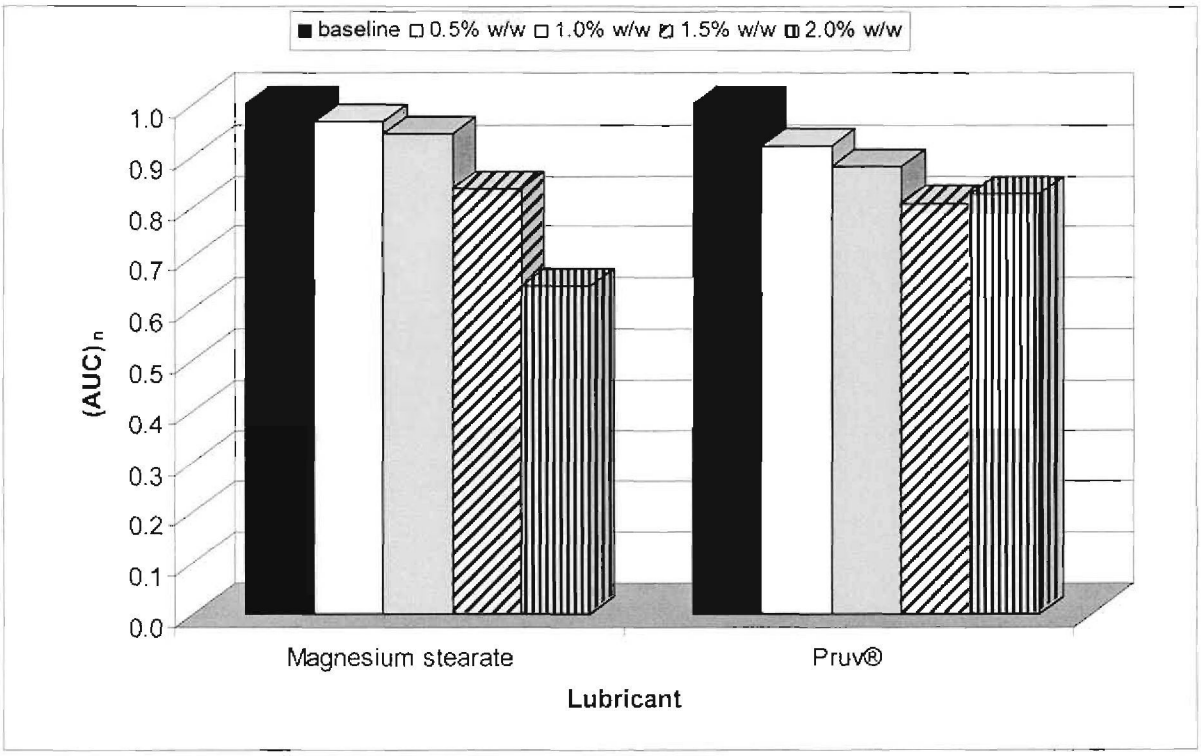


Figure 4.12: *$(AUC)_n$ of Avicel® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

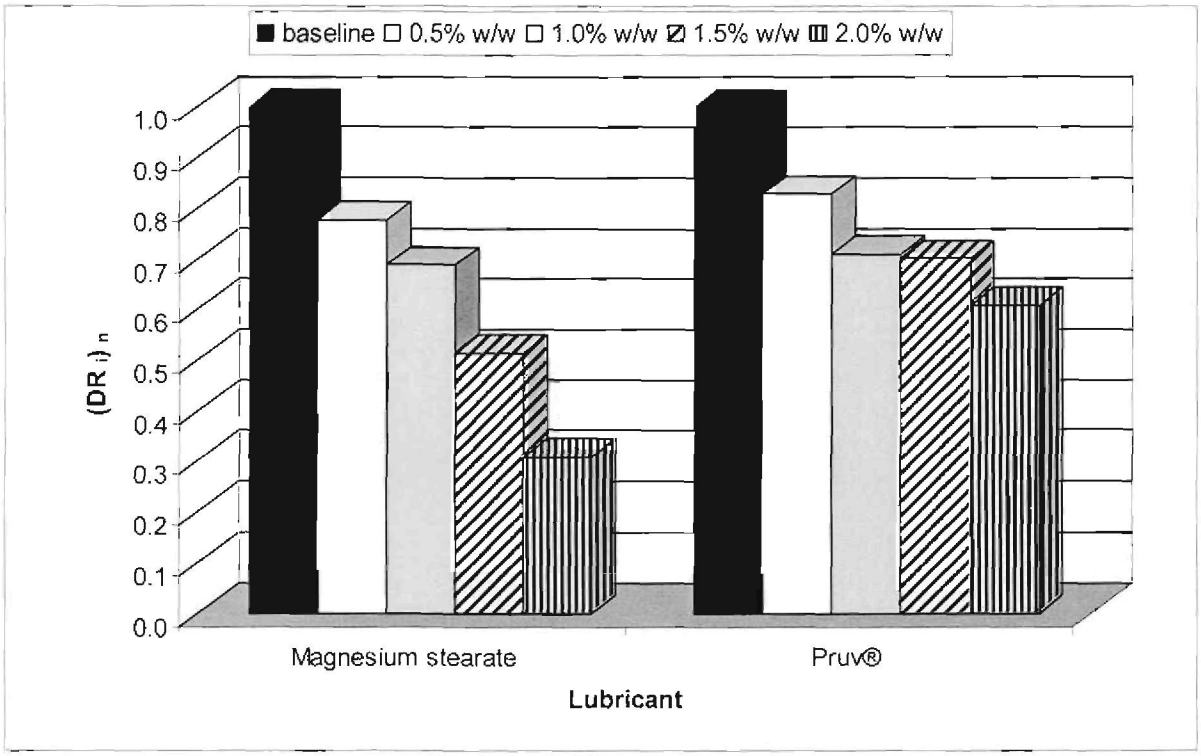


Figure 4.13: *$(DR_i)_n$ of Avicel® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

The addition of Pruv® affected a decrease in AUC to a level comparable to that of magnesium stearate. Coinciding with this observation was an decrease in $(DR_i)_n$. The hydrophilic nature of Pruv® most probably resulted in a comparatively more hydrophilic tablet interior than found for the magnesium stearate formulations. Consequently, a larger quantity of the dissolution medium could be sorbed into the tablet which increased wetting and dissolution of tracer particles.

The increase in mixing time affected an increase in $(AUC)_n$ and $(DR_i)_n$ for magnesium stearate formulations and a decrease for Pruv® formulations. This indicated the sensitivity of both lubricants towards mixing conditions. The increase in mixing time towards the 8 minute level gave the same results obtained for the 4 minute level, but with a positive effect towards both dissolution parameters for formulations containing magnesium stearate and the opposite for those containing Pruv®. The alteration in both parameters was, however, still in agreement with the contributions of both mixing time and lubricant concentration variables. The addition of mixing time gave rise to more film formation of lubricant on the carrier particle, resulting in more negative water wettability and disintegration. A hydrophobic nature and decreasing particle wetting consequently forestalled the negative effects imparted by magnesium stearate, therefore the $(AUC)_n$ was declined to the baseline formulation.

It should be realized that the disintegrating formulations produced good dissolution profiles. Nonetheless it presented basic notions on the decrease of dissolution that could be applied in the non-disintegrating systems. It was seen that the $(DR_i)_n$ could be altered by formulation variables other than the lubricant.

The surface area of lubricants might be the most important parameter to monitor, in terms of lubricant efficiency and tablet wettability. Lubricants with high surface areas might be more sensitive to changes in mixing time than lubricants with low surface areas. Thus, if a particular drug or formulation is deleteriously affected by prolonged mixing of lubricants, adequate characterizations and monitoring of a lubricant surface area should be an integral part of product development and quality control.

Effective surface coverage (equation 1.18) has been estimated by comparing the dissolution rate of unlubricated tracer tablets to that of lubricated tracer tablets. Magnesium stearate had definitely the biggest surface coverage (figure 4.14), especially at higher concentrations (2.0% w/w) as a result of its bigger surface area compared to Pruv®.

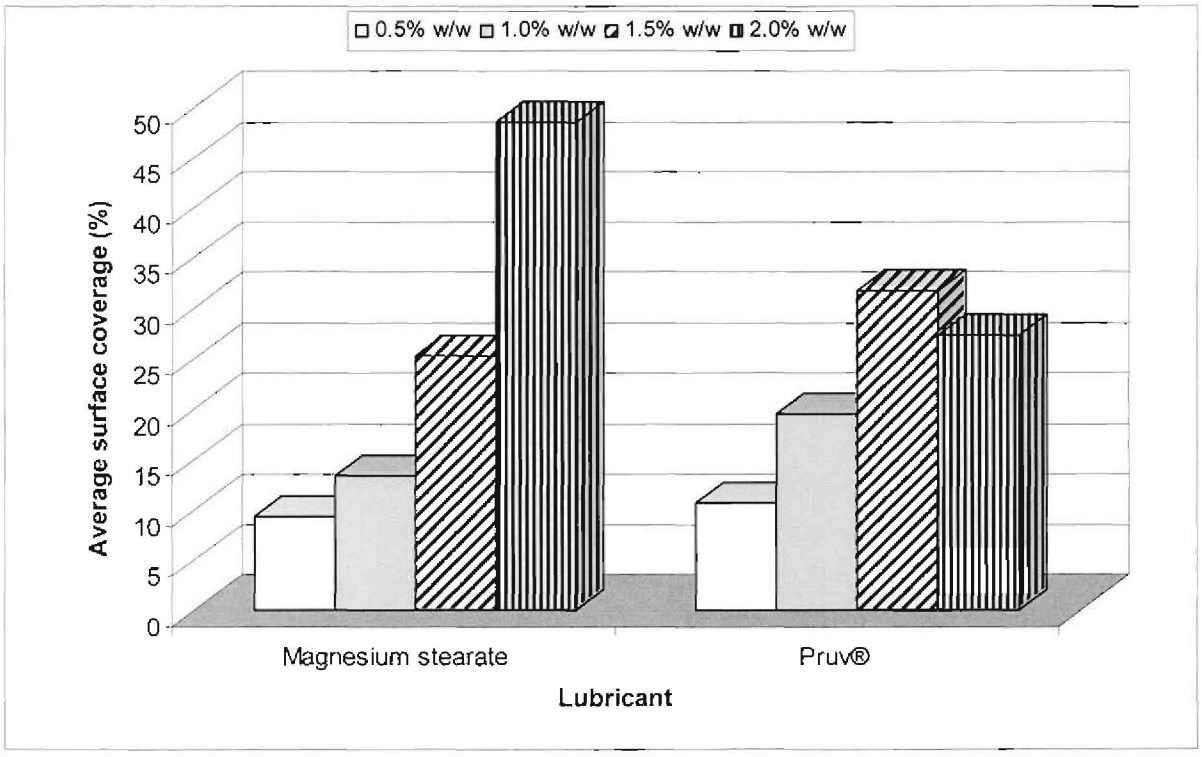


Figure 4.14: *Average surface area of Avicel® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

Pruv® covered Avicel® particles better at lower concentration as a result of smaller particle size, but at higher concentrations the effect of cohesive forces between lubricant particles

caused agglomeration and poor lubricant distribution and thus the conclusion that longer mixing times had to be applied for effective Pruv® distribution. Prolonged mixing decreased the surface coverage due to a larger surface of separation (or an increase in carrier surface area).

At first glance, it would seem that the $(AUC)_n$ of formulations could be correlated to the average surface coverage (figure 4.15). Both the disintegrants showed erratic dependencies of $(AUC)_n$ on average surface coverage. Therefore, surface coverage could be seen as one of the determinants of $(AUC)_n$. Due to the prodigious disintegration of all formulations it was supposed that exposed surface area played a lesser role in dissolution efficiency than for non-disintegrating carrier systems. However, two continuances regarding the dependence of $(AUC)_n$ on surface area for disintegrating carrier systems were found – one for magnesium stearate formulations, the other for Pruv®. Magnesium stearate formulations illustrated a significant negative linear dependence ($r^2 = 0.9483$) of $(AUC)_n$ on average surface coverage, whilst Pruv® formulations illustrated a less apparent dependence ($r^2 > 0.9475$). On closer inspection of lubricant formulations, the y-intercept corresponded closely to the $(AUC)_n$ of the baseline formulation (~ 1%) and linear equations could be derived for disintegrating carrier systems with magnesium stearate (equation 4.3) and Pruv® (equation 4.4).

$$(AUC)_n^f = -0.0082\,(\text{Average surface coverage})_n^f + (AUC)_n^y \qquad 4.3$$

where:

$(AUC)_n^f$ = predicted $(AUC)_n$ of magnesium stearate in disintegrating formulations, $(AUC)_n^y$ = calculated $(AUC)_n$ of the baseline formulation, $(\text{Average surface coverage})_n^f$ = Average surface coverage of magnesium stearate in disintegrating formulations.

$$(AUC)_n^f = -0.0058\,(\text{Average surface coverage})_n^f + (AUC)_n^y \qquad 4.4$$

where:

$(AUC)_n^f$ = predicted $(AUC)_n$ of Pruv® in disintegrating formulations, $(AUC)_n^y$ = calculated $(AUC)_n$ of the baseline formulation, $(\text{Average surface coverage})_n^f$ = Average surface coverage of Pruv® in disintegrating formulations.

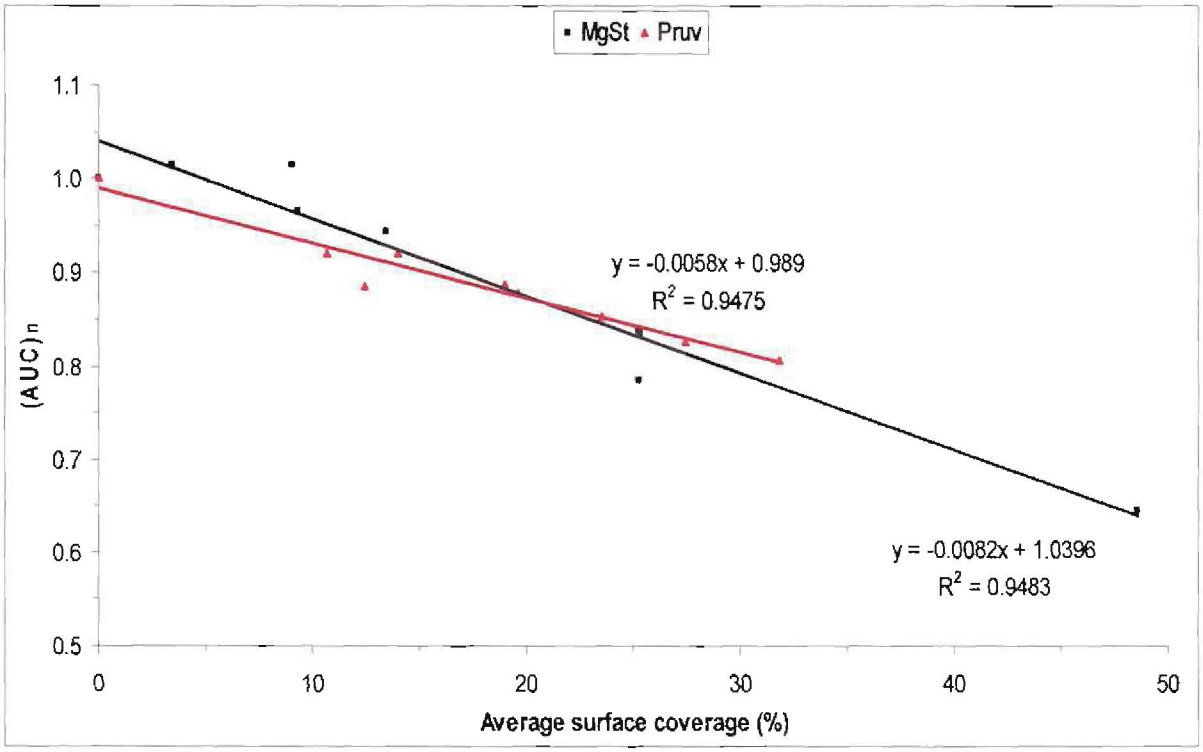


Figure 4.15: *The dependence of the extent of dissolution $(AUC)_n$ on the average surface coverage of disintegrating carrier systems (Avicel®) with different lubricant (magnesium stearate [MgSt] or Pruv®) concentration levels mixed for 4 minutes at 69 rpm. Real data points were utilised to construct linear regression trendlines.*

Some conclusions were made regarding equation 4.3 and 4.4. The improvement seen in the extent of dissolution for the formulations could primarily be attributed to the acceleration in the average surface coverage. The gradient of the curve could be described as a system constant indicating the sensitivity of change in $(AUC)_n$ to change in average surface coverage. The constant could most probably be a lubricant dependent constant. The mere presence of lubricants implicated a constant dependence of AUC on surface coverage and the magnitude of this dependence was altered by modifications in surface area. In turn the changes in surface area could most likely be attributed to formulation variables such as mixing time, lubricant concentration and particle size.

4.4.2.2 Non-disintegrating carrier systems (Tablettose® tablets)

When lubricants are incorporated into non-disintegration powder systems (Tablettose®), the true altering characteristics of the lubricant comes into play. Since Avicel® performs as Tablettose® would in the presence of disintegrants, the effect lubrication has on the disintegration and dissolution properties of filler/binder systems will be revealed for non-disintegrating systems. Disintegration of tablets containing Pruv® is dependent of mixing

time during blending of the tablet ingredients. Consequently prolonged mixing of formulations containing Pruv® did not alter dissolution of the tracer from tablets to the same extent as magnesium stearate did (figure 4.16).

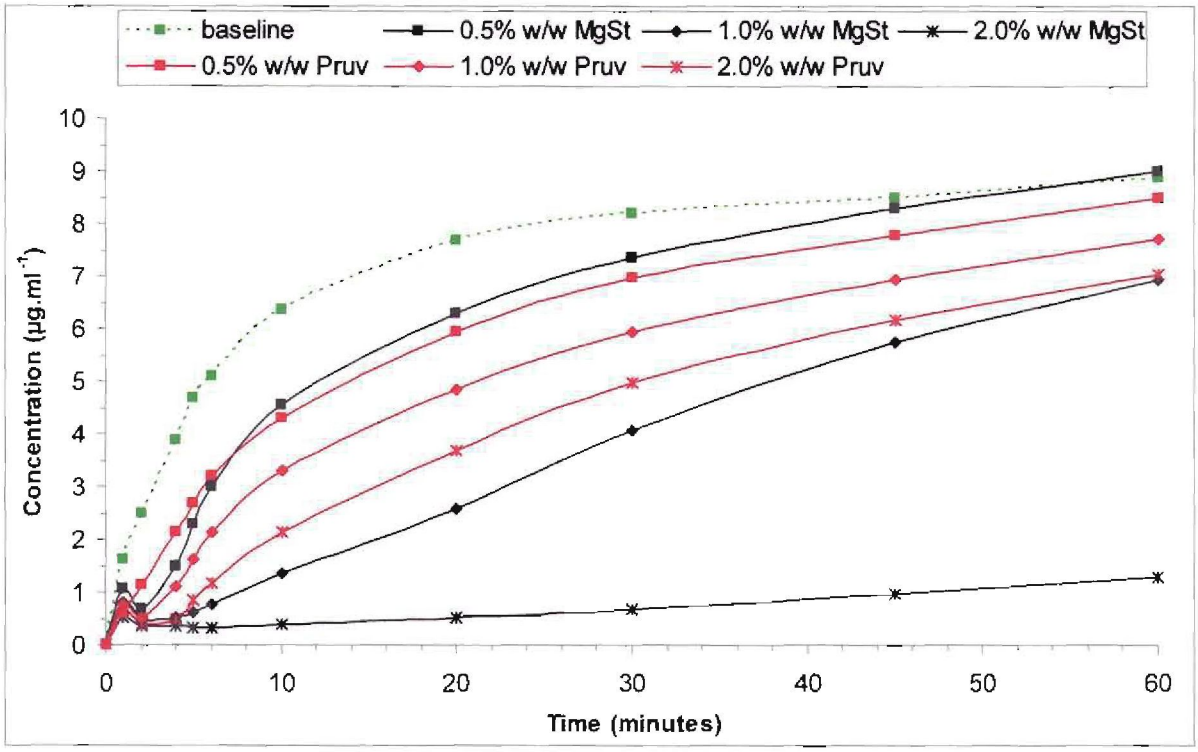


Figure 4.16: *Reference dissolution profiles for Tablettose® tablets. Disintegrating formulations comprise of different lubricant (magnesium stearate [MgSt] or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

The amount of tracer released into the dissolution medium (AUC) decreased with the addition of lubricants and mixing (figure 4.17), but to a much smaller extent for formulation containing Pruv® (44% variation compared to 91% variation for magnesium stearate). Formulations with Pruv® led to an average 50% increase in the amount of drug released compared to magnesium stearate. Prolonged mixing, however, did have an altering effect on the tablet strength, resulting in faster disintegration and thus better dissolution. Thus, as with other lubricants, attention should be paid to minimize the blending time.

The rate of drug release (DR_i) followed the same pattern AUC did for hydrophobic lubricants (magnesium stearate), but for hydrophilic lubricants (Pruv®) mixing time increased the drug release rate as a result of better surface coverage (figure 4.18). The Pruv® concentration level, however, also had a negative impact on drug release. The initial slow release of drug from Pruv® formulations compared to magnesium stearate was proof of the poor surface

coverage of Pruv®. At the 8 minute mixing condition, concentration levels resulted in the same phenomena observed for the 4 minute level, but to a larger extent.

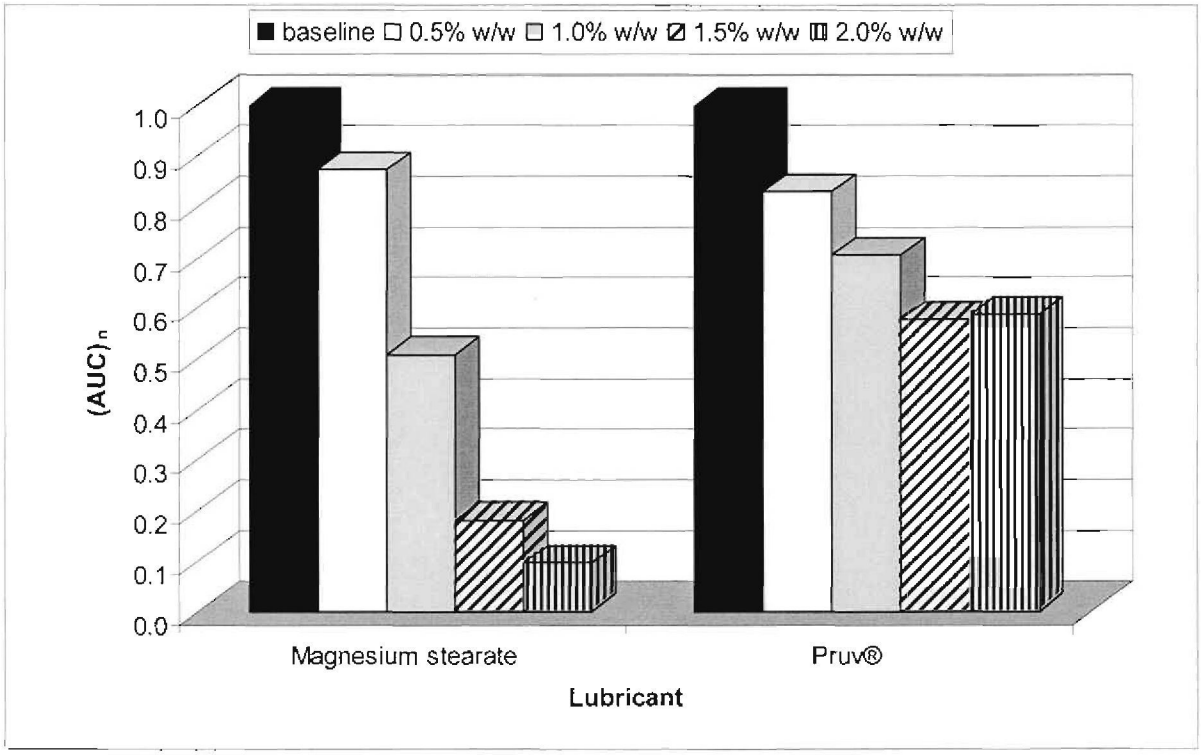


Figure 4.17: *$(AUC)_n$ of Tablettose® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

The same observation and conclusions towards non-linearity between $(AUC)_n$ and $(DR_i)_n$ for Tablettose® tablets could be made as was seen from figure 4.11 for Avicel® tablets. However, the relationship was smaller for non-disintegrating than for disintegrating systems (figure 4.19). The notable observation was actually the crossing of formulation trendlines. This crossing indicated that for poor disintegrating formulas of Tablettose®, drug substances are quicker being released for formulations containing hydrophilic lubricants, but as the amount of drug released increased, the rate of drug release decreased. This could be seen in that Pruv® formulations had a slower drug release and lower plato than low concentration magnesium stearate formulations, but the opposite was also true for formulations with high amounts of hydrophobic lubricants.

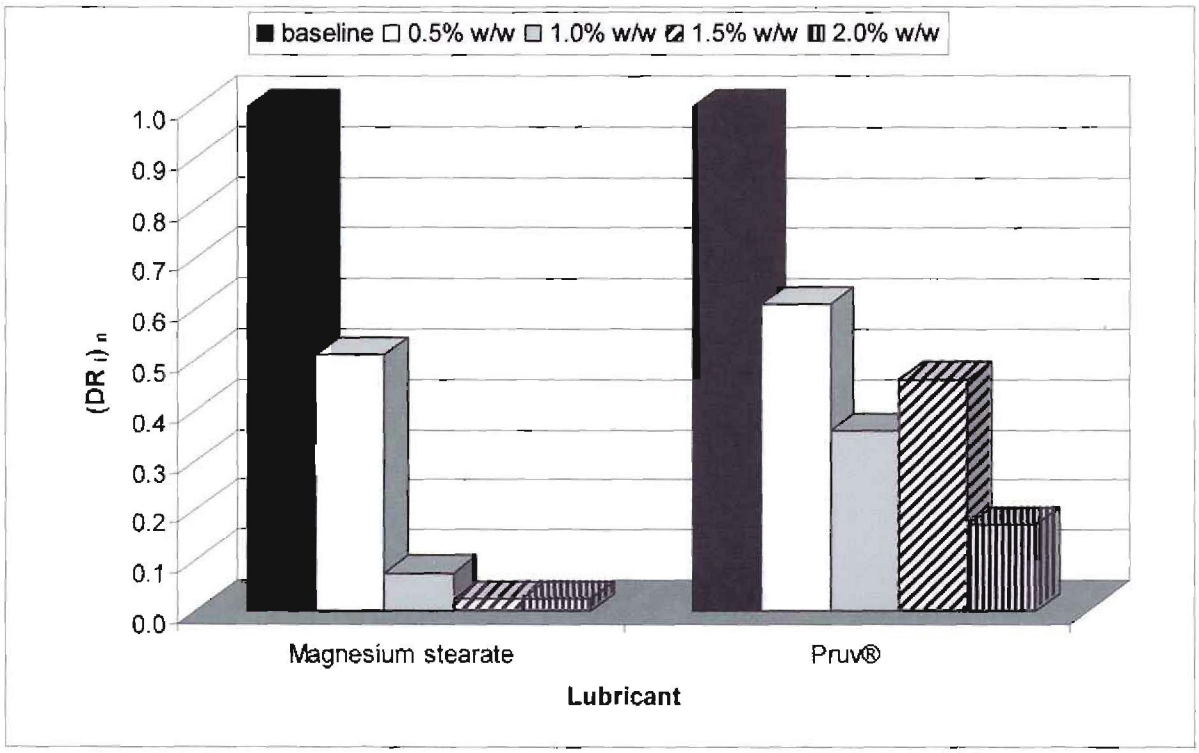


Figure 4.18: *$(DR_i)_n$ of Tablettose® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

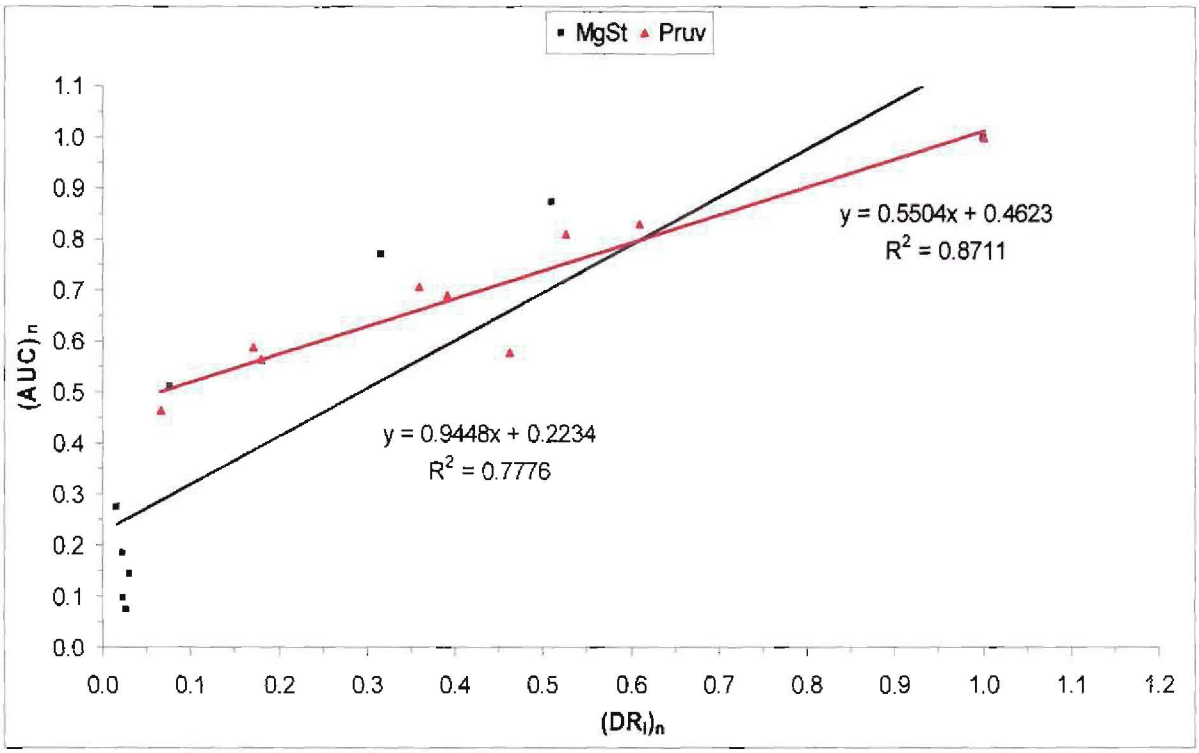


Figure 4.19: *The dependence of the extent of dissolution $(AUC)_n$ on the initial rate of dissolution $(DR_i)_n$ for Tablettose® tablets. Real data points were utilized to construct linear regression trendlines.*

Effective surface coverage (equation 1.18) has been estimated by comparing the dissolution rate of unlubricated tracer tablets to that of lubricated tracer tablets. Superior surface coverage was again observed for magnesium stearate (figure 4.20) at all concentration ranges when incorporated with Tablettose® tablets, as a result of its bigger surface area compared to Pruv®.

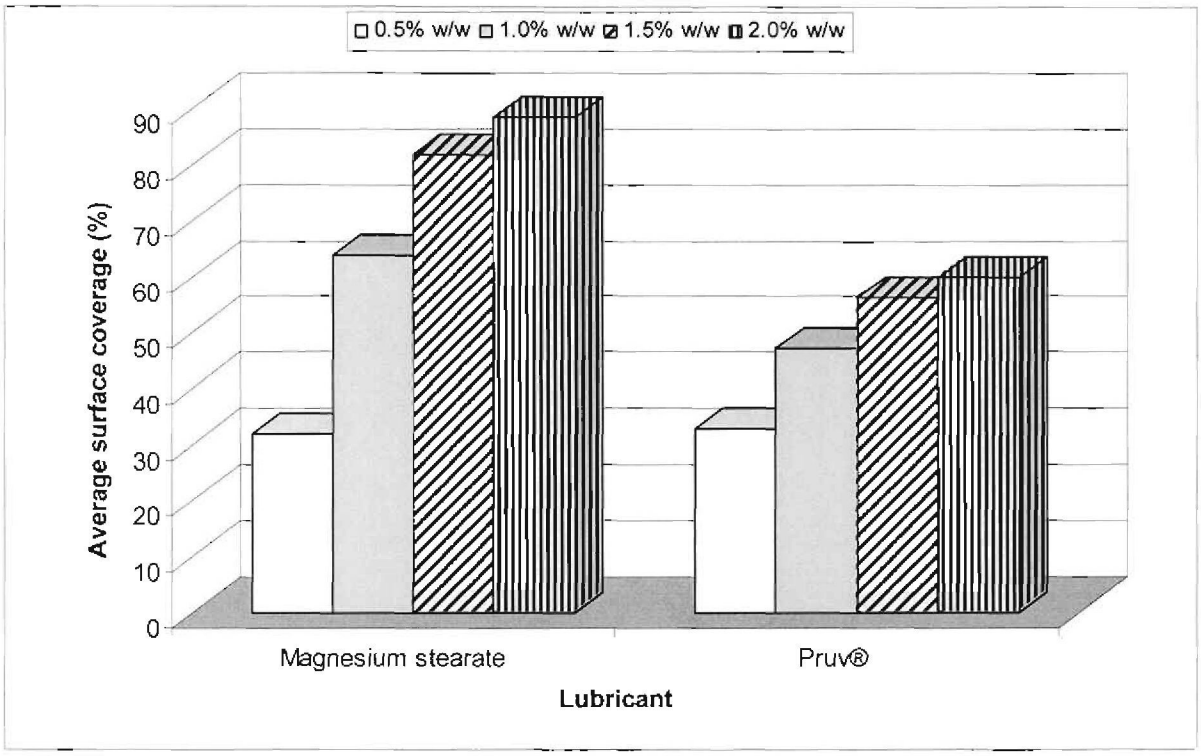


Figure 4.20: *Average surface area of Tablettose® tablets comprising of different lubricant (magnesium stearate or Pruv®) concentration levels mixed for 4 minutes at 69 rpm.*

Pruv® covered Tablettose® particles better at lower concentrations as a result of smaller particle size, but at higher concentrations the effect of cohesive forces between lubricant particles caused agglomeration and poor lubricant distribution and thus the conclusion that longer mixing times had to be applied for effective Pruv® distribution. Prolonged mixing decreased the surface coverage due to a larger surface of separation (or an increase in carrier surface area).

The same dependence of $(AUC)_n$ on the average surface coverage could be seen for both magnesium stearate and Pruv® in non-disintegrating carrier systems (figure 4.21). Again both the disintegrants showed erratic dependencies of $(AUC)_n$ on average surface coverage. Therefore, surface coverage could be seen as one of the determinants of $(AUC)_n$ and linear equations could be derived for non-disintegrating carrier systems with magnesium stearate (equation 4.5) and Pruv® (equation 4.6) as was the case with disintegrating carrier systems.

$$(AUC)_n^f = -0.0113\,(\text{Average surface coverage})_n^f + (AUC)_n^y \qquad 4.5$$

where:

$(AUC)_n^f$ = predicted $(AUC)_n$ of magnesium stearate in non-disintegrating formulations, $(AUC)_n^y$ = calculated $(AUC)_n$ of the baseline formulation, $(\text{Average surface coverage})_n^f$ = Average surface coverage of magnesium stearate in non-disintegrating formulations.

$$(AUC)_n^f = -0.0078\,(\text{Average surface coverage})_n^f + (AUC)_n^y \qquad 4.6$$

where:

$(AUC)_n^f$ = predicted $(AUC)_n$ of Pruv® in non-disintegrating formulations, $(AUC)_n^y$ = calculated $(AUC)_n$ of the baseline formulation, $(\text{Average surface coverage})_n^f$ = Average surface coverage of Pruv® in non-disintegrating formulations.

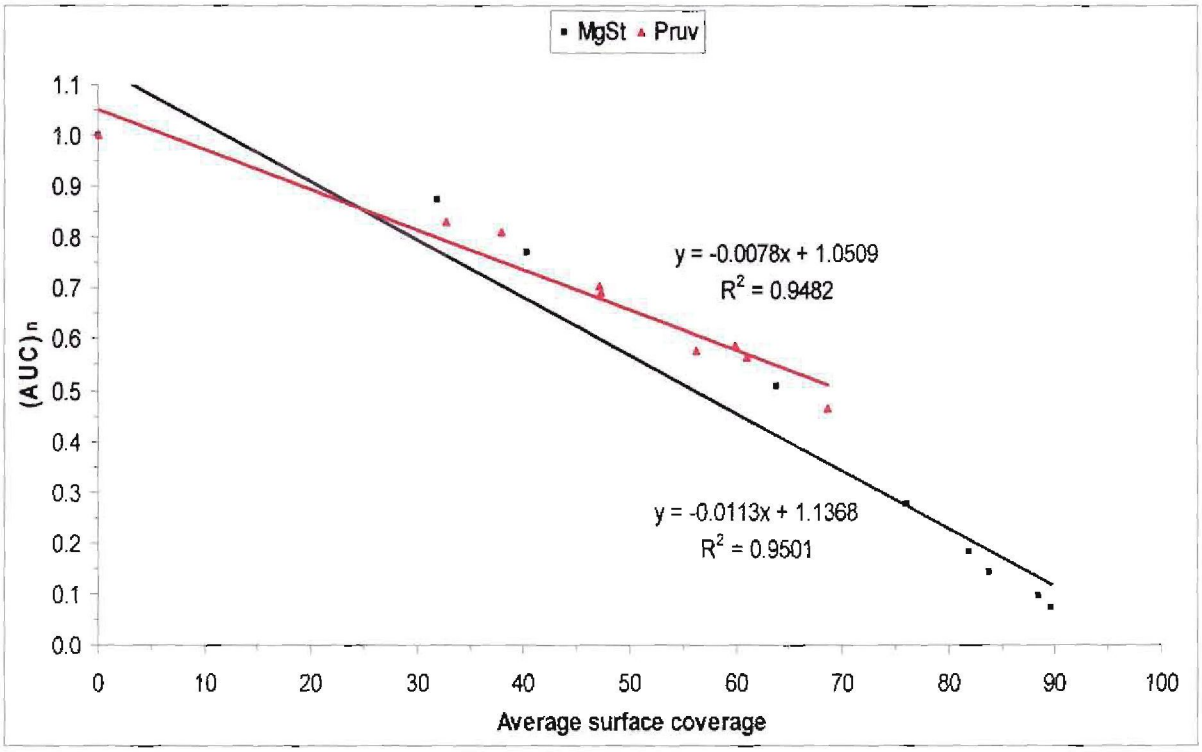


Figure 4.21: *The dependence of the extent of dissolution $(AUC)_n$ on the average surface coverage of non-disintegrating carrier systems (Tablettose®) with different lubricant (magnesium stearate [MgSt] or Pruv®) concentration levels mixed for 4 minutes at 69 rpm. Real data points were utilised to construct linear regression trendlines.*

4.4.2.3 Conclusion

It may be concluded from the results of this investigation that tablet lubricants could retard the dissolution of drugs from compressed tablets. The magnitude of this effect may be expected to depend, among other factors, upon the particular lubricant, its concentration, its particle size, the drug, the tablet formulation, various processing variables, the conditions (particularly with respect to aggravated intensity) under which dissolution is taking place, and the surface coverage of the lubricant.

The difference in drug release properties for disintegrating and non-disintegrating carrier systems differs as a result of the water-solubility characteristics of the lubricant incorporated. Magnesium stearate decrease drug release and the rate at which this process takes place due to the hydrophobic film formation of lubricant upon carrier particles. This lubricant affected disintegrating carrier system to a much smaller extent than non-disintegrating carrier systems. Pruv® also decreased the amount of drug released from disintegrating filler systems, but with less variation between increasing concentration levels. The small decrease is due to the hydrophilic nature of this lubricant and the decrease a result of increasing surface tension. Hydrophilic lubricants apparently do not retard dissolution and, if they have surface tension lowering capability, they may enhance the rate of dissolution of drugs contained in non-disintegrating compressed tablets with prolonged mixing as a result of larger surface of separation.

4.5 CONCLUSION

Lubrication had a negative impact on tablet hardness, but Pruv® increased the tablet strength when incorporated at low concentrations (0.5% w/w) under the optimum mixing conditions. Tablet hardness increased as mixing times increase, with the opposite effect when magnesium stearate was used. This was also confirmed by Rizk *et al.* (1995:61) and could be attributed to the decrease in friction and the formation of interparticulate bondings due the hydrophilic nature of Pruv®. The negative effect mixing and lubricant concentration had on tablet strength was due to less interparticulate bonding and more surface of separation as a result of mixing. Altered disintegration was due to the water-wettability characteristics of the lubricants, with Pruv® affecting disintegration less than magnesium stearate. The negative impact of hydrophilic lubricants on disintegration was due to fewer capillaries between carrier particles, inhibiting water distribution and uptake.

Increasing lubricant concentration and mixing energy was found to be weakening factors contributing to weaker tablets and increasing disintegration times. The drug release (AUC)

and rate of release (DR_i) were also negatively affected by lubricant concentration increases and prolonged mixing. Pruv® increased drug release with an average of 50% when incorporated in non-disintegrating carrier systems compared to the same amount of magnesium stearate. By comparison to magnesium stearate, a less hydrophobic film is formed around excipient particles, resulting in better drug release. Thus Pruv® is particularly suitable for those formulations where rapid dissolution is desirable and magnesium stearate seems problematic towards drug release.

The lubricants affected different carrier systems to varying levels. Disintegrating and non-disintegrating systems was affected in opposing directions, with the first less affected by the retardant disintegration effect of lubricants due to its disintegration mechanism. The true effect lubricants have on filler systems was best viewed in non-disintegrating systems like Tablettose®. Emcompress® was least affected by lubrication due to its fragmented particle structure.

From the physical characteristics evaluated it is evident that due to the negative effect magnesium stearate had on disintegration and dissolution, it should be kept at a minimum of 0.5% w/w. Due to its poor lubrication and surface coverage characteristics, Pruv® performed best at a higher optimum concentration of 1.0% w/w. This is contradictory to the recommended 1.5 - 2.0% w/w concentration range as was suggested by the manufacturers (Mendell, 2002:5). Optimum mixing conditions was found to be 4 minutes at 69 rpm for all carrier systems evaluated.

CHAPTER 5

Evaluation of lubricant efficiency

5.1 INTRODUCTION

The addition of a lubricant to a tablet formulation reduces the coefficient of friction between the granulation and the die, the transmission of force between the upper and lower punches and the die wall becomes more efficient, and the force required to eject the finished tablet is reduced.

These changes are sometimes readily observed, but as with any scientific evaluation, a quantitative method for evaluation is needed to evaluate the effect of different lubricant types and concentrations for different powder systems. The best quantitative measurement so far found is the evaluation based on resolution of forces in compaction, measured from die wall stresses with strain gauges, as described in section 1.3.4. From section 1.3.4 the friction coefficient of lubricants could be calculated and lubricant efficiency could be measured. The problem was that an instrument had to be assembled for these measurements, as die wall stress is probably one of the least well-characterized measurements in the area of tablet compression. The reason being that tablet technology, from formulation to production, involves many problems of measurement and control and its implementation is usually one of the responsibilities of the pharmacist. Instrumentation, on the other hand, has its roots in engineering, physics, and electronics. There has been little work of reference that could conveniently bridge this gap between disciplines. A book by Watt (1988:289) was, however, a guideline for the unaware and unwary, and proved to be of immense value in this regard – *a sine qua non*.

It has been possible to assess such variables as punch force, displacement, and temperature, without much alteration to the normal mechanical operation of the tableting machine, but it has proved much more difficult to estimate die wall stress without such alteration. The main reason for this has been that the stress levels at the outer edge of the die are too low to give adequate signals from foil strain gauges, and it has therefore been necessary to produce modified dies with local concentrations of stress. Removing some of the metal from the die is one way of achieving this, and strain gauges applied to the thinned regions are then able to provide larger signals.

Various schemes for the modification of standard dies have been proposed, but most of these are open to some criticism on the grounds that they affect either the compaction itself,

or that they give results of debatable reliability. It is, nevertheless, interesting to consider, briefly, the methods that have been used to set about this measurement, starting with the earliest published work in this area.

5.2 INSTRUMENTATION FOR FRICTION MEASUREMENT

As already explained (section 1.3.4.3), the Windheuser segmented die was the most practical and appropriate instrumentation model for this study. Apart from construction, the main purpose was to compensate for shortcomings, i.e. segmented die and temperature compensation, of this model. Another shortfall of this model was technology related, since there were no computerized systems in 1963. Thus, a computer interface had to be designed to replace their Sanborn magnetic oscillograph. To compensate for temperature changes a Wheatstone bridge circuit, was used (by Windheuser), but with four strain gauges (two sets).

5.2.1 CYLINDRICAL DIE DESIGN AND COMPRESSION SET-UP

Since one of the pitfalls of the segmented die was the segmented shape which distort asymmetrically under load retaining its original circular symmetry was a good alternative. From studies done by Kruger (2000:29) the optimum length, thickness and diameter of the die was determined as outlined in figure 5.1. The basics of that model were adapted to fit the requirements for this study.

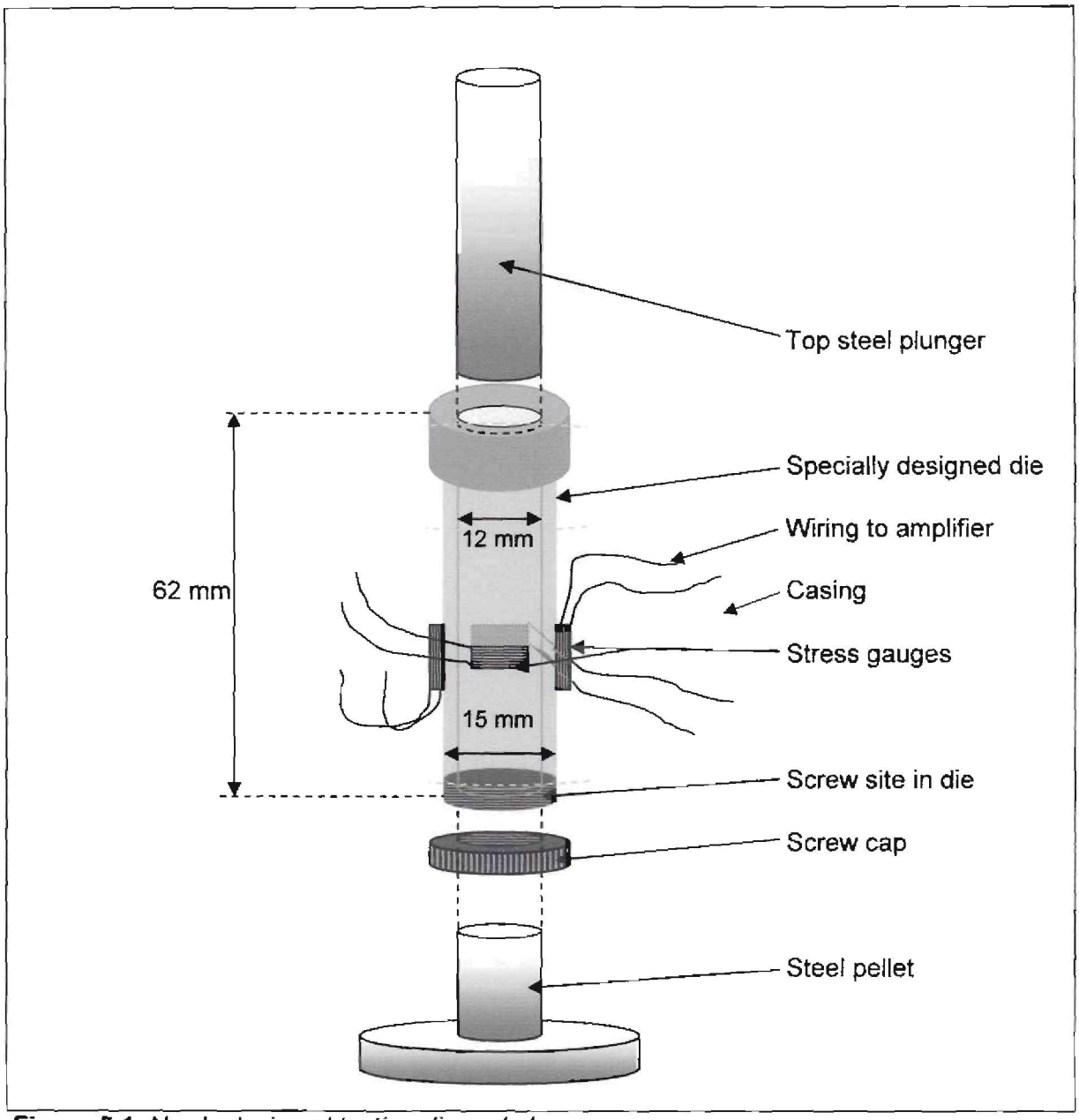


Figure 5.1: *Newly designed testing die and plungers.*

Four strain gauges (EA-06-031DE-120, Micro Measurements, Raleigh, NC) were fitted with epoxy resin to the die wall, opposing each another from four sides, with every second gauge tangential to the first gauge per set. The strain gauges were fitted on the sensing area where the tablets had to be compressed, that was about 1-2 millimetres above the depth of the steel pellet when inserted into the die. The oil reservoir used previously by Kruger (2000:29) was still used but only as a casing to cover the strain gauges and to mount electronic wiring. It was also a perfect fit for the steel pellet and upper steel plunger (punch). The die fitted perfectly into the casing and was screwed into place at the bottom of the casing with a screw cap on the bottom of the die. The new die was machined from stainless steel and the plunger and pellet were made from hardened steel.

Die newly designed test die (figure 5.1) was connected to the rest of the set-up as outlined in figure 5.2.

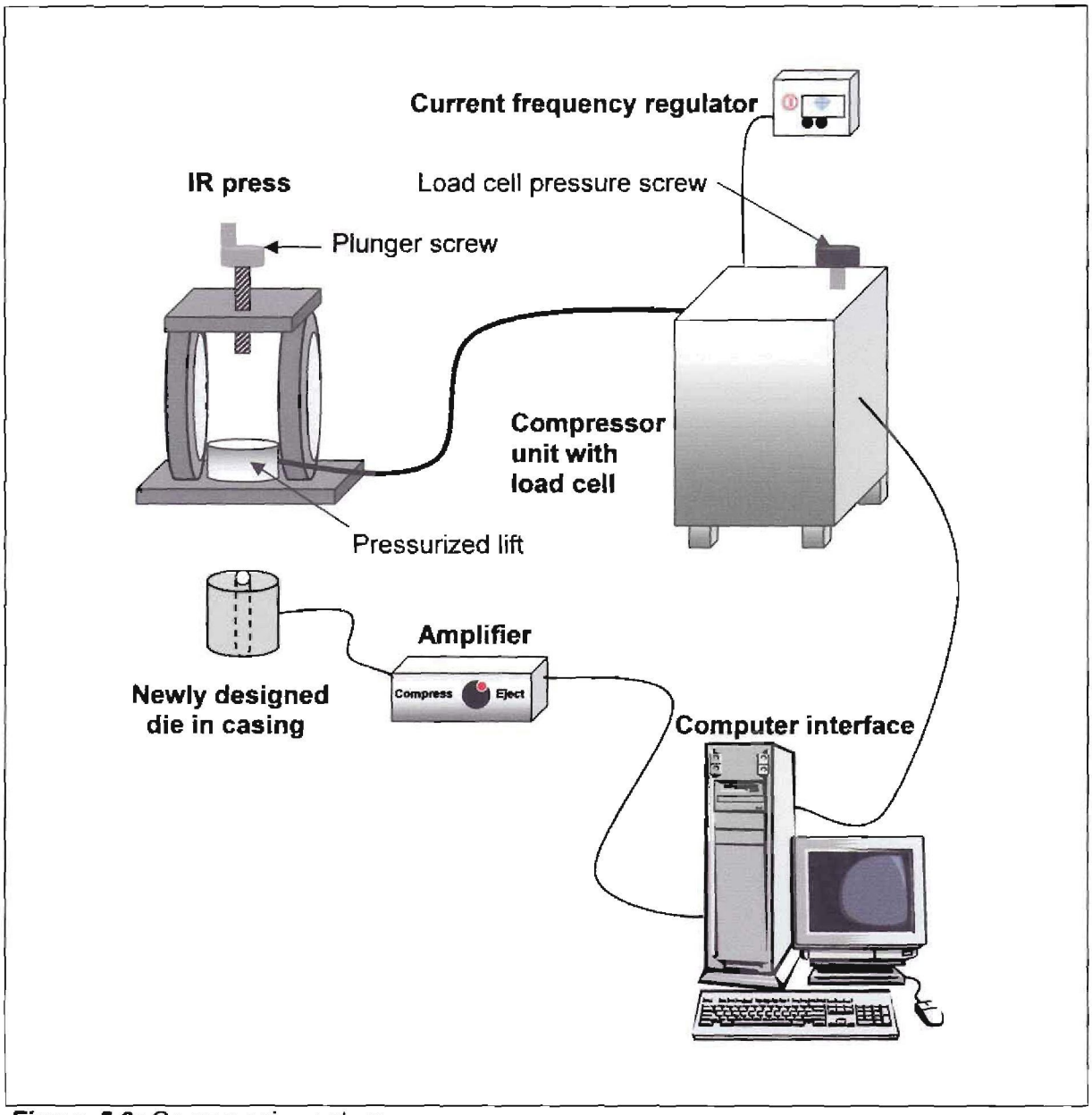


Figure 5.3: *Compression set-up*

A compressor fitted to the hydraulic (IR) press was instrumented with an electronic load cell (pressure gauge) to establish the axial pressure load during compression. This pressure was also regulated via a pressure intake system, controlled with a knob, and the compression frequency was controlled by an electric current regulator, with a range of 0 – 50 Hz. This was used to slow the ejection phase of the tableting process, so that the initial amount of pressure needed to start ejection could be registered. All signals were sent to the computer. A computer interface was designed in Visual Basic® 6 on a Windows® 98 platform.

5.3 MEASUREMENT OF FORCES IN THE TABLET DIE

Results from preceding chapters showed that the concentration of lubricants and the degree of mixing influence the agglomerate breakdown of magnesium stearate. The efficiency of the lubricant can also be affected by the spreading of the lubricant upon ejection of the tablet, the affinity for the tablet surfaces and the die wall and the migration stage of the lubricant in the tablet mass during the compaction stage.

It is customary to add lubricants as the last step in tablet formulations before compression because they must be presented on the surface of the granules and between the granules and the compression parts of the tableting machine. The measurement of the coefficient of lubrication (R-value) and a calculation of the coefficient of friction could therefore provide useful parameters to evaluate the efficiency of the lubricant during the compaction stage.

5.3.1 CALIBRATION OF COMPRESSION SET-UP

Calibration of the system was done according to the method described in section 2.5.6.3. Soft rubber was used to calibrate the system at 7, 8, 9 and 10 bar respectively, and results are graphically presented (figure 5.3).

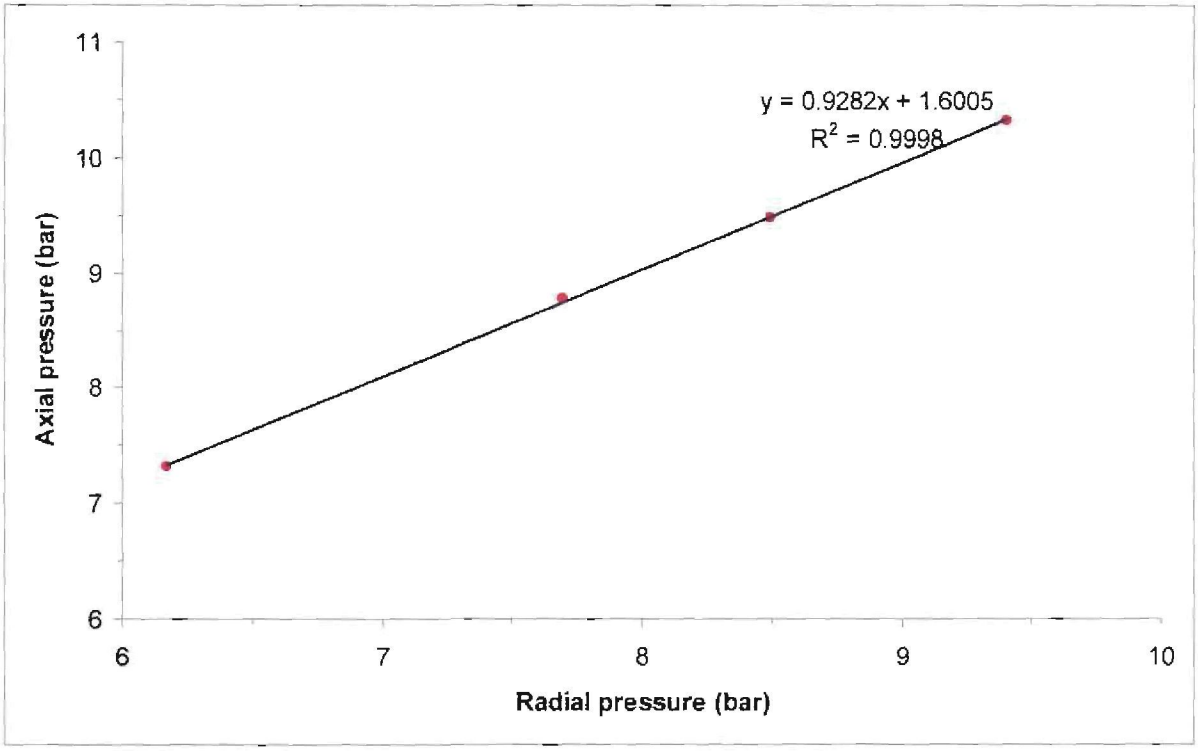


Figure 5.3: *Calibration curve.*

The axial pressure load was measured from the load cell, but the radial pressure had to be calculated according to the axial reference from the assumption that for a perfect elastic system, the amount of pressure being put into the system, will distribute evenly in all directions, and thus if 10 bar pressure was applied, the radial output signal could be interpreted as 10 bar pressure. The calibration curve was used to relate a certain radial pressure to an output signal according to the following (equation 5.1).

$$S_i = 0.9285\, S_0 + 1.6005 \qquad 5.1$$

where:

S_i represents the input signal and S_0 the output signal.

From equation 5.1, the input radial pressure (true pressure experienced by the strain gauges) could be calculated with the substitution of the radial pressure measured (S_0). These results were repeatable with a correlation coefficient of 0.9998 between input and output signals and equation 5.1 was valid for all pressure ranges up to 12 bar. When testing surpassed this limit, variation in this relationship was experienced (figure 5.4) due to mechanical failure and extrusion of the die wall.

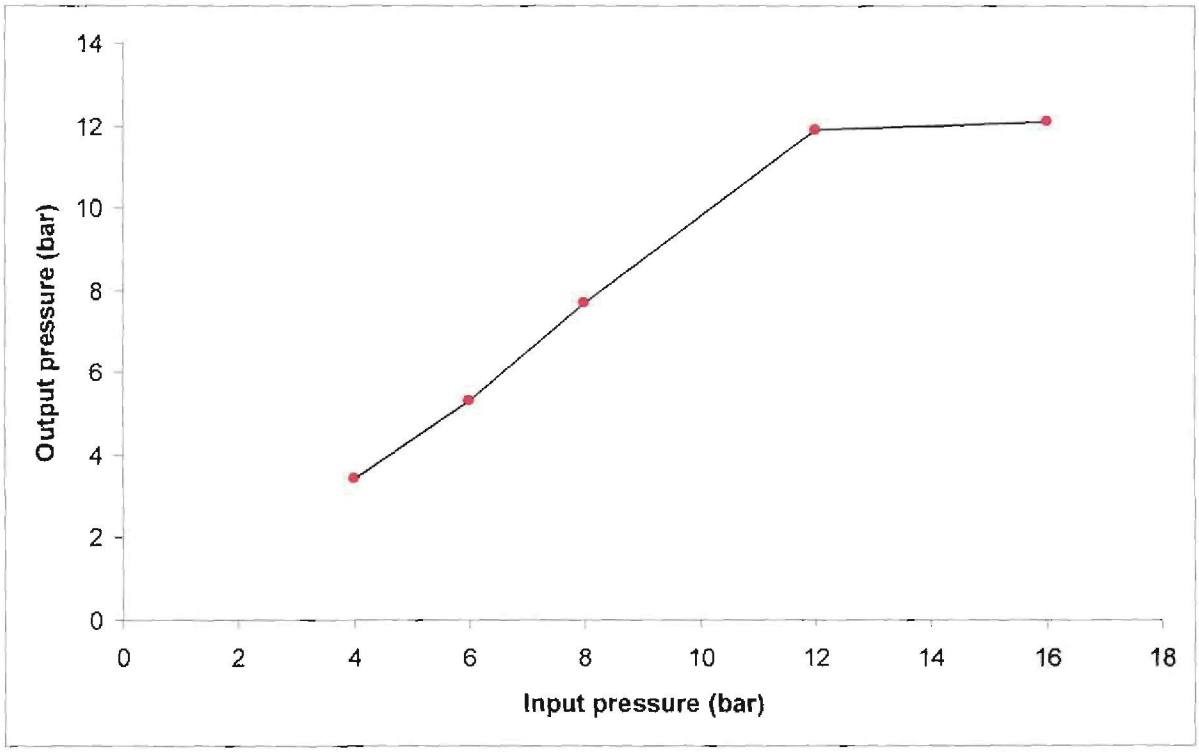


Figure 5.4: *Calibration curve indicating the relationship between input and output signals.*

5.3.2 MEASUREMENT OF LUBRICANT EFFICIENCY

It is assumed that adhesion of lubricant to the die wall occurred during compression of the first ten tablets as was previously explained in section 1.4.1.3. Therafter no adhesion was present and thus when tablets 11 – 15 were evaluated, equation 1.15 simplified to equation 1.7. Tablets were compressed from mixtures of filler (Avicel®, Emcompress® and Tablettose®) and lubricants (0.5 – 2.0 %w/w) which were mixed (4 and 8 minutes at 69 rpm) as described section 2.5.6. Results were amended in annexure D and the average friction coefficient (μ_w) and average R-value was calculated (table 5.1). The friction coefficient (μ_w) actually refers to the dynamic friction coefficient (μ_w') since this parameter is measured during the ejection process.

Table 5.1: *Lubricant parameters of Avicel® tablet formulations.*

Filler/binder			Compression phase			Ejection phase		
Lubricant	Mixing time (min)	Lubricant concentration (% w/w)	F_A (N)	F_R (N)	R-value	F_E (N)	F_D (N)	μ_w
No lubrication (baseline)			0.108	0.023	0.631	0.040	0.007	0.187
Magnesium stearate	4	0.5	0.110	0.027	0.579	0.043	0.010	0.231
		1.0	0.107	0.034	0.993	0.042	0.002	0.038
		1.5	0.109	0.032	0.912	0.043	0.002	0.045
		2.0	0.108	0.032	0.955	0.040	0.001	0.022
	8	0.5	0.108	0.033	0.781	0.042	0.004	0.104
		1.0	0.109	0.033	0.952	0.041	0.001	0.025
		1.5	0.109	0.034	0.929	0.041	0.001	0.034
		2.0	0.108	0.034	0.968	0.039	0.001	0.015
Pruv®	4	0.5	0.109	0.026	0.633	0.041	0.008	0.196
		1.0	0.108	0.024	0.664	0.036	0.006	0.170
		1.5	0.109	0.027	0.641	0.041	0.008	0.196
		2.0	0.108	0.028	0.672	0.037	0.007	0.190
	8	0.5	0.108	0.025	0.648	0.037	0.007	0.191
		1.0	0.108	0.027	0.665	0.034	0.006	0.171
		1.5	0.110	0.026	0.639	0.040	0.008	0.205
		2.0	0.108	0.029	0.672	0.037	0.007	0.187

F_A = Axial force; F_R = Radial die wall force due to confinement of powder mass in die; F_E = Ejection force; F_D = Radial force during ejection; μ_w = Friction coefficient

Lubricant efficiency is usually evaluated by calculating the ratio between the force applied on the upper punch (F_A) and the amount of force carried over to the lower punch (F_L). This ratio is better known as the coefficient of lubrication, or "R-value". Since the lower punch force was not measured, equation 1.10 was used to calculate the R-value. For that the friction coefficient (μ_w) had to be calculated with equation 1.7. The axial and radial pressures during compression and ejection were measured (table 5.1) and radial ejection forces were calculated using equation 2.10. Axial and radial ejection forces were used in calculating μ_w.

Unfortunately, Emcompress® and Tablettose® could not be evaluated due to their inability to be compressed in the absence of lubricants (this was not the case with Avicel®). This gave rise to very high ejection forces (7.439 bar for Emcompress® and 5.454 bar for Tablettose®) and radial forces (2.269 decibar for Emcompress® and 6.066 decibar for Tablettose®), which damaged the apparatus due to the weakness of the stainless steel. It is thus recommended to rebuild the die with hardened steel for a more comprehensive testing range.

The axial force (F_A) during compression was kept constant at about 1 MPa (10 bar), which resulted at ± 0.1 N axial force. Radial die wall force due to confinement of powder mass in die (F_R) increased when lubricant concentration increased as a result of more elasticity in the powder. When the powder is more elastic, the distribution of axial pressure throughout the powder mass is better and more pressure will be transmitted to the die wall. Mixing contributed to this effect as a result of more evenly distributed lubricant. The addition of magnesium stearate (0.5% w/w) to Avicel® increased F_R (18%) and at 1.0% w/w the F_R was increased by 46%. Mixing increased (25%) the F_R as a result of better distribution of magnesium stearate, but at higher concentrations there was no further increase compared to the 4 minute mixed formulas. Pruv® had the same effect on F_R, but its effect was 25% less compared to its counterpart.

Measurement of the coefficient of friction (R-value) is a differentiating measurement between lubricants, while μ_W measurements were used in optimizing lubricant usage. The R-value increased when lubricants were added (figure 5.5), nearing 1 which indicated no friction (μ_W = 0). Mixing also resulted in higher R-values.

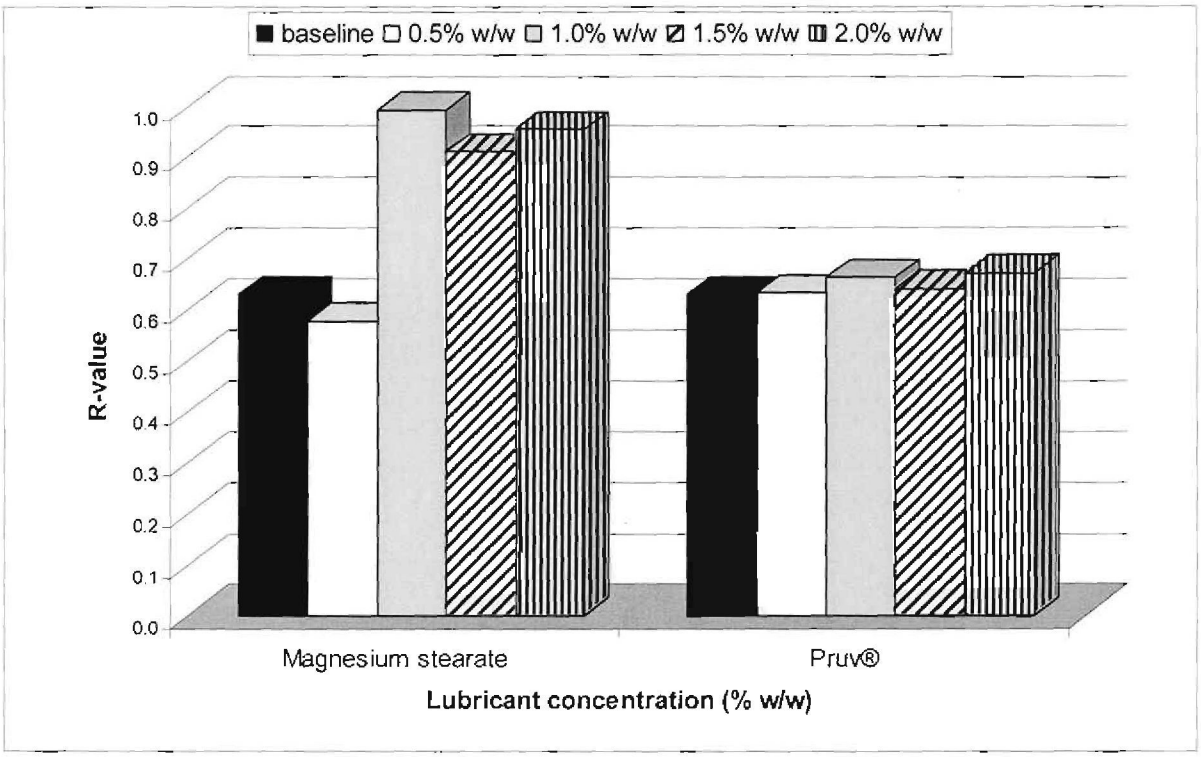


Figure 5.5: *R-values for Avicel® tablets. Filler was mixed for 4 minutes at 69 rpm with both lubricants.*

With the initial addition of magnesium stearate there was no significant increase in the R-value, but the 1% w/w concentration the R-value increased (57%) to ± 1 with no significant change in the R-value after this concentration. Pruv® had no significant influence on the R-value and the lower R-values of Pruv® were enough evidence to find magnesium stearate superior to Pruv® as lubricant. Mixing affected magnesium stearate to some extent (7%) when mixing time was prolonged from 4 to 8 minutes, but again had no significant effect on Pruv®.

Ejection forces (F_E) decrease with the addition of lubricant and increase in mixing time due to more evenly distributed lubricant between the tablet and die wall. Magnesium stearate (0.5% w/w) decreased (7%) the F_E. At higher concentrations this decrease declined. Pruv® gave the same results but to a much smaller extent (4%). Radial forces (F_D) during ejection decreased with the addition of both magnesium stearate (88%) and Pruv® (19%). Continuous mixing (8 minutes) further decreased F_D to 92% and 22% for magnesium stearate and Pruv® respectively.

Optimization of the mixing time and lubricant concentration was done by evaluation of friction coefficients (μ_W) from figure 5.6.

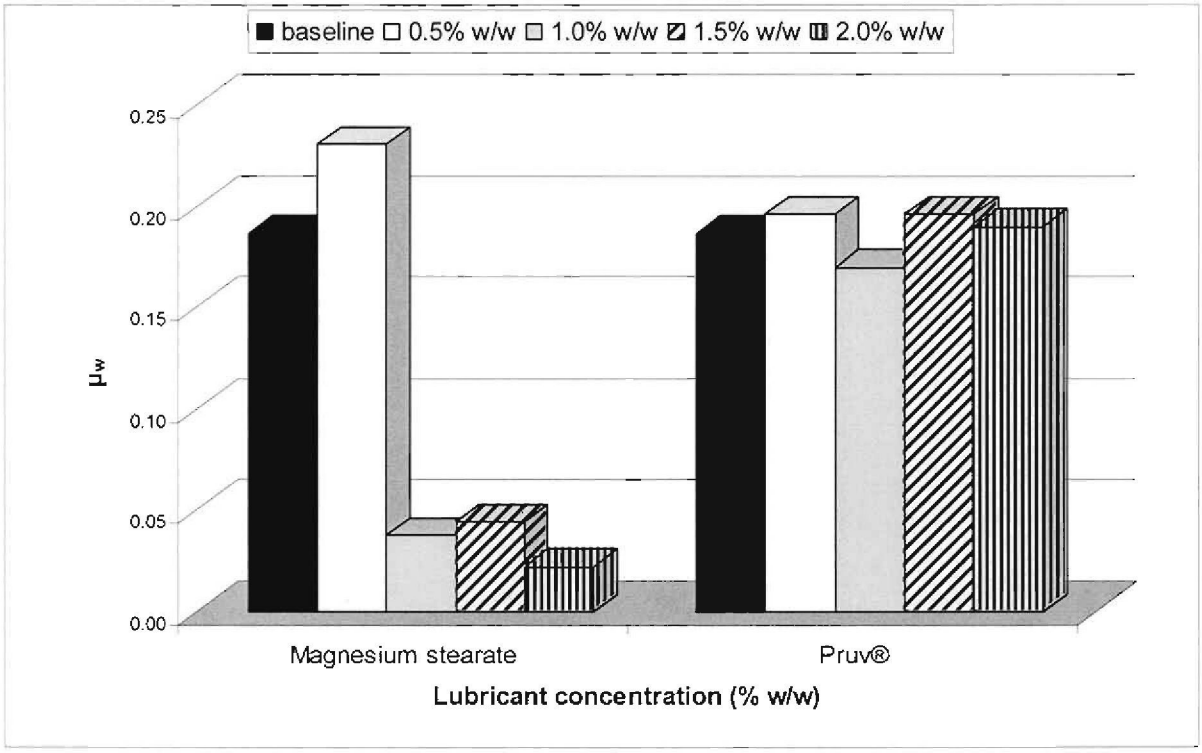


Figure 5.6: *Friction coefficients (μ_W) for Avicel® tablets. Filler was mixed for 4 minutes at 69 rpm with both lubricants.*

The initial increase in μ_W with the addition of lubricants could be attributed to some sticking in the die (although the assumption was that no sticking was present). For both lubricants the 1% w/w concentration proved to be the optimum since both had the largest influence on μ_W at this concentration. Magnesium stearate decreased (88%) μ_W to a much larger extent than Pruv® (9%), confirming again its superior lubricant effect as opposed to Pruv®. Mixing increased the effect magnesium stearate had on μ_W, but only for the 0.5% w/w concentration, and thus the conlusion that when very low concentrations (< 1% w/w) of magnesium stearate are being used, longer mixing times (8 minute) are required. Above the 1% w/w concentration 4 minutes was sufficient. Mixing had again no significant effect on μ_W in formulations containing Pruv®.

5.3.3 MEASUREMENT OF ADHESIVE FORCE

Antiadhesion activity of lubricants is usually evaluated by inspection of tooling, but to quantify it, equation 1.15 had to be applied. It was assumed that adhesion of lubricant on the die wall occurred during the first ten tablets compressed and the adhesion force had to be calculated from these data points as was previously explained in section 1.4.1.3. Tablets

were compressed from mixtures of filler (Avicel®, Emcompress® and Tablettose®) and lubricants (0.5 – 2.0 %w/w) mixed (4 and 8 minutes at 69 rpm) according to the method explained in section 2.5.6. Results were amended in annexure D and the slope and y-intercept (c) was calculated from the regression lines of data points for tablets 0 - 10 (figure 5.7).

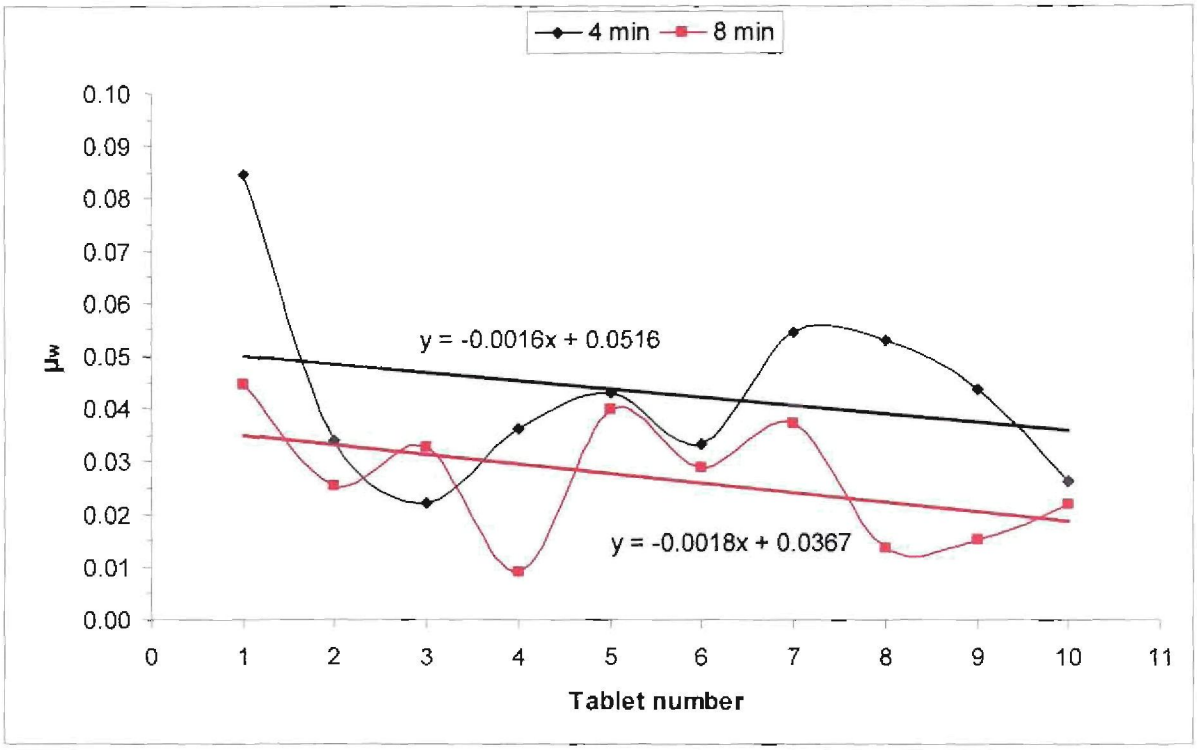


Figure 5.7: *Friction coefficients for magnesium stearate (1.0% w/w) in Avicel® tablets. Mixing occurred for 4 minutes at 69 rpm.*

The slope of the regression line indicated the amount of adhesion, which takes place at higher values, indicating more adhesion. The negative slopes indicate that adhesive forces declined as tableting proceeded. The higher the slope, the higher the y-intercept and thus the higher the adhesion (table 5.2). Results was again only generated for Avicel® tablets, since problems occurred during the evaluation of Emcompress® and Tablettose® tablets as was discussed previously.

Table 5.2: *Adhesive forces of Avicel® tablet formulations.*

		Magnesium stearate		Pruv®	
Mixing time (min)	Lubricant concentration (% w/w)	slope (m)	y-intercept (Adhesive force)	slope (m)	y-intercept (Adhesive force)
No lubrication (baseline)		-0.009	0.251	-0.009	0.251
4	0.5	0.005	0.225	-0.002	0.213
	1.0	-0.002	0.052	-0.008	0.218
	1.5	-0.003	0.061	0.002	0.177
	2.0	-0.002	0.034	-0.003	0.219
8	0.5	-0.015	0.205	0.001	0.197
	1.0	-0.002	0.037	-0.002	0.182
	1.5	-0.000	0.037	-0.001	0.212
	2.0	-0.001	0.020	-0.002	0.190

The adhesive force decreased when magnesium stearate was added as a result of more lubricant on the tablet surface (figure 5.8). The same decrease (9%) in adhesive force was experienced when mixing continued for 8 minutes (figure 5.9) and the adhesive force decreased with 40% when magnesium stearate was added (2.0% w/w).

There was a significant decrease (~ 80%) in adhesive force when magnesium stearate reached 1%. Thereafter the decrease declined to 7% as lubricant concentration increased to 2% w/w. Pruv® also decreased the adhesive force, but to a much smaller extent (nearly 3.5 times) compared to magnesium stearate. Mixing also had little to no effect (4.6%) on the antiadherent properties of Pruv®, as a result of the low sensitivity Pruv® had for mixing. The increase in the amount of Pruv® decreased the adhesive force to some extent (18%).

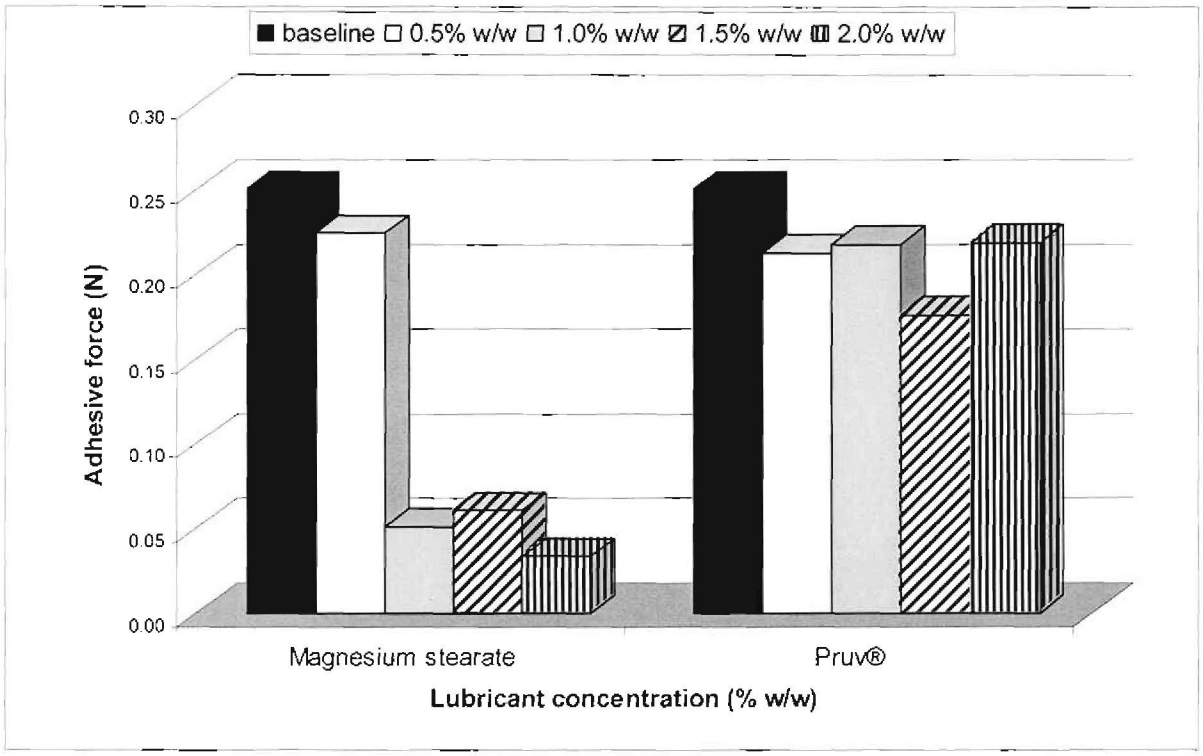


Figure 5.8: *Adhesive force of varying concentrations of lubricants in Avicel® tablets. Mixing occurred for 4 minutes at 69 rpm.*

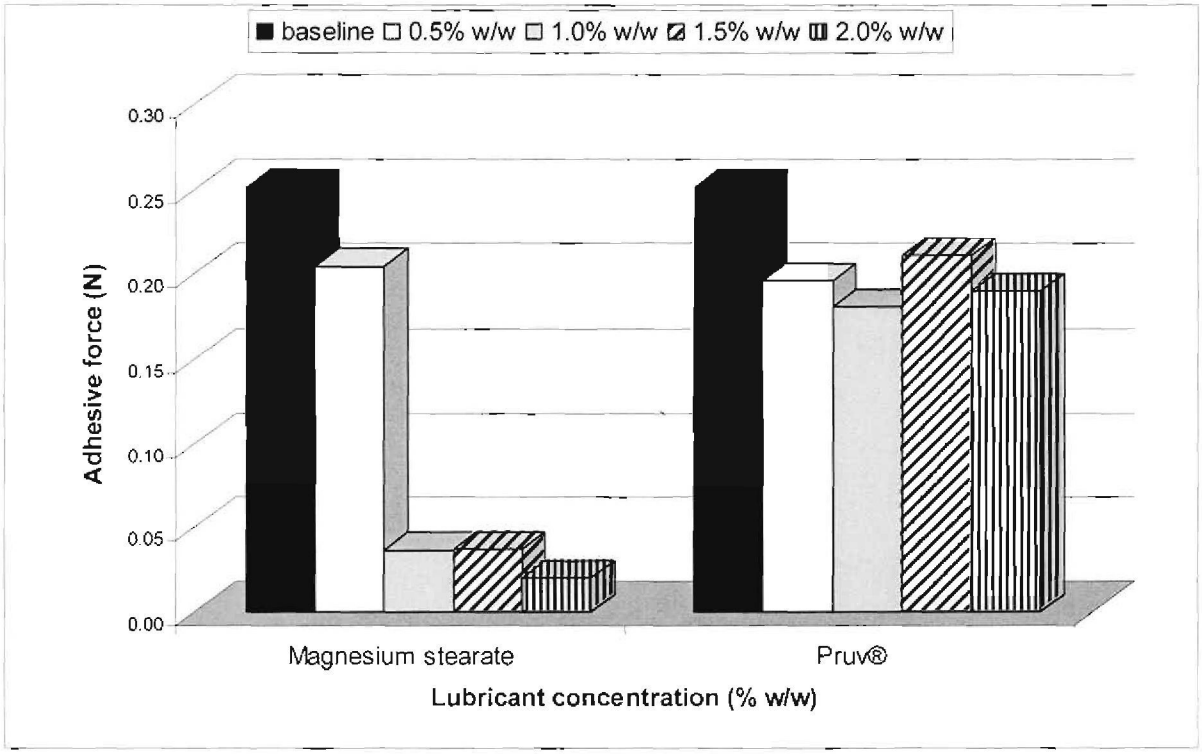


Figure 5.9: *Adhesive force of varying concentrations of lubricants in Avicel® tablets. Mixing occurred for 8 minutes at 69 rpm.*

5.4 CONCLUSION

The apparatus gave successful readings with enough sensitivity to evaluate lubricants. The only constraint was the material used to build the apparatus and hardened steel is recommended. The strain gauge range was good enough to uphold the pressure on it, with enough sensitivity. Care should be taken for compression pressure not to exceed 12 bar, since this is the maximum pressure the strain gauges could take.

The radial pressure (F_R) during compression increased with the addition of lubricant and mixing time as a result of better elastic properties between the carrier particles. Thus, better distribution of compression forces was experienced and more pressure was carried over towards the die wall.

The ejection force (F_D) with both lubricants decreased when concentration and mixing time increased which agrees with tendencies noted in the literature. The decrease in ejection force can be attributed to the fact that it is the force that initiates the movement (ejection) of the tablet and therefore the better film formation with an increase in concentration and mixing time.

The difference between R-values of lubricants are an indication of lubricant properties. Magnesium stearate was superior to Pruv® in the lubricant efficiency evaluation. It could be concluded that although magnesium stearate was the best lubricant, Pruv® had sufficient lubricant properties to be used as an alternative.

The initial increase in the coefficient (μ_W) of friction (at 0.5% w/w lubrication) indicates that the better the film formation the less the lubricant film on the tablet surfaces. This suggests that with better film formation, more lubricant will cover the carrier particles and less of the film and free fraction of magnesium stearate cover the tablet surfaces. When the concentration increased above 0.5% w/w, the μ_W decreased with an optimum found at 1% w/w for both lubricants. The initial decrease in ejection force with an increase in mixing time (8 minutes) at low concentrations (< 1% w/w) initiates the movement (better film formation) followed by a decrease in coefficient of friction since magnesium stearate loses it surface activity properties. It could be concluded that low lubricant concentrations should be mixed for longer periods than higher concentrations to decrease μ_W significantly. Pruv® showed no sensitivity towards mixing.

Adhesive forces (C) decreased with an increase in lubricant concentration and mixing time as was seen with most of the friction parameters. At 1% w/w concentration the adhesive

force decreased significantly. Magnesium stearate proved to be superior to Pruv® in lowering the adhesive force. Mixing had little effect on the antiadherent properties of Pruv®, but magnesium stearate reacted positively towards prolonged mixing in lowering the adhesive force.

No correlation was drawn between the different compression forces and the tensile or crushing strength of tablets.

CHAPTER 6

Conclusion and recommendations

The theories of compression of pharmaceutical materials and their subsequent application to developments in tableting formulation methodology and manufacturing processes have been extensively studied. Several investigations attempted to evaluate characteristics of compression for a particular excipient or new drug and to use them to predict the compression properties of another related or unrelated medicament. Knowledge of compression properties is important to ensure that the newly formed compacted mass will remain bonded after compression forces are released. Compression is dependent upon lubrication, since the latter is the principle excipient needed to compress a powder bed. Lubricants are incorporated into solid dosage formulations to reduce the frictional forces between the tablet surfaces and the die wall during the tableting process. Apart from the lubricant effect of lubricants, it also have antiadherent and glidant properties.

Flow testing indicated that particle shape had a larger effect (on the flow properties of fillers) than particle size. The addition of lubricant and mixing time and speed had a negative effect on the flow characteristics of all the fillers evaluated, necessitating the formation of cohesive forces between lubricant particles. Cognizance was taken of the poor correlation between angle of repose and the other parameters used to evaluate powder flow. A new parameter, static flow index (I_v), was proposed, since remarkable differences were observed for different fillers, which was coherent with visual flow observations. It was concluded that magnesium stearate had better glidant properties than its counterpart as a result of its flatter particle shape and larger specific surface area. Lubricant concentrations below 0.5% w/w gave optimum glidancy for both lubricants and mixing times between 4 and 8 minutes was sufficient to optimize this glidant effect. Although stunted flowability could be identified in all fillers, Avicel® PH-200 formulations, still resided in superior flow characteristics compared to Emcompress® and Tablettose® formulations, as a result of its spherical shaped and larger particles.

The suggested decrease in tablet strength was observed for both lubricants when lubricant concentration increased, due to less interparticulate binding surfaces between the carrier particles. This decrease subsided when lubrication surpassed the 1.5% w/w concentration level. Mixing, however, had the opposite effect on Pruv® compared to magnesium stearate, since Pruv® increased the tablet strength with continuance mixing. Due to the hydrophilic nature of Pruv®, more interparticulate bondings occurred than was observed with

magnesium stearate. The same phenomenon was found for friability, which increased with the addition of lubricants and increased mixing time and speed. Tablets containing Pruv® resulted in harder tablets than those containing magnesium stearate, due to the lower sensitivity of Pruv® towards mixing conditions. Tablet hardness and friability were optimized when magnesium stearate and Pruv® were added to carrier systems at concentrations of 0.5% and 1.0% w/w respectively. Mixing time had again to be kept between 4 and 8 minutes and 69 rpm proved an efficient mixing speed.

Both tablet disintegration and drug dissolution deteriorated with the addition of magnesium stearate and Pruv®. In the case of magnesium stearate this results could be related to the hydrophobic nature of magnesium stearate. Pruv®, however, was hydrophilic and a positive influence on disintegration and dissolution should have been observed. The decrease in these properties (although much lower than for magnesium stearate) was the consequence of the increase in tablet strength. Mixing improved disintegration due to a larger surface of separation. It was also found that the extent of surface coverage determined the amount of drug release. The evaluation of the extent of drug release (AUC) and rate of release (DR_i) indicated an average increase of 50% in dissolution in formulations with Pruv® compared to magnesium stearate.

Evaluation of friction coefficients (μ), coefficients of friction (R-values) and adhesive forces (C) revealed that magnesium stearate had superior lubricant and antiadherent properties as opposed to Pruv®. According to these parameters, optimum lubricant efficiency (for both lubricants) was achieved at low concentrations (< 1% w/w) and short mixing times (< 4 minutes). The suitability of Pruv® in directly compressible tablet drug formulations was aptly illustrated, advocating its increased utilisation and optimization for relevant formulations. The effect of Pruv® was best observed in Tablettose® formulations and further study should be considered on the effect of Pruv®, and/or mixtures of magnesium stearate and Pruv® on the different lactose fillers. The magnesium-salts also give better lubrication than the sodium-salts (Bowden & Tabor, 1950:61) and the synthesis of a magnesium stearyl fumarate should be considered as alternative lubricant, since it is expected that such a lubricant might give better lubrication than Pruv®, but with the same advantages of better tablet disintegration and drug release.

The measurement of lubricant properties during the tableting process also gave an indication of the effect that friction has on the film formation of magnesium stearate during the mixing process. The apparatus and method was newly developed and gave accurate, repeatable measurements. Care should be taken with the use of this apparatus, due to its sensitivity

and range. Upgrade on the material used for the die wall is necessary for the evaluation of formulations without lubricants and where very high ejection forces are required.

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Publication

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Comparison of magnesium stearate and sodium stearyl fumarate (Pruv®) as lubricants in directly compressed Tablettose® tablets

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INTRODUCTION

Magnesium stearate is generally known as the universal lubricant in wet granulation and direct compression, despite its negative effect on tablet properties such as a reduction in mechanical strength, an increase in tablet disintegration and a reduction in drug dissolution. Sodium stearyl fumurate has been suggested as a suitable lubricant for direct compression.[1] It is claimed not to have the disadvantages of magnesium stearate in respect to tablet strength, disintegration and drug dissolution.[2] It is accepted that a micronised lubricant is more efficient than a coarse fraction, and it is therefore important that the surface area is standardised to obtain reproducible effects. Thus, the particle size of sodium stearyl fumurate is an important factor to be considered during formulation, especially to achieve the fore mentioned properties and effects. The effects of the excipient correlate better to the relative surface area of added lubricant than the actual amount.[3]

AIMS AND OBJECTIVES

The study compared and evaluated the effect offmagnesium stearate and sodium stearyl fumarate (Pruv®) on the physical properties of directly compressed Tablettose® tablets.

METHODS

Preparation of formulations: Mixtures containing Tablettose® and lubricant (magnesium stearate or Pruv®) at different concentrations (0.5, 1.0, 1.5 or 2.0% w/w) were prepared at various mixing times (4 and 8 minutes) at 69 rpm using a Turbula® mixer. Table 1 is a summary of all the formulations. Tablets were compressed at a constant upper punch force using a Manesty® single-punch tablet press (fitted with slightly biconcave punches – 10 mm in diameter).

Evaluation of tablets: Tablet evaluation was performed using the standard procedures described in the official pharmacopoeia (B.P.). Tablet evaluation included weight variation, crushing strength, friability (vigorous test of 50 rpm for 10 minutes) and disintegration time. All experimental data was analised statistically to determine significant differences at a 95% confidence level.

Table 1: *Summary of tablet formulations.*

Variables	Levels			
Mixing Time	4 minutes		8 minutes	
Lubricant Type	Magnesium Stearate (MgSt)		Sodium Stearyl Fumarate (Pruv®)	
Lubricant Concentration	0.5%	1.0%	1.5%	2.0%

RESULTS AND DISCUSSION

Figure 1: For both lubricants the crushing strength decreased with an increase in lubricant concentration and with mixing time, with Pruv® being less detrimental to the mechanical strength of the tablets compared to magnesium stearate. The crushing strength of tablets containing Pruv® was significantly higher ($p<0.05$) compared to magnesium stearate tablets at each lubricant concentration and each mixing time. Longer mixing times (8 min.) seemed to be less favourable, but showed the same tendency in terms of its effect on tablet crushing strength compared to 4 min. The optimum concentrations for the two lubricants were found to be 0.5 – 1.0% for Pruv® and 0.5% for magnesium stearate at both mixing speeds.

Figure 2: Tablets containing 0.5% magnesium stearate (at 4 min.) exhibited the highest hardness/friability index (HFI), mainly due to the lower friability of these tablets. The HFI, however dropped significantly with an increase in lubricant concentration as crushing strength decreased and tablet friability increased. The HFI of tablets containing Pruv® was less susceptible to an increase in lubricant concentration, especially up to 1% of the lubricant.

Figure 3: Tablets with Pruv® gave superior disintegration compared to those with magnesium stearate. The best disintegration results were obtained at a shorter mixing time (4 min.). Disintegration time increased as the lubricant concentration increased for both mixing times.

Figure 4: The negative effect of magnesium stearate, a hydrophobic excipient, on tablet disintegration was clearly visible from the disintegration results, with neither of the formulations disintegrating within the set limit of 15 minutes, resulting in the observed low disintegration/hardness index (HDI). Conversely, all the Pruv® tablets disintegrated within 5 minutes, depending on the lubricant concentration, and the HDI decreased almost linearly with an increase in lubricant concentration. This could be attributed to the hydrophilic character of Pruv®.

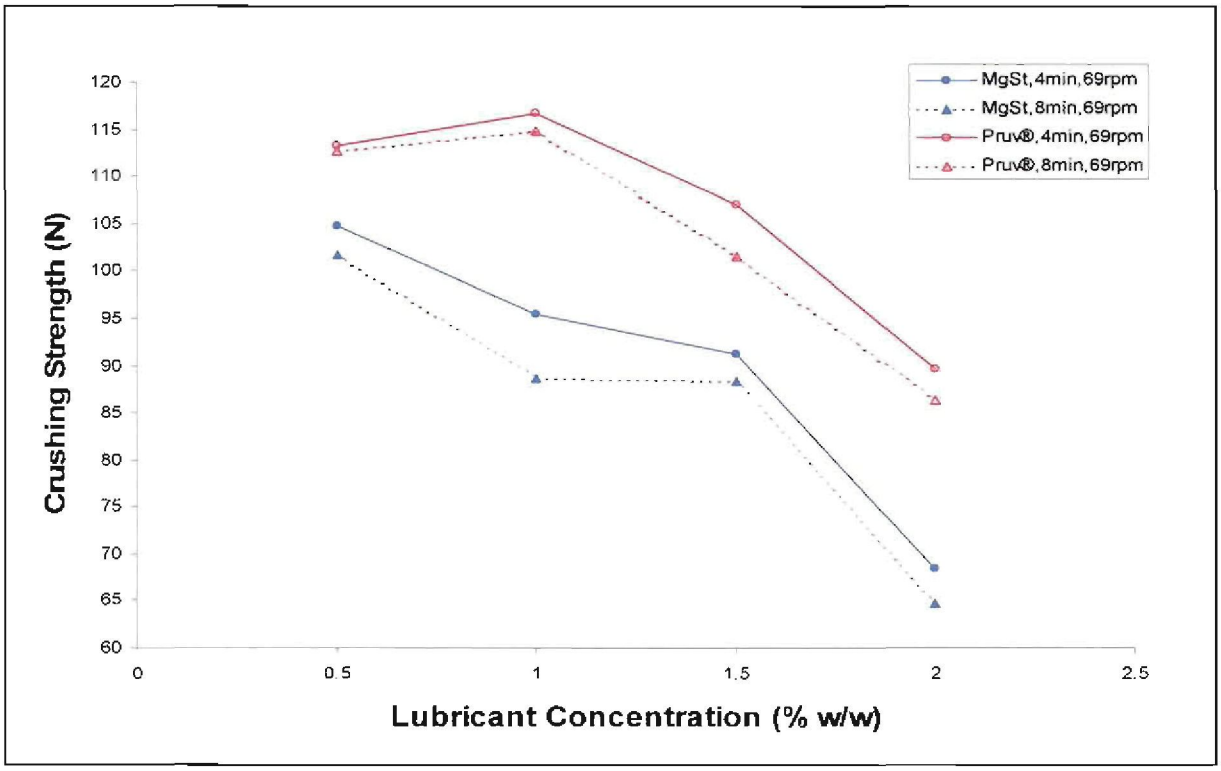

Figure 1. *Influence of mixing conditions on tablet crushing strength at various lubricant concentrations.*

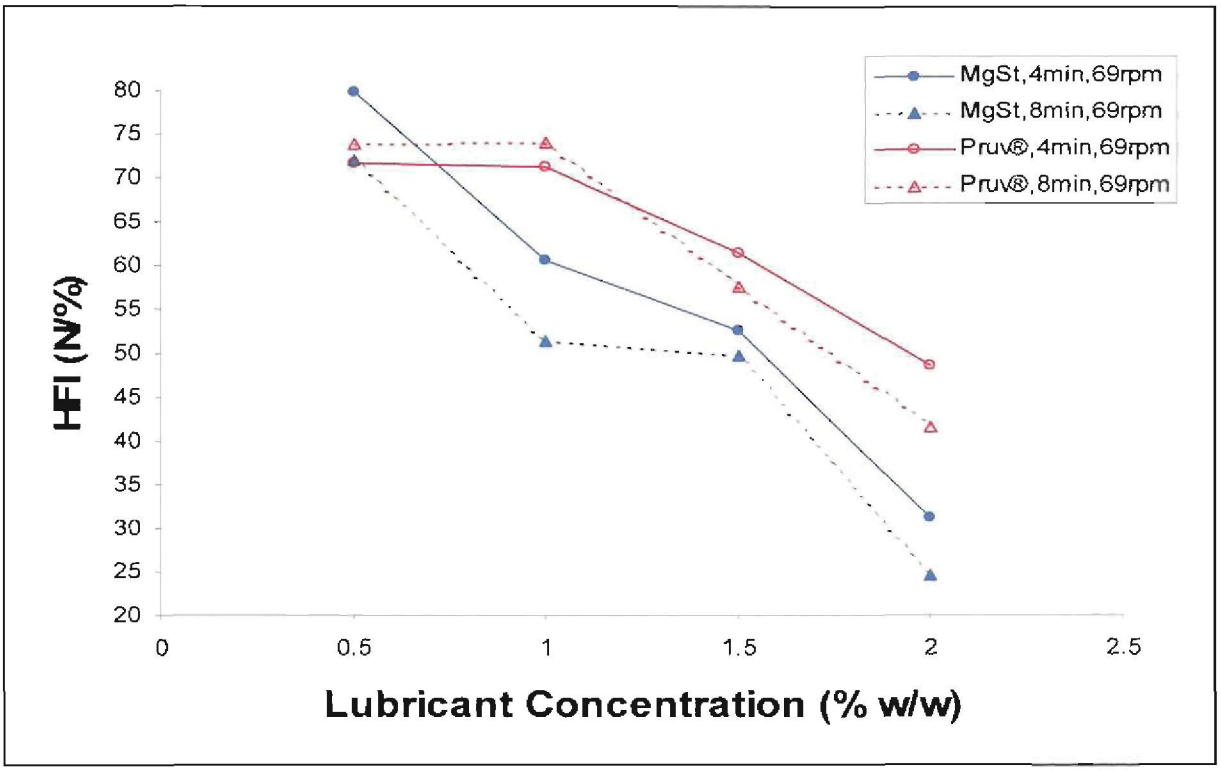

Figure 2: *Influence of mixing conditions on tablet hardness/friability index (HFI) at various lubricant concentrations.*

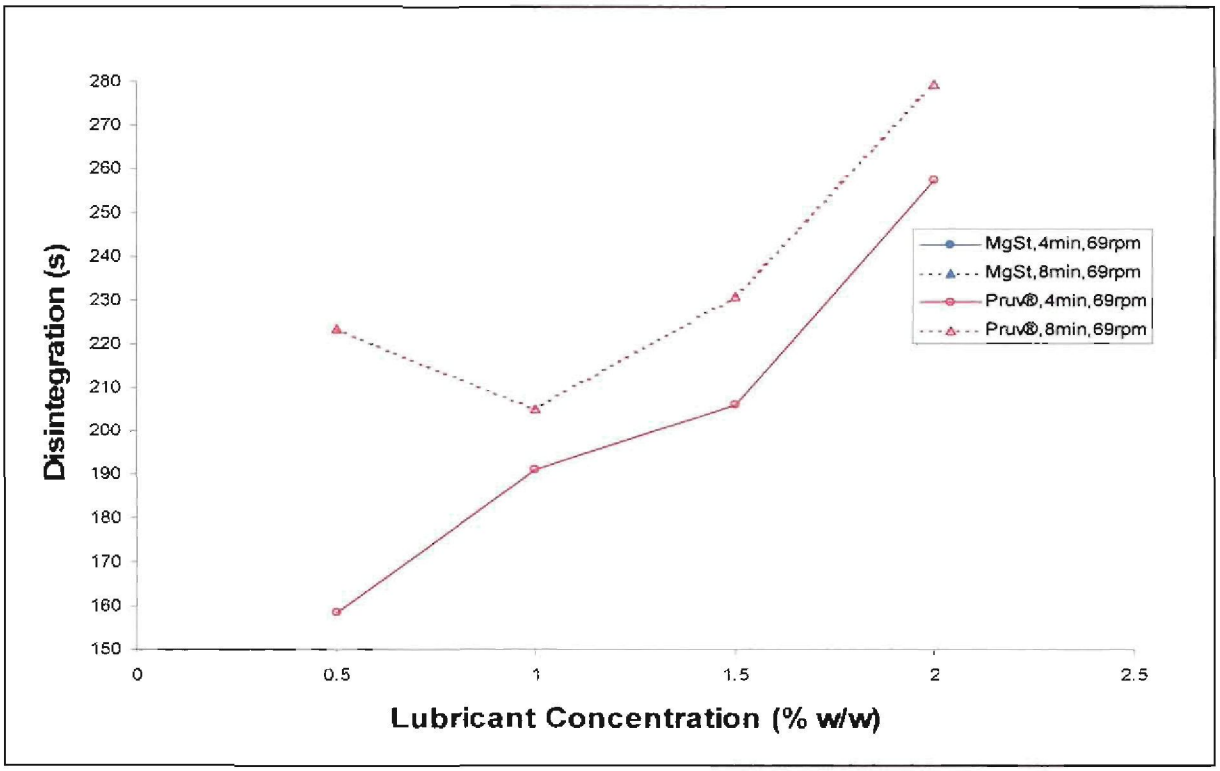

Figure 3: *Influence of mixing conditions on tablet harness/disintegration index (HDI) at various lubricant concentrations.*

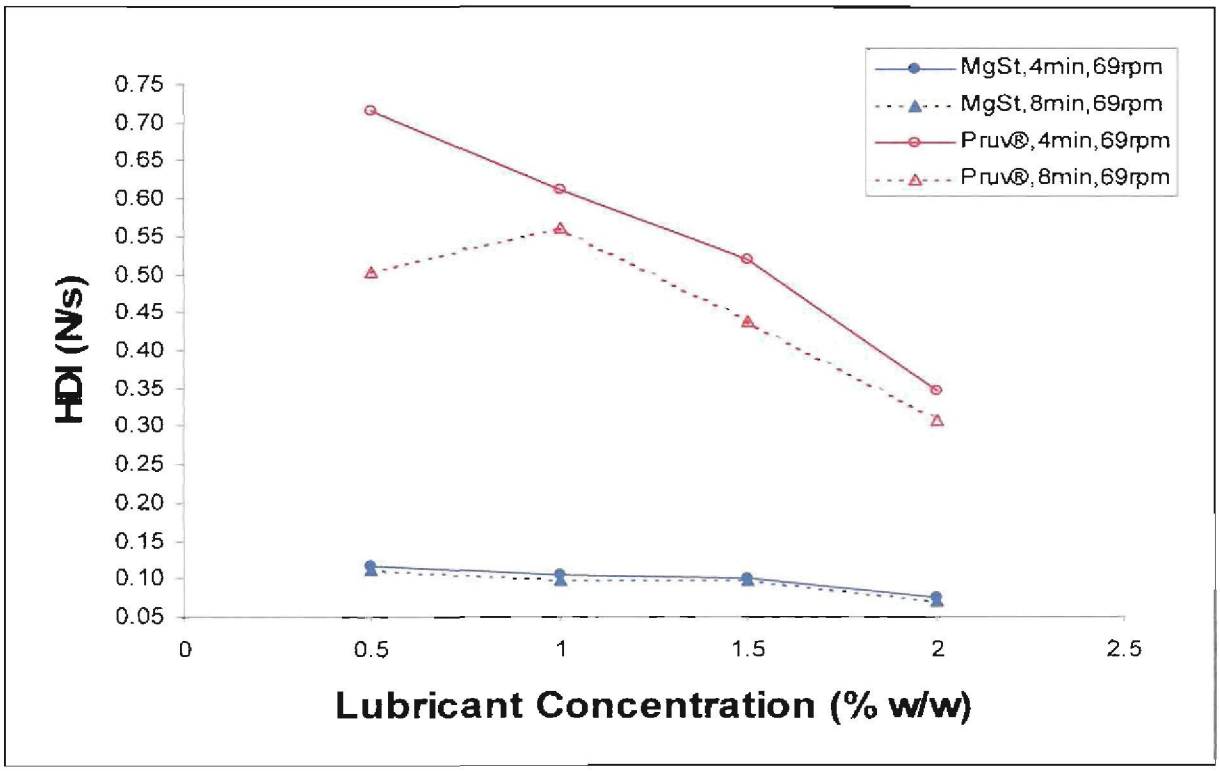

Figure 4. *Influence of mixing conditions on tablet harness/disintegration index (HDI) at various lubricant concentrations.*

SUMMARY AND CONCLUSIONS

Tablettose® tablets with Pruv® as lubricant gave harder, faster disintegrating tablets than tablets with magnesium stearate as lubricant. Pruv® reduced tablet disintegration with almost 80% and increased the mechanical strength with 22% compared to magnesium stearate.

Mixing time and lubricant concentration had a negative effect on both crushing strength and disintegration of tablets with magnesium stearate or Pruv® lubricants.

Mixing time had a big influence on Tablettose® tablets with Pruv® as lubricant.

Pruv® seemed to be efficient between concentrations of 0.5 – 1.0% w/w after 4 minutes of mixing, without showing any of the negative effects found for magnesium stearate.

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3. HÖLZER, A.W. & SJÖGREN, J. 1981. Evaluation of some lubricants by the comparison of friction coefficients and tablet properties. **Acta Pharmaceutica Suecica**, 8:139-148.

Annexures

Annexure A

CHARACTERIZATION OF AVICEL® PH-200, EMCOMPRESS® AND TABLETTOSE® POWDER MIXED WITH MAGNESIUM STEARATE OR PRUV®

A.1 PARTICLE SIZE ANALYSIS

Table A.1.1.1: Particle size analysis for Avicel® powder. Run number 1.

MALVERN INSTRUMENTS MASTERSIZER X

Version 1.2a — Thu, Oct 23, 2003 8:32AM

Avicel PH200 :Run Number 1

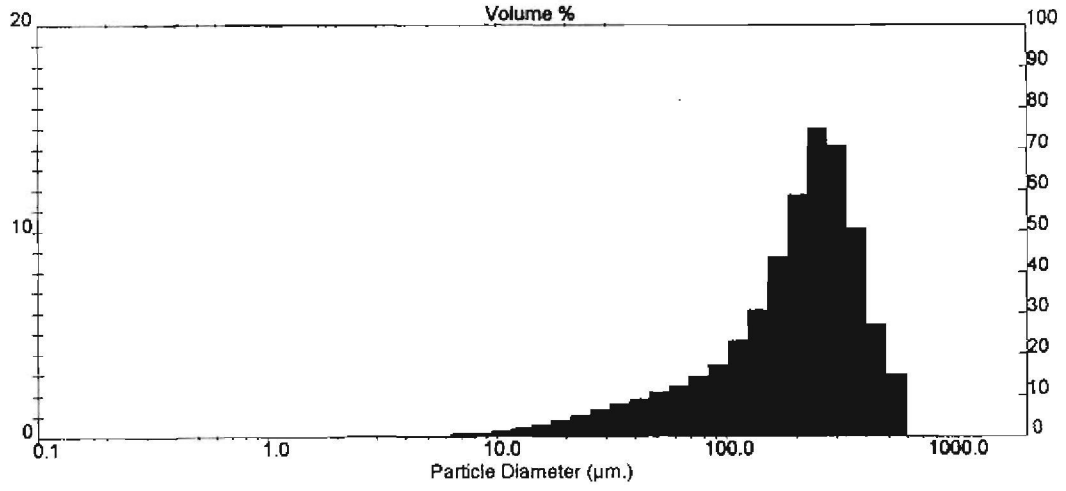
Batch nr.: M926C
Dispersant: Milli RO water in MSX1

Sample 1
Sample File Name: RUAAN_01, Record: 1 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:04PM Last saved on: Fri, Jan 04, 1980 7:05PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 0.954 % — Concentration = 0.047 % — Obscuration = 26.00 %
d (0.5) = 216.18 µm — d (0.1) = 47.02 µm — d (0.9) = 388.94 µm
D [4, 3] = 220.05 µm — Span = 1.58
Sauter Mean (D[3,2]) = 70.84 µm — Mode = 268.28 µm
Specific Surface Area = 0.0560 sq. m. / gm — Density = 1.51 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %	Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.13	1.32	0.13	25.46	1.34	31.01	6.32
1.32	0.07	1.60	0.20	31.01	1.59	37.79	7.92
1.60	0.09	1.95	0.29	37.79	1.87	46.03	9.78
1.95	0.09	2.38	0.38	46.03	2.15	56.09	11.94
2.38	0.10	2.90	0.48	56.09	2.47	68.33	14.41
2.90	0.11	3.53	0.59	68.33	2.91	83.26	17.32
3.53	0.12	4.30	0.72	83.26	3.49	101.44	20.81
4.30	0.15	5.24	0.86	101.44	4.65	123.59	25.45
5.24	0.18	6.39	1.04	123.59	6.18	150.57	31.63
6.39	0.22	7.78	1.27	150.57	8.76	183.44	40.39
7.78	0.28	9.48	1.55	183.44	11.89	223.51	52.28
9.48	0.36	11.55	1.91	223.51	14.77	272.31	67.05
11.55	0.48	14.08	2.39	272.31	14.51	331.77	81.56
14.08	0.64	17.15	3.04	331.77	9.81	404.21	91.37
17.15	0.85	20.90	3.89	404.21	5.60	492.47	96.97
20.90	1.09	25.46	4.98	492.47	3.03	600.00	100.00



Malvern Instruments Ltd.
Malvern, U.K.

MasterSizer X Ver. 1.2a
Serial No.

p. 1
23 Oct 03 08:32

Table A.1.1.2: *Particle size analysis for Avicel® powder. Run number 2.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:32AM

Avicel PH200 :Run Number 3

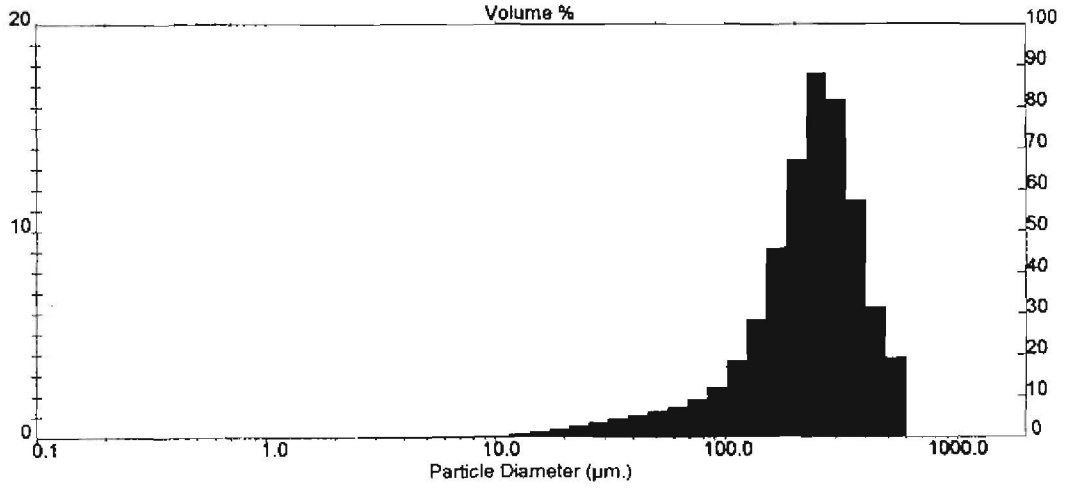
Batch nr.: M926C
Dispersant: Milli RO water in MSX1

Sample 2
Sample File Name: RUAAN_01, Record: 3 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:14PM Last saved on: Fri, Jan 04, 1980 7:14PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 1.048 % — Concentration = 0.046 % — Obscuration = 13.64 %
d (0.5) = 228.52 µm — d (0.1) = 61.67 µm — d (0.9) = 398.95 µm
D [4, 3] = 232.76 µm — Span = 1.48
Sauter Mean (D[3,2]) = 93.26 µm — Mode = 263.77 µm
Specific Surface Area = 0.0426 sq. m. / gm — Density = 1.51 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.06	1.32	0.06
1.32	0.04	1.60	0.10
1.60	0.04	1.95	0.14
1.95	0.05	2.38	0.19
2.38	0.05	2.90	0.24
2.90	0.06	3.53	0.31
3.53	0.08	4.30	0.39
4.30	0.10	5.24	0.49
5.24	0.13	6.39	0.62
6.39	0.16	7.78	0.78
7.78	0.20	9.48	0.98
9.48	0.26	11.55	1.24
11.55	0.35	14.08	1.60
14.08	0.48	17.15	2.08
17.15	0.65	20.90	2.72
20.90	0.85	25.46	3.57
25.46	1.06	31.01	4.63
31.01	1.26	37.79	5.89
37.79	1.48	46.03	7.37
46.03	1.72	56.09	9.09
56.09	1.99	68.33	11.08
68.33	2.39	83.26	13.47
83.26	2.97	101.44	16.44
101.44	4.19	123.59	20.63
123.59	5.99	150.57	26.62
150.57	9.01	183.44	35.63
183.44	12.65	223.51	48.29
223.51	16.12	272.31	64.41
272.31	15.60	331.77	80.00
331.77	10.48	404.21	90.49
404.21	6.06	492.47	96.54
492.47	3.46	600.00	100.00



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MasterSizer X Ver. 1.2a
Serial No.

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Table A.1.2.1: *Particle size analysis for Emcompress® powder. Run number 1.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:34AM

Emcompress :**Run Number** 1

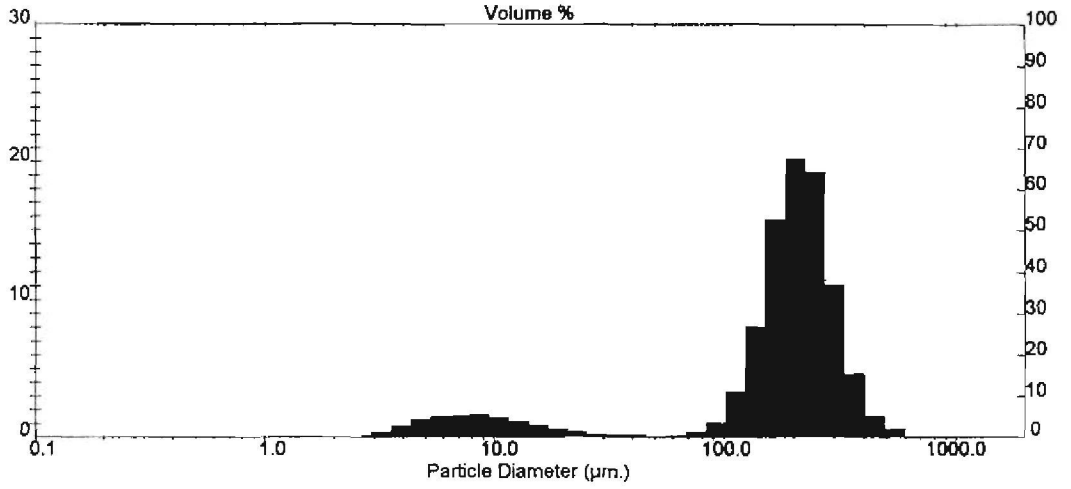
Batch nr.: C06D
Dispersant: Milli RO water in MSX1

Sample 1
Sample File Name: RUAAN_02, Record: 1 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:42PM Last saved on: Fri, Jan 04, 1980 7:42PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 0.958 % — Concentration = 0.035 % — Obscuration = 32.53 %
d (0.5) = 197.98 µm — d (0.1) = 12.72 µm — d (0.9) = 307.67 µm
D [4, 3] = 193.70 µm — Span = 1.49
Sauter Mean (D[3,2]) = 41.42 µm — Mode = 215.27 µm
Specific Surface Area = 0.0606 sq. m. / gm — Density = 2.39 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.07	1.32	0.07
1.32	0.06	1.60	0.14
1.60	0.03	1.95	0.17
1.95	0.07	2.38	0.24
2.38	0.19	2.90	0.43
2.90	0.43	3.53	0.86
3.53	0.90	4.30	1.76
4.30	1.35	5.24	3.11
5.24	1.55	6.39	4.66
6.39	1.62	7.78	6.28
7.78	1.64	9.48	7.91
9.48	1.46	11.55	9.38
11.55	1.21	14.08	10.59
14.08	0.92	17.15	11.51
17.15	0.66	20.90	12.16
20.90	0.46	25.46	12.63
25.46	0.32	31.01	12.95
31.01	0.29	37.79	13.23
37.79	0.19	46.03	13.42
46.03	0.07	56.09	13.50
56.09	0.19	68.33	13.69
68.33	0.44	83.26	14.13
83.26	1.11	101.44	15.24
101.44	3.41	123.59	18.65
123.59	8.04	150.57	26.69
150.57	15.73	183.44	42.42
183.44	20.43	223.51	62.85
223.51	18.91	272.31	81.76
272.31	11.57	331.77	93.33
331.77	4.17	404.21	97.51
404.21	1.87	492.47	99.37
492.47	0.63	600.00	100.00



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MasterSizer X Ver. 1.2a
Serial No.

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Table A.1.2.2: *Particle size analysis for Emcompress® powder. Run number 2.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:34AM

Emcompress :Run Number 3

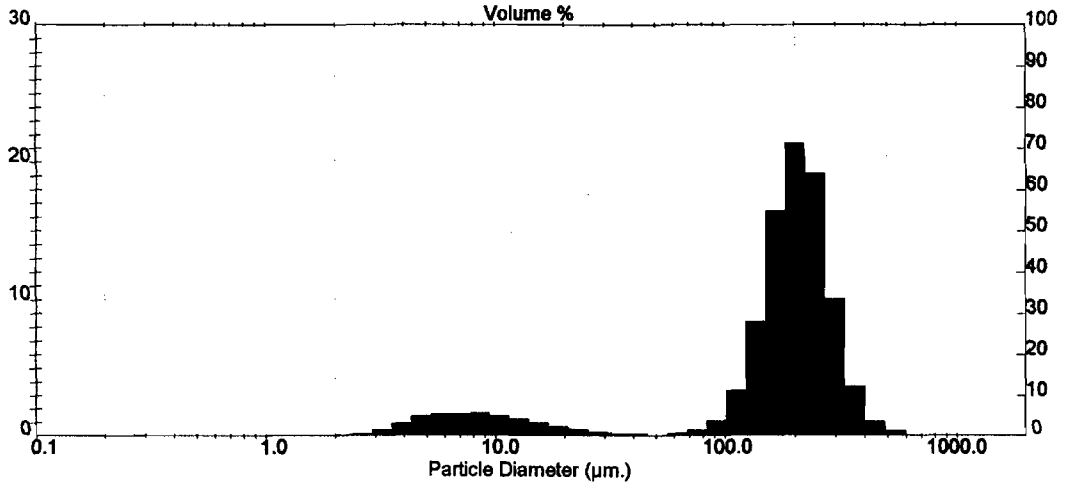
Batch nr.: C06D
Dispersant: Milli RO water in MSX1

Sample 2
Sample File Name: RUAAN_02, Record: 3 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:46PM Last saved on: Fri, Jan 04, 1980 7:46PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 0.798 % — Concentration = 0.028 % — Obscuration = 27.40 %
d (0.5) = 195.90 µm — d (0.1) = 12.26 µm — d (0.9) = 301.54 µm
D [4, 3] = 190.38 µm — Span = 1.48
Sauter Mean (D[3,2]) = 40.73 µm — Mode = 213.79 µm
Specific Surface Area = 0.0617 sq. m. / gm — Density = 2.39 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.07	1.32	0.07
1.32	0.06	1.60	0.13
1.60	0.03	1.95	0.16
1.95	0.07	2.38	0.23
2.38	0.19	2.90	0.42
2.90	0.45	3.53	0.86
3.53	0.93	4.30	1.80
4.30	1.41	5.24	3.20
5.24	1.59	6.39	4.79
6.39	1.64	7.78	6.43
7.78	1.67	9.48	8.09
9.48	1.50	11.55	9.59
11.55	1.25	14.08	10.84
14.08	0.95	17.15	11.79
17.15	0.68	20.90	12.47
20.90	0.48	25.46	12.95
25.46	0.33	31.01	13.28
31.01	0.29	37.79	13.57
37.79	0.19	46.03	13.76
46.03	0.07	56.09	13.84
56.09	0.19	68.33	14.03
68.33	0.44	83.26	14.47
83.26	1.12	101.44	15.60
101.44	3.44	123.59	19.04
123.59	8.19	150.57	27.23
150.57	16.10	183.44	43.33
183.44	20.90	223.51	64.23
223.51	18.92	272.31	83.15
272.31	11.05	331.77	94.19
331.77	3.72	404.21	97.91
404.21	1.60	492.47	99.51
492.47	0.49	600.00	100.00



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Malvern, U.K. — Serial No. — 23 Oct 03 08:34

Table A.1.3.1: *Particle size analysis for Tablettose® powder. Run number 1.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:35AM

Tablettose :Run Number 1

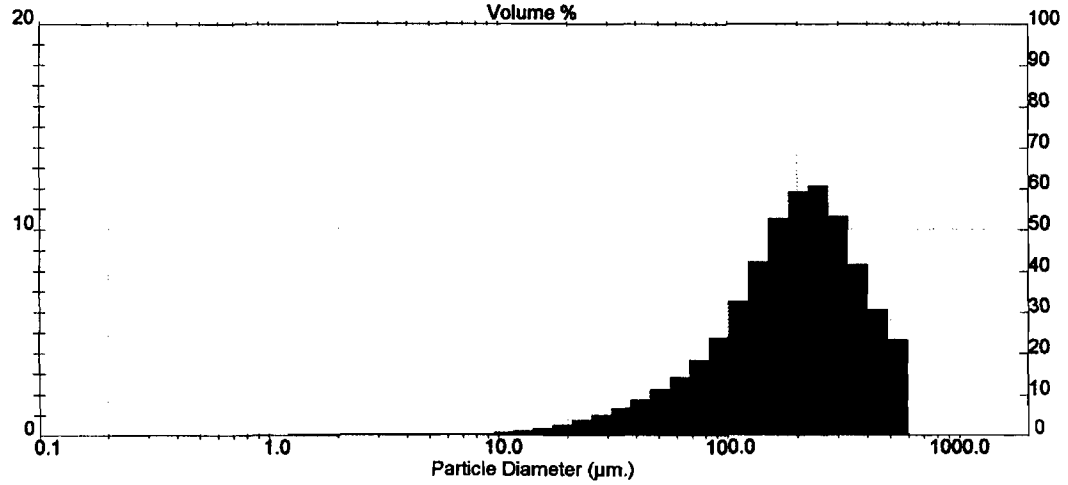
Batch nr.: 0116
Dispersant: Ethanol in MSX1

Sample 1
Sample File Name: RUAAN_03, Record: 1 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:02PM Last saved on: Fri, Jan 04, 1980 7:02PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 0.547 % — Concentration = 0.046 % — Obscuration = 21.48 %
d (0.5) = 195.71 µm — d (0.1) = 58.68 µm — d (0.9) = 413.68 µm
D [4, 3] = 217.58 µm — Span = 1.81
Sauter Mean (D[3,2]) = 85.03 µm — Mode = 228.25 µm
Specific Surface Area = 0.0455 sq. m. / gm — Density = 1.55 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.11	1.32	0.11
1.32	0.07	1.60	0.18
1.60	0.06	1.95	0.24
1.95	0.06	2.38	0.30
2.38	0.06	2.90	0.36
2.90	0.06	3.53	0.42
3.53	0.06	4.30	0.48
4.30	0.06	5.24	0.54
5.24	0.08	6.39	0.61
6.39	0.10	7.78	0.71
7.78	0.13	9.48	0.84
9.48	0.18	11.55	1.02
11.55	0.26	14.08	1.29
14.08	0.39	17.15	1.67
17.15	0.55	20.90	2.23
20.90	0.77	25.46	3.00
25.46	1.03	31.01	4.03
31.01	1.36	37.79	5.39
37.79	1.76	46.03	7.15
46.03	2.26	56.09	9.41
56.09	2.87	68.33	12.28
68.33	3.68	83.26	15.96
83.26	4.77	101.44	20.73
101.44	6.49	123.59	27.23
123.59	8.48	150.57	35.71
150.57	10.49	183.44	46.20
183.44	11.92	223.51	58.12
223.51	12.07	272.31	70.18
272.31	10.68	331.77	80.86
331.77	8.31	404.21	89.17
404.21	6.12	492.47	95.30
492.47	4.70	600.00	100.00



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Serial No.

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Table A.1.3.2: *Particle size analysis for Tablettose® powder. Run number 2.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:35AM

Tablettose :Run Number 3

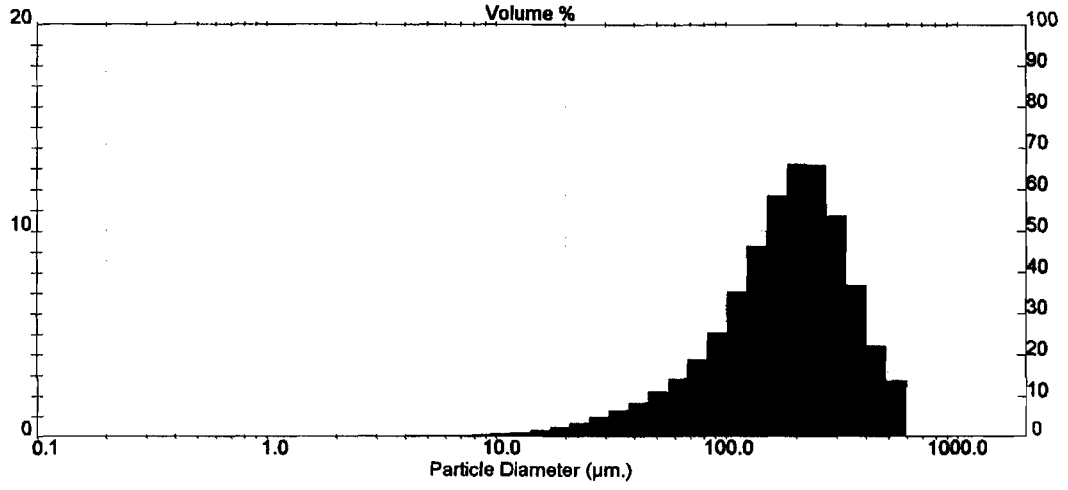
Batch nr.: 0116
Dispersant: Ethanol in MSX1

Sample 2
Sample File Name: RUAAN_03, Record: 3 — Source: Analysed
Measured on: Fri, Jan 04, 1980 7:07PM Last saved on: Fri, Jan 04, 1980 7:07PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 300 mm.

Residual = 0.535 % — Concentration = 0.085 % — Obscuration = 27.42 %
d (0.5) = 191.96 µm — d (0.1) = 60.82 µm — d (0.9) = 392.70 µm
D [4, 3] = 211.75 µm — Span = 1.73
Sauter Mean (D[3,2]) = 97.93 µm — Mode = 223.34 µm
Specific Surface Area = 0.0395 sq. m. / gm — Density = 1.55 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.50	0.05	1.32	0.05
1.32	0.03	1.60	0.09
1.60	0.03	1.95	0.12
1.95	0.03	2.38	0.15
2.38	0.03	2.90	0.19
2.90	0.04	3.53	0.22
3.53	0.04	4.30	0.26
4.30	0.05	5.24	0.32
5.24	0.07	6.39	0.38
6.39	0.08	7.78	0.47
7.78	0.11	9.48	0.58
9.48	0.16	11.55	0.74
11.55	0.24	14.08	0.99
14.08	0.36	17.15	1.34
17.15	0.52	20.90	1.87
20.90	0.74	25.46	2.61
25.46	1.01	31.01	3.62
31.01	1.33	37.79	4.95
37.79	1.74	46.03	6.68
46.03	2.23	56.09	8.92
56.09	2.86	68.33	11.78
68.33	3.73	83.26	15.51
83.26	4.92	101.44	20.43
101.44	6.77	123.59	27.20
123.59	8.90	150.57	36.10
150.57	11.09	183.44	47.19
183.44	12.61	223.51	59.80
223.51	12.59	272.31	72.39
272.31	10.74	331.77	83.14
331.77	7.84	404.21	90.97
404.21	5.29	492.47	96.26
492.47	3.74	600.00	100.00



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Serial No.

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Table A.1.4.1: *Particle size analysis for magnesium stearate powder. Run number 1.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:37AM

Magnesium stearate :Run Number 1

Batch nr.: ART 5876
Dispersant: Ethanol in MSX1

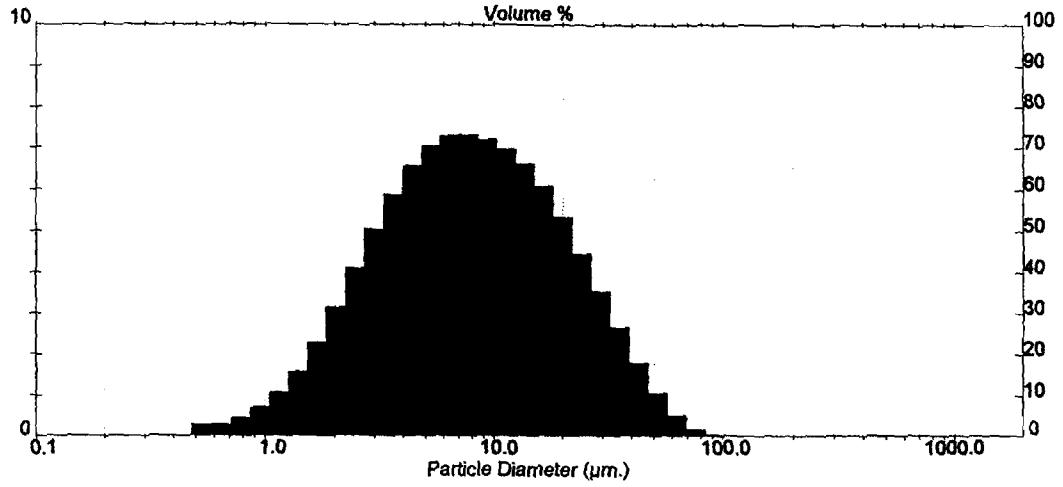
Sample 1.
Sample File Name: RUAAN_05, Record: 1 — Source: Analysed
Measured on: Fri, Jan 04, 1980 9:11PM Last saved on: Fri, Jan 04, 1980 9:11PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 100 mm.

Residual = 0.749 % — Concentration = 0.003 % — Obscuration = 22.74 %
d (0.5) = 7.75 µm — d (0.1) = 2.21 µm — d (0.9) = 26.47 µm
D [4, 3] = 11.68 µm — Span = 3.13
Sauter Mean (D[3,2]) = 4.74 µm — Mode = 7.56 µm
Specific Surface Area = 1.1582 sq. m. / gm — Density = 1.09 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.27	0.48	0.27
0.48	0.29	0.59	0.56
0.59	0.30	0.71	0.86
0.71	0.46	0.86	1.33
0.86	0.72	1.04	2.05
1.04	1.09	1.26	3.13
1.26	1.58	1.52	4.71
1.52	2.28	1.84	6.99
1.84	3.16	2.23	10.15
2.23	4.10	2.70	14.25
2.70	5.06	3.27	19.32
3.27	5.88	3.95	25.20
3.95	6.57	4.79	31.77
4.79	7.05	5.79	38.82
5.79	7.32	7.01	46.14
7.01	7.31	8.48	53.45

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
8.48	7.22	10.27	60.68
10.27	6.96	12.43	67.64
12.43	6.64	15.05	74.28
15.05	6.08	18.21	80.36
18.21	5.34	22.04	85.71
22.04	4.46	26.68	90.16
26.68	3.54	32.29	93.70
32.29	2.66	39.08	96.37
39.08	1.80	47.30	98.17
47.30	1.05	57.25	99.22
57.25	0.53	69.30	99.75
69.30	0.18	83.87	99.93
83.87	0.06	101.52	99.99
101.52	0.01	122.87	100.00
122.87	0.00	148.72	100.00
148.72	0.00	180.00	100.00



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MasterSizer X Ver. 1.2a
Serial No.

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Table A.1.4.2: *Particle size analysis for magnesium stearate powder. Run number 2.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:37AM

Magnesium stearate :Run Number 3

Batch nr.: ART 5876
Dispersant: Ethanol in MSX1

Sample 2
Sample File Name: RUAAN_05, Record: 3 — Source: Analysed
Measured on: Fri, Jan 04, 1980 9:17PM Last saved on: Fri, Jan 04, 1980 9:17PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 100 mm.

Residual = 0.241 % — Concentration = 0.006 % — Obscuration = 36.34 %
d (0.5) = 7.72 µm — d (0.1) = 2.15 µm — d (0.9) = 27.90 µm
D [4, 3] = 12.23 µm — Span = 3.34
Sauter Mean (D[3,2]) = 4.66 µm — Mode = 5.95 µm
Specific Surface Area = 1.1803 sq. m. / gm — Density = 1.09 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %	Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.31	0.48	0.31	8.48	6.97	10.27	60.46
0.48	0.32	0.59	0.63	10.27	6.71	12.43	67.17
0.59	0.33	0.71	0.96	12.43	6.42	15.05	73.60
0.71	0.51	0.86	1.47	15.05	5.90	18.21	79.50
0.86	0.77	1.04	2.24	18.21	5.21	22.04	84.71
1.04	1.15	1.26	3.39	22.04	4.39	26.68	89.10
1.26	1.65	1.52	5.05	26.68	3.53	32.29	92.63
1.52	2.37	1.84	7.41	32.29	2.73	39.08	95.36
1.84	3.24	2.23	10.65	39.08	1.95	47.30	97.31
2.23	4.17	2.70	14.82	47.30	1.26	57.25	98.57
2.70	5.10	3.27	19.93	57.25	0.73	69.30	99.30
3.27	5.89	3.95	25.81	69.30	0.39	83.87	99.69
3.95	6.52	4.79	32.33	83.87	0.18	101.52	99.87
4.79	6.94	5.79	39.27	101.52	0.09	122.87	99.96
5.79	7.14	7.01	46.41	122.87	0.03	148.72	99.99
7.01	7.08	8.48	53.49	148.72	0.01	180.00	100.00

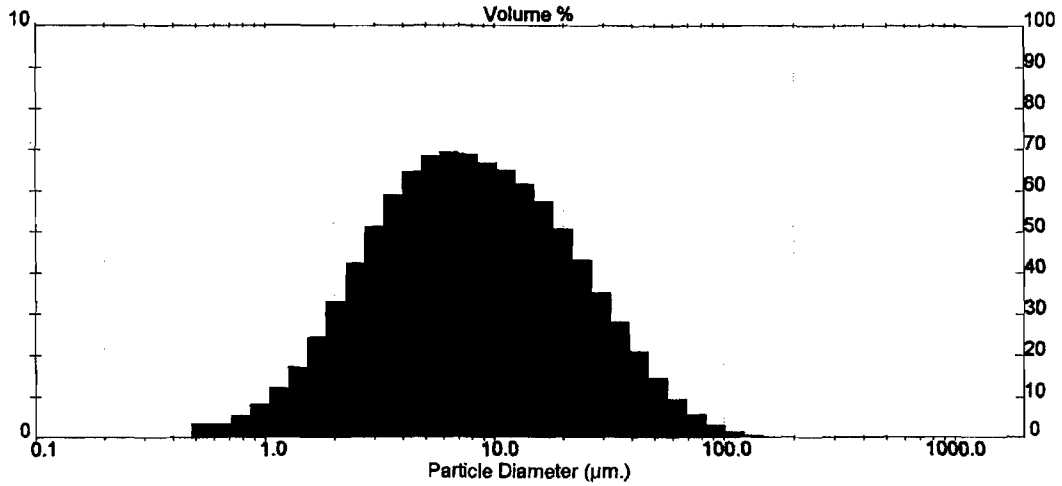

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Table A.1.5.1: *Particle size analysis for Pruv® powder. Run number 1.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:36AM

Pruv **:Run Number 1**

Batch nr.: 30003103
Dispersant: Ethanol in MSX1

Sample 1
Sample File Name: RUAAN_04, Record: 1 — Source: Analysed
Measured on: Fri, Jan 04, 1980 8:45PM Last saved on: Fri, Jan 04, 1980 8:45PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 100 mm.

Residual = 0.305 % — Concentration = 0.003 % — Obscuration = 16.91 %
d (0 .5) = 8.76 µm — d (0.1) = 3.32 µm — d (0.9) = 19.20 µm
D [4, 3] = 11.25 µm — Span = 1.81
Sauter Mean (D[3,2]) = 6.24 µm — Mode = 9.43 µm
Specific Surface Area = 0.8685 sq. m. / gm — Density = 1.11 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %	Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.08	0.48	0.08	8.48	12.59	10.27	60.45
0.48	0.09	0.59	0.18	10.27	11.78	12.43	72.23
0.59	0.10	0.71	0.28	12.43	9.62	15.05	81.85
0.71	0.16	0.86	0.44	15.05	6.75	18.21	88.60
0.86	0.27	1.04	0.72	18.21	4.22	22.04	92.81
1.04	0.45	1.26	1.17	22.04	2.47	26.68	95.29
1.26	0.70	1.52	1.87	26.68	1.46	32.29	96.74
1.52	1.08	1.84	2.95	32.29	0.93	39.08	97.67
1.84	1.58	2.23	4.52	39.08	0.62	47.30	98.30
2.23	2.19	2.70	6.72	47.30	0.45	57.25	98.75
2.70	2.98	3.27	9.70	57.25	0.36	69.30	99.11
3.27	4.01	3.95	13.71	69.30	0.30	83.87	99.41
3.95	5.47	4.79	19.17	83.87	0.26	101.52	99.68
4.79	7.38	5.79	26.55	101.52	0.18	122.87	99.86
5.79	9.68	7.01	36.23	122.87	0.10	148.72	99.96
7.01	11.63	8.48	47.85	148.72	0.04	180.00	100.00

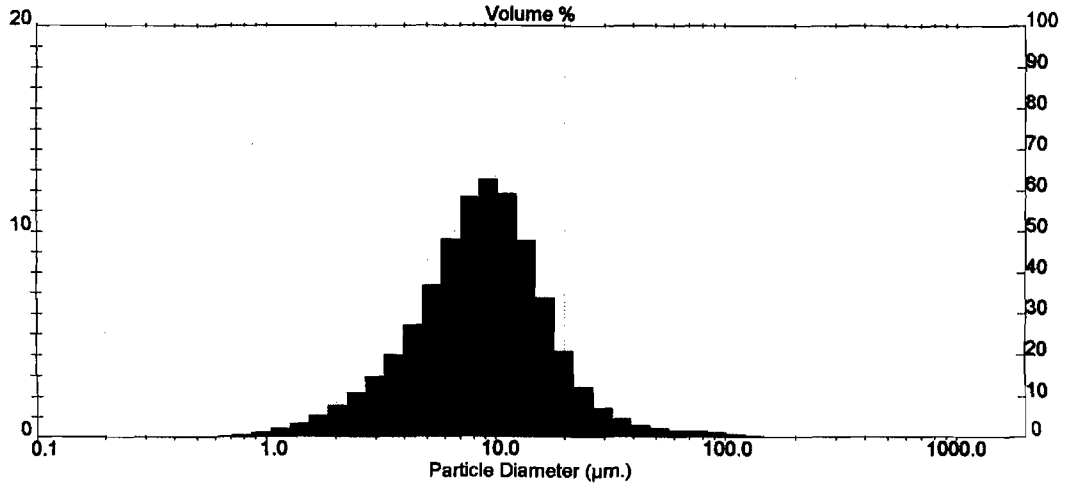

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Table A.1.5.2: *Particle size analysis for Pruv® powder. Run number 2.*

MALVERN INSTRUMENTS **MASTERSIZER X**

Version 1.2a — Thu, Oct 23, 2003 8:36AM

Pruv :Run Number 3

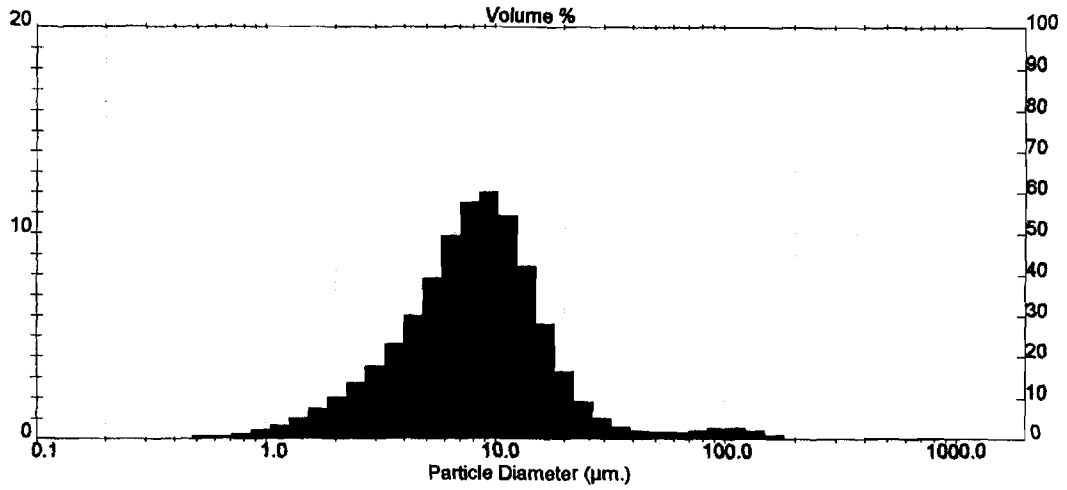
Batch nr.: 30003103
Dispersant: Ethanol in MSX1

Sample 2
Sample File Name: RUAAN_04, Record: 3 — Source: Analysed
Measured on: Fri, Jan 04, 1980 8:51PM Last saved on: Fri, Jan 04, 1980 8:52PM

Presentation: 2THD
Very Polydisperse model — Volume Result — Focus = 100 mm.

Residual = 0.169 % — Concentration = 0.008 % — Obscuration = 41.40 %
d (0.5) = 8.44 µm — d (0.1) = 3.05 µm — d (0.9) = 18.87 µm
D [4, 3] = 11.56 µm — Span = 1.88
Sauter Mean (D[3,2]) = 5.80 µm — Mode = 9.18 µm
Specific Surface Area = 0.9337 sq. m. / gm — Density = 1.11 gm. / c.c.

Size (Lo) µm	Result In %	Size (Hi) µm	Result Below %
0.20	0.13	0.48	0.13
0.48	0.14	0.59	0.27
0.59	0.15	0.71	0.41
0.71	0.23	0.86	0.64
0.86	0.37	1.04	1.01
1.04	0.58	1.26	1.59
1.26	0.87	1.52	2.46
1.52	1.29	1.84	3.75
1.84	1.82	2.23	5.57
2.23	2.46	2.70	8.03
2.70	3.27	3.27	11.30
3.27	4.31	3.95	15.61
3.95	5.75	4.79	21.36
4.79	7.61	5.79	28.97
5.79	9.80	7.01	38.76
7.01	11.56	8.48	50.33
8.48	12.31	10.27	62.63
10.27	11.30	12.43	73.93
12.43	9.03	15.05	82.96
15.05	6.17	18.21	89.14
18.21	3.76	22.04	92.90
22.04	2.15	26.68	95.04
26.68	1.24	32.29	96.28
32.29	0.79	39.08	97.07
39.08	0.54	47.30	97.61
47.30	0.42	57.25	98.03
57.25	0.37	69.30	98.40
69.30	0.38	83.87	98.78
83.87	0.41	101.52	99.19
101.52	0.39	122.87	99.58
122.87	0.27	148.72	99.86
148.72	0.14	180.00	100.00



Malvern Instruments Ltd.
Malvern, U.K.

MasterSizer X Ver. 1.2a
Serial No.

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A.2. POWDER FLOW CHARACTERISTICS

Table A.2.1: *Flow properties of fillers/binders mixed with no lubricant.*

Binder/ filler		Avicel® PH-200				Emcompress®				Tablettose®			
% Lub	Sample	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)
0	1	34	127	21	64.552	20	64	21	43.580	42	130	23	64.558
	2	36	127	20	64.512	20	59	21	43.540	47	125	23	64.518
	3	35	127	18	64.652	20	59	21	43.680	42	130	23	64.658
	Average	35	127	20	64.572	20	61	21	43.600	44	128	23	64.578

Table A.2.2: *Flow properties of fillers/binders mixed with magnesium stearate for 4 minutes at 69 rpm.*

Binder/ filler		Avicel® PH-200				Emcompress®				Tablettose®			
% Lub	Sample	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)
0.5	1	45	153	24	98.786	21	59	19	42.250	40	145	21	93.918
	2	39	153	26	98.746	16	55	19	42.210	36	150	21	93.878
	3	41	148	26	98.886	19	64	21	42.350	39	140	20	94.018
	Average	42	151	25	98.806	19	59	20	42.270	38	145	21	93.938
1.0	1	55	132	24	97.161	21	59	20	41.305	37	145	23	91.805
	2	42	137	26	97.121	23	57	20	41.265	42	145	23	91.765
	3	37	137	28	97.261	19	59	25	41.405	46	140	22	91.905
	Average	45	135	26	97.181	21	58	22	41.325	42	143	23	91.825
1.5	1	45	137	28	96.063	21	57	20	41.154	42	140	23	91.721
	2	44	127	26	96.023	21	59	21	41.114	42	145	23	91.681
	3	44	137	26	96.163	22	57	24	41.254	43	140	22	91.821
	Average	44	134	27	96.083	21	58	22	41.174	42	142	23	91.741
2.0	1	48	132	28	92.469	22	55	20	40.703	43	140	25	82.930
	2	45	132	24	92.429	22	55	22	40.663	45	135	24	82.890
	3	46	137	28	92.569	22	59	26	40.803	45	140	24	83.030
	Average	46	134	27	92.489	22	56	23	40.723	44	138	24	82.950

Table A.2.3: *Flow properties of fillers/binders mixed with magnesium stearate for 8 minutes at 69 rpm.*

Binder/ filler		Avicel® PH-200				Emcompress®				Tablettose®			
% Lub	Sample	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)
0.5	1	40	121	21	93.125	15	59	20	44.631	43	140	22	95.494
	2	36	132	20	93.085	21	59	21	44.591	38	140	21	95.454
	3	37	132	18	93.225	23	61	24	44.731	41	150	22	95.594
	Average	38	128	20	93.145	20	60	22	44.651	41	143	22	95.514
1.0	1	54	137	21	91.554	21	59	20	42.942	43	140	22	87.621
	2	42	148	21	91.514	21	59	21	42.902	41	140	22	87.581
	3	37	137	22	91.654	21	61	21	43.042	43	145	22	87.721
	Average	44	141	21	91.574	21	60	21	42.962	42	142	22	87.641
1.5	1	45	148	29	90.542	24	59	24	42.727	45	140	23	84.500
	2	46	143	27	90.502	23	59	24	42.687	42	140	24	84.460
	3	49	137	26	90.642	24	59	24	42.827	43	140	24	84.600
	Average	47	143	27	90.562	24	59	24	42.747	43	140	24	84.520
2.0	1	47	137	40	89.692	24	57	21	38.224	45	135	26	83.341
	2	50	127	27	89.652	24	55	22	38.184	46	140	23	83.301
	3	50	137	27	89.792	24	57	22	38.324	46	140	23	83.441
	Average	49	134	31	89.712	24	56	22	38.244	46	138	24	83.361

Table A.2.4: *Flow properties of fillers/binders mixed with Pruv® for 4 minutes at 69 rpm.*

Binder/ filler		Avicel® PH-200				Emcompress®				Tablettose®			
% Lub	Sample	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)
0.5	1	30	132	19	60.764	20	57	18	40.147	N/D	N/D	N/D	N/D
	2	29	132	16	60.724	20	55	19	40.107	N/D	N/D	N/D	N/D
	3	32	127	13	60.864	20	57	20	40.247	N/D	N/D	N/D	N/D
	Average	30	130	16	60.784	20	56	19	40.167	N/D	N/D	N/D	N/D
1.0	1	31	106	17	57.901	20	55	20	38.321	N/D	N/D	N/D	N/D
	2	25	106	14	57.861	20	55	20	38.281	N/D	N/D	N/D	N/D
	3	36	121	19	58.001	20	57	20	38.421	N/D	N/D	N/D	N/D
	Average	31	111	17	57.921	20	56	20	38.341	N/D	N/D	N/D	N/D
1.5	1	30	74	18	57.126	22	55	19	37.894	N/D	N/D	N/D	N/D
	2	33	69	19	57.086	22	55	18	37.854	N/D	N/D	N/D	N/D
	3	30	79	19	57.226	21	55	24	37.994	N/D	N/D	N/D	N/D
	Average	31	74	19	57.146	22	55	20	37.914	N/D	N/D	N/D	N/D
2.0	1	43	79	19	22.311	22	55	20	36.009	N/D	N/D	N/D	N/D
	2	37	74	20	22.271	22	55	20	35.969	N/D	N/D	N/D	N/D
	3	37	90	20	22.411	24	55	21	36.109	N/D	N/D	N/D	N/D
	Average	39	81	20	22.331	23	55	20	36.029	N/D	N/D	N/D	N/D

N/D – No data available

Table A.2.5: *Flow properties of fillers/binders mixed with Pruv® for 8 minutes at 69 rpm.*

Binder/ filler		Avicel® PH-200				Emcompress®				Tablettose®			
% Lub	Sample	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)	Height (mm)	Diameter (mm)	Flow time (s)	Mass flowed (g)
0.5	1	33	132	8	42.565	24	57	20	39.718	N/D	N/D	N/D	N/D
	2	33	131	9	42.525	21	57	20	39.678	N/D	N/D	N/D	N/D
	3	34	130	9	42.665	22	61	22	39.818	N/D	N/D	N/D	N/D
	Average	33	131	9	42.585	22	58	21	39.738	N/D	N/D	N/D	N/D
1.0	1	31	137	10	35.365	22	59	19	31.449	N/D	N/D	N/D	N/D
	2	36	127	6	35.325	23	55	19	31.409	N/D	N/D	N/D	N/D
	3	36	127	12	35.465	23	59	19	31.549	N/D	N/D	N/D	N/D
	Average	34	130	9	35.385	23	58	19	31.469	N/D	N/D	N/D	N/D
1.5	1	36	116	14	34.806	22	57	21	29.543	N/D	N/D	N/D	N/D
	2	37	111	14	34.766	22	59	20	29.503	N/D	N/D	N/D	N/D
	3	37	111	18	34.906	24	55	21	29.643	N/D	N/D	N/D	N/D
	Average	37	113	15	34.826	23	57	21	29.563	N/D	N/D	N/D	N/D
2.0	1	51	111	19	32.212	23	52	21	24.872	N/D	N/D	N/D	N/D
	2	51	111	21	32.172	23	52	20	24.832	N/D	N/D	N/D	N/D
	3	53	100	20	32.312	23	55	20	24.972	N/D	N/D	N/D	N/D
	Average	52	107	20	32.232	23	53	20	24.892	N/D	N/D	N/D	N/D

N/D – No data available

Annexure B

INFLUENCE OF MAGNESIUM STEARATE AND PRUV® ON AVICEL® PH-200, EMCOMPRESS® AND TABLETTOSE® TABLETS AT VARIOUS MIXING CONDITIONS

Table B.1.1.1.1: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 0.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	442.000 (0.483)	0.021	6.632 (0.095)	10.050 (0.047)	141.050 (2.349)	50.833 (40.458)
	2	450.550 (1.966)	0.022	6.663 (0.174)	10.057 (0.067)	128.920 (8.444)	40.000 (15.811)
	4	468.220 (0.872)	0.028	6.699 (0.131)	10.058 (0.042)	127.970 (3.629)	34.167 (40.784)
	8	495.450 (1.066)	0.033	6.742 (0.182)	10.060 (0.066)	121.960 (6.897)	16.500 (30.844)
	16	513.970 (1.029)	0.047	6.783 (0.197)	10.062 (0.078)	104.790 (2.900)	10.167 (4.016)
69	1	439.120 (4.131)	0.060	6.063 (15.666)	10.066 (0.051)	115.480 (23.745)	17.167 (2.378)
	2	480.150 (1.545)	0.066	6.633 (0.143)	10.067 (0.082)	117.180 (9.494)	11.000 (8.131)
	4	497.140 (1.514)	0.039	6.668 (0.243)	10.069 (0.087)	100.320 (6.713)	11.000 (8.131)
	8	499.970 (2.332)	0.056	6.705 (0.202)	10.075 (0.084)	77.160 (11.636)	8.833 (8.522)
	16	488.220 (3.039)	0.096	6.468 (0.535)	10.096 (0.069)	73.710 (24.964)	18.000 (11.653)
97	1	484.270 (1.189)	0.064	6.828 (0.180)	10.061 (0.119)	90.140 (3.841)	10.500 (17.817)
	2	495.070 (1.053)	0.031	6.853 (0.138)	10.054 (0.051)	82.410 (2.640)	10.500 (17.817)
	4	505.710 (0.872)	0.087	6.907 (0.098)	10.059 (0.073)	67.110 (4.165)	11.167 (6.741)
	8	505.530 (0.521)	0.098	6.924 (0.155)	10.069 (0.073)	56.500 (3.387)	19.167 (3.928)
	16	509.070 (0.697)	0.151	6.929 (0.144)	10.069 (0.056)	52.840 (3.011)	34.167 (11.323)

Table B.1.1.1.2: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 1.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	450.110 (0.801)	0.064	6.658 (0.063)	10.061 (0.031)	122.550 (4.558)	39.000 (17.466)
	2	459.930 (0.549)	0.134	6.708 (0.196)	10.072 (0.139)	113.090 (3.098)	28.333 (38.122)
	4	473.200 (1.181)	0.149	6.746 (0.104)	10.080 (0.047)	106.970 (4.179)	53.667 (74.223)
	8	493.050 (2.101)	0.166	6.794 (0.186)	10.082 (0.091)	86.030 (11.064)	16.000 (22.361)
	16	511.610 (0.783)	0.228	6.834 (0.231)	10.089 (0.056)	83.110 (4.305)	17.500 (15.649)
69	1	450.330 (5.035)	0.186	6.457 (0.220)	10.028 (0.092)	99.210 (26.222)	14.000 (7.825)
	2	474.020 (1.988)	0.242	6.507 (0.178)	10.028 (0.079)	84.130 (13.069)	13.667 (7.557)
	4	492.410 (1.523)	0.248	6.581 (0.242)	10.053 (0.082)	76.280 (4.435)	24.667 (2.094)
	8	501.920 (0.927)	0.274	6.617 (0.143)	10.056 (0.051)	68.220 (2.990)	57.333 (13.405)
	16	499.150 (1.466)	0.379	6.627 (0.202)	10.059 (0.073)	59.970 (2.985)	134.000 (13.614)
97	1	486.220 (0.917)	0.183	6.850 (0.154)	10.071 (0.073)	71.790 (3.132)	15.167 (7.708)
	2	495.790 (0.468)	0.196	6.882 (0.134)	10.070 (0.047)	60.810 (2.063)	35.833 (6.930)
	4	503.900 (0.795)	0.317	6.926 (0.155)	10.073 (0.048)	52.520 (3.340)	95.833 (17.590)
	8	506.540 (0.504)	0.395	6.953 (0.118)	10.077 (0.067)	48.460 (2.666)	136.667 (30.929)
	16	513.200 (1.339)	0.504	6.962 (0.260)	10.071 (0.031)	46.420 (3.490)	378.333 (39.908)

Table B.1.1.1.3: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 1.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	454.660 (1.026)	0.178	6.718 (0.137)	10.063 (0.048)	99.550 (5.744)	35.667 (37.097)
	2	468.800 (0.727)	0.253	6.753 (0.100)	10.068 (0.063)	93.480 (4.414)	25.000 (17.889)
	4	478.840 (1.093)	0.275	6.789 (0.224)	10.076 (0.051)	82.840 (3.666)	20.500 (25.766)
	8	491.890 (1.662)	0.314	6.817 (0.071)	10.077 (0.067)	69.210 (12.120)	36.500 (14.981)
	16	506.810 (1.923)	0.347	6.839 (0.175)	10.076 (0.069)	66.860 (5.320)	93.333 (22.389)
69	1	465.530 (1.217)	0.409	6.444 (0.266)	10.064 (0.084)	83.320 (14.630)	22.833 (1.788)
	2	482.310 (1.193)	0.389	6.684 (0.161)	10.076 (0.051)	67.990 (7.345)	49.500 (19.367)
	4	493.000 (0.310)	0.442	6.713 (0.158)	10.073 (0.094)	64.710 (2.155)	130.500 (22.043)
	8	494.950 (0.772)	0.539	6.735 (0.201)	10.081 (0.056)	54.670 (5.292)	480.500 (22.383)
	16	473.940 (3.910)	0.568	6.426 (0.488)	10.103 (0.048)	53.890 (22.717)	1038.333 (80.764)
97	1	491.180 (0.371)	0.374	6.879 (0.145)	10.073 (0.048)	59.820 (3.305)	91.333 (18.922)
	2	498.040 (1.139)	0.371	6.918 (0.202)	10.085 (0.052)	49.230 (1.932)	332.000 (20.156)
	4	502.810 (0.666)	0.498	6.943 (0.137)	10.077 (0.082)	47.970 (3.209)	624.167 (23.253)
	8	504.370 (0.777)	0.600	6.951 (0.143)	10.075 (0.052)	44.050 (4.223)	1440.833 (37.048)
	16	507.310 (0.722)	0.684	6.954 (0.139)	10.075 (0.070)	42.740 (2.797)	261.667 (49.794)

Table B.1.1.1.4: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 2.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	461.620 (0.719)	0.114	6.699 (2.468)	10.080 (0.094)	98.670 (3.309)	44.167 (23.108)
	2	469.340 (0.944)	0.245	6.774 (0.124)	10.075 (0.084)	83.150 (4.911)	31.167 (6.549)
	4	484.880 (0.348)	0.294	6.831 (0.146)	10.089 (0.087)	72.280 (2.935)	78.333 (46.498)
	8	494.980 (1.075)	0.377	6.854 (0.141)	10.107 (0.067)	64.270 (3.261)	242.500 (24.596)
	16	506.490 (0.920)	0.410	6.884 (0.140)	10.107 (0.048)	61.230 (3.369)	781.333 (17.348)
69	1	471.910 (0.592)	0.544	6.595 (0.129)	10.062 (0.063)	73.230 (1.841)	142.167 (24.082)
	2	481.470 (0.759)	0.557	6.629 (0.048)	10.069 (0.056)	62.640 (4.437)	588.333 (19.062)
	4	492.760 (0.919)	0.749	6.648 (0.185)	10.065 (0.052)	58.400 (3.166)	1630.000 (14.497)
	8	498.770 (1.074)	0.709	6.675 (0.215)	10.071 (0.056)	54.670 (2.751)	1551.667 (24.815)
	16	499.570 (1.153)	0.764	6.683 (0.187)	10.068 (0.063)	51.830 (2.614)	1581.667 (33.813)
97	1	488.860 (0.414)	0.573	6.880 (0.181)	10.074 (0.069)	52.470 (2.374)	751.667 (26.413)
	2	494.950 (0.239)	0.688	6.915 (0.102)	10.075 (0.052)	47.720 (1.968)	971.667 (44.483)
	4	502.350 (0.531)	0.539	6.951 (0.143)	10.076 (0.051)	43.110 (2.972)	874.167 (85.433)
	8	503.220 (0.698)	0.720	6.952 (0.132)	10.081 (0.099)	40.620 (3.247)	1105.833 (53.019)
	16	507.640 (0.693)	0.827	6.958 (0.113)	10.075 (0.052)	42.170 (3.110)	424.167 (41.324)

Table B.1.1.1.5: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 2.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	459.290 (0.946)	0.417	6.800 (0.098)	10.112 (0.042)	82.510 (5.670)	86.167 (85.242)
	2	468.510 (0.912)	0.430	6.833 (0.120)	10.112 (0.063)	71.180 (4.353)	67.667 (17.047)
	4	484.030 (0.344)	0.563	6.878 (0.092)	10.114 (0.051)	60.510 (2.745)	463.333 (23.031)
	8	493.060 (0.595)	0.564	6.892 (0.092)	10.115 (0.052)	56.630 (4.781)	1302.500 (12.883)
	16	505.610 (0.715)	0.574	6.913 (0.168)	10.114 (0.069)	53.970 (3.201)	1800.000 (0.000)
69	1	458.390 (3.064)	0.519	6.480 (0.252)	10.070 (0.066)	65.000 (19.122)	629.167 (22.726)
	2	483.820 (0.575)	0.642	6.740 (0.171)	10.085 (0.096)	54.570 (2.853)	1800.000 (0.000)
	4	495.550 (0.247)	0.627	6.778 (0.136)	10.099 (0.073)	48.690 (2.404)	1800.000 (0.000)
	8	508.830 (6.039)	0.634	6.792 (0.167)	10.109 (0.056)	47.630 (3.170)	1800.000 (0.000)
	16	469.430 (2.728)	0.703	6.401 (0.341)	10.108 (0.063)	45.500 (15.383)	1515.000 (31.027)
97	1	483.920 (0.387)	0.665	6.887 (0.120)	10.081 (0.031)	48.750 (2.649)	1467.500 (33.869)
	2	499.450 (0.100)	0.709	6.932 (0.114)	10.081 (0.073)	43.910 (2.980)	1463.333 (31.683)
	4	498.260 (0.435)	0.761	6.943 (0.153)	10.080 (0.066)	39.340 (3.371)	988.333 (58.690)
	8	503.320 (0.218)	0.908	6.954 (0.139)	10.080 (0.081)	38.480 (2.932)	326.333 (41.561)
	16	505.150 (0.384)	0.927	6.954 (0.121)	10.074 (0.051)	38.880 (1.354)	321.167 (13.665)

Table B.1.1.2.1: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 0.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	449.050 (0.418)	0.056	6.874 (0.075)	10.065 (0.070)	145.380 (3.163)	135.000 (10.476)
	2	449.950 (0.489)	0.067	6.876 (0.141)	10.067 (0.048)	140.350 (3.621)	143.333 (9.784)
	4	456.060 (0.841)	0.072	6.888 (0.092)	10.063 (0.048)	132.190 (1.883)	102.500 (9.126)
	8	460.630 (0.510)	0.089	6.896 (0.140)	10.068 (0.091)	132.350 (2.970)	105.000 (13.469)
	16	477.730 (0.600)	0.126	6.914 (0.207)	10.076 (0.157)	146.360 (2.759)	99.500 (10.025)
69	1	454.700 (0.361)	0.161	6.839 (0.128)	10.063 (0.048)	133.170 (4.097)	113.667 (6.852)
	2	462.600 (0.307)	0.177	6.856 (0.123)	10.066 (0.051)	134.650 (3.014)	123.833 (12.975)
	4	436.860 (0.461)	0.106	6.793 (0.241)	10.022 (0.063)	153.720 (4.363)	27.500 (9.959)
	8	485.350 (0.278)	0.150	6.855 (0.077)	10.016 (0.052)	148.050 (3.877)	95.833 (18.495)
	16	513.200 (0.426)	0.259	6.877 (0.120)	10.015 (0.053)	174.930 (3.170)	87.000 (30.498)
97	1	463.640 (0.811)	0.172	6.926 (0.122)	10.067 (0.048)	127.660 (2.369)	98.333 (16.607)
	2	472.290 (0.426)	0.085	6.938 (0.091)	10.066 (0.069)	135.740 (2.813)	120.000 (21.246)
	4	494.260 (0.417)	0.235	6.961 (0.158)	10.065 (0.052)	151.010 (3.295)	100.833 (14.568)
	8	509.020 (0.526)	0.265	6.968 (0.091)	10.067 (0.082)	164.580 (3.671)	48.500 (11.274)
	16	522.030 (0.391)	0.408	6.963 (0.097)	10.068 (0.063)	165.810 (2.803)	32.667 (6.891)

Table B.1.1.2.2: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 1.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	453.830 (0.502)	0.172	6.913 (0.098)	10.101 (0.109)	130.500 (1.745)	113.333 (14.136)
	2	458.430 (0.693)	0.360	6.930 (0.118)	10.105 (0.052)	120.860 (2.086)	83.333 (12.961)
	4	454.150 (0.426)	0.432	6.910 (0.118)	10.098 (0.063)	135.750 (2.638)	105.000 (13.469)
	8	480.240 (0.786)	0.448	6.949 (0.082)	10.102 (0.063)	137.910 (2.802)	85.000 (20.035)
	16	494.370 (0.322)	0.613	6.985 (0.075)	10.113 (0.048)	139.290 (3.044)	80.833 (22.615)
69	1	465.690 (0.618)	0.500	6.838 (0.115)	10.021 (0.057)	123.350 (2.293)	95.333 (18.128)
	2	473.980 (0.660)	0.652	6.860 (0.069)	10.024 (0.052)	128.550 (3.737)	91.167 (8.366)
	4	485.620 (0.449)	0.667	6.873 (0.070)	10.023 (0.067)	134.890 (3.057)	92.500 (22.612)
	8	498.790 (0.420)	0.738	6.888 (0.133)	10.022 (0.063)	143.010 (2.557)	72.500 (12.902)
	16	524.010 (0.306)	1.021	6.891 (0.046)	10.017 (0.048)	158.700 (3.712)	50.500 (50.776)
97	1	475.220 (0.534)	0.494	6.976 (0.154)	10.081 (0.128)	112.700 (6.491)	63.333 (17.055)
	2	485.970 (0.597)	0.529	6.983 (0.069)	10.077 (0.048)	125.320 (3.520)	81.167 (9.396)
	4	507.080 (0.338)	0.854	6.986 (0.100)	10.079 (0.087)	134.610 (1.817)	38.167 (14.004)
	8	521.870 (0.340)	1.064	7.017 (0.117)	10.080 (0.066)	139.010 (2.670)	16.000 (6.847)
	16	522.440 (0.501)	1.359	7.033 (0.135)	10.096 (0.096)	124.240 (2.461)	14.500 (12.902)

Table B.1.1.2.3: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 1.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	459.350 (0.432)	0.479	6.923 (0.070)	10.107 (0.067)	123.430 (2.181)	97.500 (9.594)
	2	467.580 (0.623)	0.682	6.945 (0.102)	10.106 (0.083)	117.973 (2.586)	94.167 (25.446)
	4	475.950 (0.467)	0.740	6.949 (0.126)	10.102 (0.063)	123.000 (1.601)	80.833 (19.723)
	8	492.380 (0.238)	0.845	6.972 (0.091)	10.107 (0.048)	124.410 (2.815)	62.500 (14.967)
	16	504.050 (0.237)	0.936	6.979 (0.081)	10.107 (0.067)	135.620 (1.959)	47.500 (11.040)
69	1	475.200 (0.825)	1.101	6.914 (0.101)	10.084 (0.051)	111.270 (3.788)	79.167 (69.579)
	2	488.690 (0.415)	1.049	6.932 (0.133)	10.083 (0.048)	119.230 (4.036)	51.167 (8.777)
	4	497.570 (0.613)	1.191	6.935 (0.123)	10.073 (0.067)	122.170 (1.840)	40.333 (12.803)
	8	515.660 (0.413)	1.452	6.963 (0.069)	10.081 (0.056)	131.500 (1.576)	29.500 (11.495)
	16	516.870 (0.507)	1.531	6.976 (0.100)	10.084 (0.051)	125.570 (3.267)	23.667 (12.439)
97	1	483.870 (0.774)	1.007	7.033 (0.117)	10.115 (0.070)	104.020 (2.689)	44.667 (7.841)
	2	493.380 (0.385)	0.999	7.030 (0.134)	10.106 (0.096)	111.550 (2.657)	45.000 (0.000)
	4	511.610 (0.637)	1.341	7.030 (0.116)	10.108 (0.078)	120.050 (3.392)	17.333 (12.986)
	8	525.540 (0.757)	1.616	7.045 (0.075)	10.104 (0.069)	118.250 (3.211)	11.667 (11.711)
	16	528.500 (0.493)	1.842	7.052 (0.112)	10.110 (0.081)	102.350 (4.335)	11.667 (11.711)

Table B.1.1.2.4: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 2.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	463.860 (0.507)	0.308	6.928 (0.091)	10.110 (0.047)	110.330 (2.598)	90.000 (17.568)
	2	473.490 (0.382)	0.659	6.953 (0.097)	10.110 (0.047)	108.070 (2.649)	62.333 (9.500)
	4	484.710 (0.652)	0.793	6.976 (0.138)	10.115 (0.052)	107.100 (2.699)	54.167 (6.750)
	8	499.650 (0.475)	1.017	6.983 (0.069)	10.106 (0.051)	122.730 (3.128)	55.000 (18.506)
	16	514.730 (0.421)	1.104	6.997 (0.118)	10.110 (0.066)	125.990 (2.667)	30.833 (24.220)
69	1	479.840 (0.519)	1.466	6.933 (0.070)	10.086 (0.051)	103.300 (2.443)	54.500 (23.747)
	2	488.870 (0.668)	1.499	6.939 (0.082)	10.082 (0.042)	108.200 (3.233)	43.833 (8.587)
	4	504.160 (0.437)	2.018	6.952 (0.091)	10.082 (0.042)	109.240 (3.590)	30.000 (12.293)
	8	518.120 (0.329)	1.910	6.969 (0.106)	10.079 (0.056)	109.310 (2.442)	20.500 (11.440)
	16	521.550 (0.566)	2.060	6.993 (0.069)	10.082 (0.063)	103.960 (2.779)	16.000 (28.777)
97	1	498.960 (0.580)	1.543	7.044 (0.099)	10.119 (0.056)	95.770 (1.851)	28.333 (10.390)
	2	519.740 (0.371)	1.853	7.055 (0.120)	10.118 (0.042)	100.720 (3.388)	17.500 (10.690)
	4	490.980 (0.215)	1.453	7.041 (0.105)	10.118 (0.063)	95.660 (2.250)	37.500 (4.989)
	8	529.420 (0.392)	1.940	7.061 (0.104)	10.110 (0.066)	107.090 (3.361)	14.167 (21.604)
	16	535.420 (0.352)	2.227	7.072 (0.112)	10.112 (0.078)	92.710 (3.282)	14.500 (12.902)

Table B.1.1.2.5: *Physical characterization of Avicel® tablets. Filler/binder is mixed with 2.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	1	470.620 (0.653)	1.124	6.953 (0.118)	10.114 (0.069)	99.950 (2.656)	74.167 (15.618)
	2	475.850 (0.312)	1.160	6.966 (0.121)	10.110 (0.066)	102.090 (3.543)	72.833 (40.734)
	4	486.180 (0.531)	1.517	6.985 (0.075)	10.120 (0.066)	98.370 (3.404)	40.667 (10.277)
	8	503.810 (0.369)	1.519	6.997 (0.069)	10.113 (0.048)	107.860 (2.716)	35.000 (10.537)
	16	517.730 (0.394)	1.547	7.013 (0.096)	10.109 (0.056)	112.580 (1.735)	22.667 (9.931)
69	1	485.580 (0.326)	1.399	6.943 (0.097)	10.085 (0.052)	96.060 (1.877)	45.000 (7.027)
	2	493.770 (0.323)	1.729	6.953 (0.118)	10.082 (0.063)	99.940 (3.468)	39.500 (8.585)
	4	505.980 (0.418)	1.690	6.967 (0.097)	10.082 (0.063)	100.240 (3.070)	25.833 (7.902)
	8	524.100 (0.270)	1.709	6.994 (0.138)	10.087 (0.067)	99.690 (2.848)	17.500 (15.649)
	16	524.900 (0.521)	1.893	7.017 (0.135)	10.089 (0.031)	92.950 (3.676)	19.500 (18.561)
97	1	491.880 (0.519)	1.792	7.039 (0.105)	10.115 (0.070)	89.200 (3.122)	31.500 (9.785)
	2	498.510 (0.660)	1.911	7.051 (0.105)	10.120 (0.066)	87.500 (2.335)	21.500 (14.336)
	4	520.920 (0.340)	2.050	7.040 (0.095)	10.111 (0.073)	95.950 (3.029)	15.500 (12.070)
	8	534.760 (0.537)	2.446	7.063 (0.134)	10.116 (0.069)	94.550 (2.737)	17.000 (5.261)
	16	537.920 (0.437)	2.497	7.041 (0.156)	10.073 (0.067)	85.200 (3.125)	22.500 (8.315)

Table B.1.2.1.1: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 0.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	865.840 (0.259)	2.801	6.730 (0.280)	10.049 (0.110)	106.610 (5.938)	900.00 (0.000)
	4	884.170 (0.210)	2.639	6.872 (0.355)	10.083 (0.175)	110.500 (5.723)	900.00 (0.000)
	8	900.275 (0.319)	2.568	6.943 (0.236)	10.087 (0.048)	117.320 (5.904)	900.00 (0.000)
69	2	897.005 (0.279)	2.560	7.227 (13.045)	10.089 (0.073)	118.570 (5.298)	900.00 (0.000)
	4	910.370 (0.241)	2.672	6.985 (0.272)	10.094 (0.051)	115.960 (6.194)	900.00 (0.000)
	8	919.870 (0.213)	2.904	7.032 (0.161)	10.095 (0.084)	105.220 (5.116)	900.00 (0.000)
97	2	906.680 (0.310)	2.167	6.977 (0.253)	10.088 (0.063)	126.090 (2.968)	900.00 (0.000)
	4	917.785 (0.279)	2.469	7.020 (0.269)	10.091 (0.073)	116.320 (5.088)	900.00 (0.000)
	8	911.420 (0.358)	2.836	6.969 (0.257)	10.091 (0.056)	105.460 (7.167)	900.00 (0.000)

Table B.1.2.1.2: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 1.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	870.530 (0.244)	2.983	6.788 (0.181)	10.088 (0.063)	107.350 (4.463)	900.00 (0.000)
	4	883.615 (0.240)	2.891	6.852 (0.246)	10.087 (0.067)	108.860 (4.676)	900.00 (0.000)
	8	897.065 (0.307)	2.742	6.916 (0.238)	10.090 (0.000)	107.590 (4.959)	900.00 (0.000)
69	2	891.290 (0.454)	2.903	6.853 (0.169)	10.055 (0.107)	113.640 (6.445)	900.00 (0.000)
	4	903.350 (0.315)	2.827	6.940 (0.152)	10.073 (0.094)	110.330 (5.350)	900.00 (0.000)
	8	912.070 (0.272)	2.753	6.980 (0.151)	10.083 (0.048)	108.620 (5.804)	900.00 (0.000)
97	2	901.630 (0.217)	2.472	6.917 (0.193)	10.091 (0.056)	113.740 (4.073)	900.00 (0.000)
	4	909.200 (0.275)	2.581	6.951 (0.291)	10.090 (0.093)	109.710 (4.560)	900.00 (0.000)
	8	913.590 (0.344)	2.678	6.957 (0.225)	10.082 (0.042)	107.880 (5.353)	900.00 (0.000)

Table B.1.2.1.3: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 1.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	870.365 (0.500)	2.947	6.779 (0.129)	10.091 (0.056)	103.960 (3.522)	900.00 (0.000)
	4	877.895 (0.326)	2.991	6.807 (0.240)	10.090 (0.047)	104.560 (7.143)	900.00 (0.000)
	8	889.055 (0.296)	2.886	6.855 (0.172)	10.089 (0.056)	103.710 (6.024)	900.00 (0.000)
69	2	888.050 (0.284)	2.192	6.851 (0.145)	10.085 (0.070)	113.800 (4.189)	900.00 (0.000)
	4	896.815 (0.288)	2.816	6.898 (0.203)	10.087 (0.067)	111.470 (6.310)	900.00 (0.000)
	8	908.790 (0.245)	2.817	6.948 (0.114)	10.086 (0.069)	108.360 (4.024)	900.00 (0.000)
97	2	895.485 (0.409)	2.622	6.880 (0.283)	10.084 (0.051)	111.840 (7.000)	900.00 (0.000)
	4	903.990 (0.132)	2.687	6.915 (0.196)	10.086 (0.069)	108.450 (4.317)	900.00 (0.000)
	8	910.690 (0.256)	2.723	6.943 (0.236)	10.093 (0.067)	103.660 (4.106)	900.00 (0.000)

Table B.1.2.1.4: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 2.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	864.740 (0.330)	3.066	6.739 (0.284)	10.090 (0.047)	103.830 (2.582)	900.00 (0.000)
	4	873.965 (0.319)	2.997	6.782 (0.218)	10.093 (0.067)	103.350 (6.532)	900.00 (0.000)
	8	884.980 (0.259)	2.799	6.834 (0.141)	10.089 (0.056)	103.820 (5.720)	900.00 (0.000)
69	2	884.010 (0.442)	2.779	6.824 (0.427)	10.082 (0.259)	108.700 (5.771)	900.00 (0.000)
	4	892.005 (0.260)	2.640	6.862 (0.165)	10.089 (0.099)	108.600 (3.967)	900.00 (0.000)
	8	898.850 (0.213)	2.720	6.891 (0.277)	10.089 (0.073)	109.260 (6.311)	900.00 (0.000)
97	2	889.025 (0.278)	2.638	6.854 (0.157)	10.083 (0.048)	109.100 (4.673)	900.00 (0.000)
	4	899.340 (0.202)	2.579	6.898 (0.165)	10.085 (0.070)	108.250 (4.864)	900.00 (0.000)
	8	909.600 (0.210)	2.680	6.935 (0.207)	10.085 (0.084)	109.860 (2.967)	900.00 (0.000)

Table B.1.2.2.1: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 0.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	866.955 (0.409)	2.368	6.749 (0.410)	10.049 (0.056)	123.160 (4.552)	900.00 (0.000)
	4	874.060 (0.231)	2.469	6.786 (0.320)	10.046 (0.051)	123.680 (5.440)	900.00 (0.000)
	8	884.935 (0.325)	2.580	6.845 (0.294)	10.047 (0.067)	123.110 (3.995)	900.00 (0.000)
69	2	890.050 (0.203)	2.901	6.871 (0.174)	10.051 (0.073)	106.080 (5.888)	900.00 (0.000)
	4	902.115 (0.218)	2.805	6.932 (0.310)	10.049 (0.031)	112.400 (4.993)	900.00 (0.000)
	8	930.665 (0.219)	3.033	7.063 (0.306)	10.054 (0.084)	106.670 (5.452)	900.00 (0.000)
97	2	913.890 (0.247)	3.077	6.946 (0.256)	10.046 (0.051)	105.760 (5.414)	900.00 (0.000)
	4	928.565 (0.365)	2.856	7.054 (0.277)	10.050 (0.047)	113.010 (5.292)	900.00 (0.000)
	8	946.420 (0.230)	3.188	7.133 (0.350)	10.054 (0.051)	106.030 (4.819)	900.00 (0.000)

Table B.1.2.2.2: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 1.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	873.305 (0.404)	2.856	6.778 (0.285)	10.050 (0.066)	119.490 (5.204)	900.00 (0.000)
	4	882.695 (0.160)	2.861	6.831 (0.188)	10.058 (0.113)	115.590 (5.020)	900.00 (0.000)
	8	895.860 (0.231)	2.710	6.918 (0.213)	10.078 (0.078)	121.180 (3.629)	900.00 (0.000)
69	2	900.105 (0.327)	3.581	6.899 (0.316)	10.049 (0.099)	100.610 (3.864)	900.00 (0.000)
	4	912.485 (0.188)	3.472	6.958 (0.201)	10.052 (0.078)	107.590 (5.738)	900.00 (0.000)
	8	932.165 (0.285)	3.683	7.052 (0.371)	10.053 (0.067)	91.030 (30.117)	900.00 (0.000)
97	2	912.570 (0.200)	3.315	6.958 (0.261)	10.054 (0.051)	109.710 (5.654)	900.00 (0.000)
	4	931.960 (0.245)	3.418	7.051 (0.216)	10.058 (0.091)	101.020 (7.394)	900.00 (0.000)
	8	944.505 (0.359)	3.692	7.095 (0.306)	10.053 (0.067)	92.550 (5.370)	900.00 (0.000)

Table B.1.2.2.3: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 1.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	874.205 (0.393)	3.126	6.810 (0.240)	10.085 (0.070)	114.730 (5.277)	900.00 (0.000)
	4	885.545 (0.368)	3.073	6.867 (0.218)	10.089 (0.073)	114.530 (5.620)	900.00 (0.000)
	8	897.675 (0.281)	3.114	6.924 (0.228)	10.085 (0.052)	115.600 (4.549)	900.00 (0.000)
69	2	894.505 (0.237)	3.009	6.876 (0.184)	10.048 (0.079)	112.650 (4.004)	900.00 (0.000)
	4	913.660 (0.308)	3.694	6.949 (0.172)	10.051 (0.056)	105.220 (2.943)	900.00 (0.000)
	8	932.705 (0.244)	3.427	7.039 (0.216)	10.050 (0.066)	96.180 (5.588)	900.00 (0.000)
97	2	919.530 (0.325)	3.491	6.984 (0.377)	10.052 (0.042)	100.440 (4.158)	900.00 (0.000)
	4	929.750 (0.292)	3.766	7.032 (0.161)	10.053 (0.067)	97.320 (3.052)	900.00 (0.000)
	8	938.050 (0.365)	3.870	7.061 (0.205)	10.057 (0.082)	91.850 (4.994)	900.00 (0.000)

Table B.1.2.2.4: *Physical characterization of Emcompress® tablets. Filler/binder is mixed with 2.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	875.380 (0.311)	3.341	6.807 (0.196)	10.084 (0.051)	112.120 (4.016)	900.00 (0.000)
	4	885.065 (0.330)	3.325	6.849 (0.252)	10.084 (0.051)	111.790 (4.146)	900.00 (0.000)
	8	900.820 (0.270)	3.081	6.930 (0.215)	10.085 (0.052)	109.100 (4.822)	900.00 (0.000)
69	2	899.165 (0.313)	3.141	6.897 (0.138)	10.050 (0.047)	112.840 (6.464)	900.00 (0.000)
	4	913.745 (0.404)	3.286	6.950 (0.225)	10.048 (0.042)	106.480 (6.126)	900.00 (0.000)
	8	930.800 (0.194)	3.689	7.033 (0.135)	10.053 (0.067)	100.110 (5.571)	900.00 (0.000)
97	2	917.670 (0.209)	3.559	6.973 (0.203)	10.051 (0.031)	99.990 (6.601)	900.00 (0.000)
	4	929.095 (0.293)	3.631	7.018 (0.348)	10.050 (0.066)	95.630 (2.774)	900.00 (0.000)
	8	937.615 (0.330)	3.715	7.049 (0.170)	10.054 (0.051)	92.260 (4.668)	900.00 (0.000)

Table B.1.3.1.1: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 0.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	580.195 (1.288)	1.447	6.449 (0.802)	10.068 (0.042)	99.030 (4.983)	221.667 (4.873)
	4	612.125 (2.198)	1.507	6.753 (1.306)	10.108 (0.102)	101.000 (10.506)	607.500 (9.955)
	8	617.420 (1.693)	1.569	6.764 (1.415)	10.114 (0.069)	85.530 (5.471)	900.000 (0.000)
69	2	604.715 (1.355)	1.430	6.616 (1.001)	10.073 (0.115)	97.740 (10.057)	636.667 (23.715)
	4	598.925 (0.820)	1.311	6.619 (0.501)	10.080 (0.047)	104.660 (3.267)	900.000 (0.000)
	8	594.700 (0.383)	1.409	6.572 (0.429)	10.086 (0.069)	101.590 (7.177)	900.000 (0.000)
97	2	597.780 (0.575)	1.600	6.592 (0.553)	10.075 (0.070)	87.600 (8.396)	900.000 (0.000)
	4	591.965 (1.741)	1.594	6.616 (1.120)	10.128 (0.078)	95.350 (7.269)	900.000 (0.000)
	8	592.125 (1.068)	3.068 [a]	6.600 (0.423)	10.123 (0.140)	89.090 (7.965)	900.000 (0.000)

[a] *Tablets capped during testing*

Table B.1.3.1.2: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 1.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	587.155 (2.172)	1.733	6.553 (0.941)	10.071 (0.073)	88.430 (5.760)	900.00 (0.000)
	4	600.560 (2.541)	1.759	6.646 (1.873)	10.108 (0.078)	85.320 (6.750)	900.00 (0.000)
	8	599.890 (1.076)	1.925	6.637 (0.599)	10.111 (0.073)	85.530 (5.471)	900.00 (0.000)
69	2	597.290 (0.640)	1.815	6.545 (0.591)	10.075 (0.052)	87.850 (6.351)	900.00 (0.000)
	4	585.905 (1.066)	1.573	6.507 (0.967)	10.103 (0.457)	95.490 (12.756)	900.00 (0.000)
	8	586.490 (0.969)	1.723	6.539 (0.976)	10.117 (0.187)	88.670 (6.958)	900.00 (0.000)
97	2	596.640 (1.552)	2.110	6.562 (1.534)	10.070 (0.047)	80.810 (4.269)	900.00 (0.000)
	4	583.680 (2.045)	1.913	6.553 (0.644)	10.132 (0.308)	78.780 (10.666)	900.00 (0.000)
	8	586.505 (0.954)	4.371 [a]	6.547 (0.717)	10.131 (0.157)	81.020 (9.910)	900.00 (0.000)

[a] *Tablets capped during testing*

Table B.1.3.1.3: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 1.5% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	586.305 (1.527)	1.874	6.506 (1.369)	10.105 (0.070)	87.280 (6.477)	900.00 (0.000)
	4	594.110 (0.690)	1.907	6.564 (0.444)	10.112 (0.112)	81.930 (7.914)	900.00 (0.000)
	8	597.835 (1.314)	2.066	6.604 (1.002)	10.111 (0.031)	75.600 (9.583)	900.00 (0.000)
69	2	595.905 (1.202)	1.911	6.531 (0.959)	10.070 (0.047)	77.510 (7.719)	900.00 (0.000)
	4	587.885 (0.609)	1.734	6.544 (0.339)	10.116 (0.051)	91.170 (7.154)	900.00 (0.000)
	8	584.720 (1.042)	1.775	6.500 (0.897)	10.116 (0.069)	88.300 (7.868)	900.00 (0.000)
97	2	590.505 (0.971)	2.197	6.532 (0.450)	10.076 (0.069)	79.070 (11.995)	900.00 (0.000)
	4	583.465 (0.666)	3.628 [a]	6.512 (0.346)	10.126 (0.125)	79.150 (6.498)	900.00 (0.000)
	8	585.430 (0.745)	2.049	6.527 (0.666)	10.122 (0.102)	79.030 (8.738)	900.00 (0.000)

[a] *Tablets capped during testing*

Table B.1.3.1.4: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 2.0% w/w magnesium stearate for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	587.260 (0.782)	2.095	6.523 (0.686)	10.106 (0.051)	80.170 (6.803)	900.00 (0.000)
	4	594.270 (0.607)	1.985	6.567 (0.565)	10.110 (0.047)	76.610 (7.503)	900.00 (0.000)
	8	591.455 (1.072)	2.185	6.547 (0.974)	10.111 (0.056)	74.930 (9.338)	900.00 (0.000)
69	2	590.120 (0.646)	2.055	6.492 (0.481)	10.070 (0.066)	74.950 (7.046)	900.00 (0.000)
	4	591.560 (0.798)	2.198	6.512 (0.574)	10.073 (0.048)	68.400 (4.173)	900.00 (0.000)
	8	592.070 (0.647)	2.638	6.507 (0.561)	10.076 (0.069)	64.680 (7.888)	900.00 (0.000)
97	2	588.065 (1.034)	2.571	6.490 (0.658)	10.073 (0.067)	66.610 (6.165)	900.00 (0.000)
	4	587.275 (0.599)	6.962 [a]	6.483 (0.449)	10.071 (0.056)	55.930 (17.681)	900.00 (0.000)
	8 [b]						

[a] *Tablets capped during testing;* [b] *Tablets capped during tableting process*

Table B.1.3.2.1: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 0.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2 [c]						
	4 [c]						
	8 [c]						
69	2 [c]						
	4	572.335 (0.358)	1.581	6.397 (0.338)	10.071 (0.087)	113.140 (7.573)	158.333 (3.475)
	8	593.405 (1.803)	1.526	6.574 (0.760)	10.073 (0.082)	112.570 (8.472)	223.333 (12.667)
97	2 [c]						
	4 [c]						
	8 [c]						

[c] *Tableting impossible due to poor lubrication*

Table B.1.3.2.2: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 1.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	543.995 (0.628)	1.387	6.140 (0.548)	10.099 (0.151)	100.690 (6.217)	155.000 (2.414)
	4	545.810 (4.466)	1.495	6.243 (0.740)	10.105 (0.070)	94.010 (6.761)	161.167 (4.105)
	8	550.950 (0.499)	1.776	6.180 (0.374)	10.069 (0.073)	83.600 (6.219)	183.333 (5.862)
69	2	550.970 (0.450)	1.638	6.210 (0.436)	10.109 (0.056)	93.070 (4.578)	172.500 (5.423)
	4	592.935 (0.631)	1.638	6.562 (0.392)	10.086 (0.273)	116.700 (11.213)	190.833 (3.913)
	8	600.485 (0.441)	1.551	6.630 (0.513)	10.081 (0.190)	114.820 (9.304)	205.000 (1.825)
97	2	568.190 (0.614)	7.847 [a]	6.378 (0.532)	10.113 (0.081)	87.450 [a] (17.745)	207.500 (4.508)
	4	619.385 (1.190)	1.504	6.790 (1.257)	10.109 (0.073)	110.820 (10.474)	237.500 (3.939)
	8	619.670 (1.942)	1.702	6.834 (0.862)	10.106 (0.083)	104.180 (6.750)	262.500 (3.563)

[a] *Tablets capped during testing*

Table B.1.3.2.3: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 1.5% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	552.160 (0.873)	1.649	6.217 (0.612)	10.104 (0.083)	98.300 (4.249)	168.000 (3.346)
	4	563.495 (0.245)	1.579	6.337 (0.224)	10.106 (0.051)	96.960 (5.923)	186.500 (2.932)
	8	564.675 (0.580)	1.932	6.335 (0.478)	10.100 (0.155)	84.870 (5.122)	205.000 (6.360)
69	2	561.190 (0.489)	1.892	6.315 (0.301)	10.109 (0.073)	83.880 (7.332)	199.167 (3.749)
	4	591.035 (0.746)	1.745	6.570 (0.313)	10.111 (0.356)	107.050 (12.748)	205.833 (6.412)
	8	610.795 (0.628)	1.760	6.725 (0.456)	10.122 (0.551)	101.480 (11.546)	230.833 (3.235)
97	2	583.235 (0.523)	1.861	6.494 (0.483)	10.114 (0.051)	87.370 (5.995)	223.833 (5.018)
	4	620.690 (1.146)	1.726	6.800 (1.129)	10.113 (0.168)	106.410 (8.160)	259.167 (4.469)
	8	628.010 (1.355)	1.804	6.879 (0.567)	10.105 (0.084)	99.330 (9.537)	277.500 (3.371)

Table B.1.3.2.4: *Physical characterization of Tablettose® tablets. Filler/binder is mixed with 2.0% w/w Pruv® for various periods of time at different speeds. %RSD is indicated in parentheses.*

Mixing speed (rpm)	Mixing time (min)	Average mass (mg)	Friability (%)	Average thickness (mm)	Average diameter (mm)	Average crushing strength (N)	Average disintegration (s)
33	2	557.950 (0.442)	1.653	6.283 (0.498)	10.103 (0.105)	93.090 (7.078)	173.000 (3.351)
	4	569.820 (0.385)	1.618	6.391 (0.260)	10.113 (0.203)	93.770 (7.451)	202.500 (4.619)
	8	572.275 (0.452)	2.105	6.405 (0.347)	10.105 (0.070)	82.070 (5.887)	232.500 (4.023)
69	2	571.810 (0.422)	1.976	6.395 (0.412)	10.112 (0.042)	88.260 (6.017)	234.000 (3.221)
	4	590.390 (0.454)	1.848	6.554 (0.323)	10.113 (0.067)	89.650 (6.623)	257.500 (5.985)
	8	609.720 (1.165)	2.078	6.714 (1.018)	10.114 (0.051)	86.310 (7.488)	279.333 (2.657)
97	2	591.160 (0.732)	1.897	6.564 (0.627)	10.118 (0.091)	88.360 (7.035)	259.333 (3.838)
	4	610.445 (1.033)	2.032	6.722 (0.768)	10.110 (0.047)	85.030 (4.575)	275.000 (6.803)
	8	619.105 (0.848)	3.377 [a]	6.796 (0.728)	10.120 (0.093)	78.000 (10.991)	291.667 (7.943)

[a] *Tablets capped during testing*

Annexure C

DISSOLUTION PROFILES

Table C.1: *Filler/binder in the absence of any lubricant. Dissolution data represents four repetitions.*

Filler/ binder	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
Avicel® PH-200	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.887	1.151	1.055	0.759	0.963	18.105
	2	0.780	1.438	1.477	1.452	1.287	26.274
	4	1.588	2.047	2.096	2.424	2.039	16.870
	5	2.256	2.763	3.051	2.501	2.643	12.938
	6	2.892	3.735	3.129	3.430	3.296	11.102
	10	3.856	4.613	4.689	3.979	4.284	9.983
	20	5.973	6.442	5.986	5.310	5.928	7.860
	30	7.722	7.692	7.194	6.638	7.311	6.979
	45	8.043	8.803	7.856	7.125	7.957	8.664
	60	9.181	9.362	8.316	8.128	8.747	7.032
	DR_i[b]	0.027	0.034	0.031	0.033	0.031	8.984
	AUC[c]	389.311	417.492	384.326	352.873	386.001	6.859
Tablettose®	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.919	2.791	1.367	1.423	1.625	49.808
	2	1.789	4.519	1.495	2.183	2.497	55.185
	4	3.034	5.777	2.808	3.844	3.866	34.917
	5	3.993	6.160	3.863	4.717	4.683	22.502
	6	4.350	6.202	4.629	5.178	5.090	16.061
	10	6.048	7.411	5.602	6.309	6.342	12.137
	20	7.226	7.794	7.807	7.851	7.670	3.870
	30	7.656	8.508	8.452	8.212	8.207	4.737
	45	8.331	8.632	8.199	8.798	8.490	3.224
	60	8.511	8.832	9.238	8.905	8.872	3.364
	DR_i[b]	0.046	0.059	0.045	0.053	0.051	13.262
	AUC[c]	427.276	481.830	443.171	458.286	452.641	5.129

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.1.1.1: *Avicel® mixed with magnesium stearate for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	1.194	0.983	0.907	0.957	1.010	12.532
	2	0.956	0.878	0.802	0.802	0.860	8.551
	4	1.724	1.935	1.571	1.512	1.685	11.206
	5	2.311	2.507	2.125	1.938	2.220	11.009
	6	2.890	3.001	2.618	2.439	2.737	9.326
	10	4.398	4.314	3.923	3.533	4.042	9.833
	20	6.393	6.046	5.638	4.976	5.763	10.562
	30	7.723	7.121	6.696	6.024	6.891	10.379
	45	8.719	8.319	7.699	6.968	7.926	9.642
	60	9.520	9.221	8.449	7.667	8.714	9.540
	DR_i[b]	0.025	0.028	0.023	0.021	0.024	11.266
	AUC[c]	411.062	391.667	362.058	326.665	372.863	9.871
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.805	1.456	0.839	0.771	0.968	33.747
	2	0.818	1.346	0.633	0.641	0.859	39.054
	4	1.647	1.954	1.375	1.358	1.584	17.687
	5	2.066	2.287	1.836	1.785	1.994	11.575
	6	2.567	2.653	2.295	2.278	2.448	7.763
	10	3.948	3.906	3.591	3.456	3.725	6.442
	20	5.731	5.815	5.399	5.052	5.499	6.332
	30	6.992	7.153	6.584	6.286	6.754	5.818
	45	8.166	8.353	7.698	7.384	7.900	5.577
	60	8.925	9.120	8.533	8.134	8.678	5.037
	DR_i[b]	0.023	0.022	0.020	0.020	0.021	6.719
	AUC[c]	377.218	387.251	354.430	338.371	364.318	6.062

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.1.1.2: *Avicel® mixed with magnesium stearate for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	1.346	0.788	0.881	1.093	1.027	24.141
	2	0.635	0.852	0.455	0.592	0.634	25.984
	4	1.029	1.765	0.918	1.028	1.185	32.941
	5	1.378	2.050	1.326	1.378	1.533	22.535
	6	1.751	2.761	1.717	1.768	2.000	25.415
	10	2.937	3.560	2.836	2.861	3.048	11.275
	20	4.812	4.672	4.583	4.660	4.682	2.037
	30	6.192	5.786	5.810	5.988	5.944	3.170
	45	7.409	7.035	6.984	7.222	7.162	2.703
	60	8.286	8.081	7.802	8.142	8.078	2.513
	DR_i[b]	0.012	0.025	0.014	0.013	0.016	36.498
	AUC[c]	330.778	326.199	311.698	321.938	322.653	2.525
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.509	0.518	0.695	0.661	0.596	16.148
	2	0.394	0.495	0.420	0.344	0.413	15.274
	4	0.782	0.935	0.715	0.554	0.746	21.181
	5	1.030	1.090	0.936	0.749	0.951	15.627
	6	1.259	1.217	1.174	0.970	1.155	11.092
	10	2.089	1.835	1.928	1.665	1.879	9.437
	20	3.776	3.022	3.234	2.945	3.244	11.556
	30	4.952	4.153	4.374	4.187	4.417	8.379
	45	6.523	5.740	5.742	5.555	5.890	7.317
	60	7.537	6.916	6.764	6.644	6.965	5.703
	DR_i[b]	0.011	0.011	0.009	0.007	0.010	19.944
	AUC[c]	276.335	241.120	244.845	232.760	248.765	7.663

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.1.2.1: *Avicel® mixed with magnesium stearate for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.522	0.608	0.384	0.694	0.552	23.930
	2	0.851	1.050	0.679	0.835	0.854	17.819
	4	1.877	2.187	1.592	1.679	1.834	14.409
	5	2.484	2.951	2.199	2.200	2.458	14.424
	6	3.150	3.548	2.761	2.650	3.027	13.483
	10	4.547	4.962	4.149	3.736	4.349	12.103
	20	6.395	6.802	5.912	5.195	6.076	11.369
	30	7.472	8.008	7.057	6.347	7.221	9.701
	45	8.441	9.133	8.147	7.395	8.279	8.695
	60	9.298	9.982	8.961	8.252	9.123	7.887
	DR_i[b]	0.030	0.034	0.026	0.024	0.029	14.664
	AUC[c]	403.344	435.418	381.094	346.156	391.503	9.595
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	1.261	1.046	1.089	1.124	1.130	8.229
	2	1.079	1.069	0.958	1.027	1.033	5.345
	4	1.930	1.998	1.619	1.697	1.811	10.025
	5	2.493	2.528	2.130	2.157	2.327	9.143
	6	3.038	3.004	2.598	2.563	2.801	9.111
	10	4.409	4.391	3.744	3.753	4.074	9.239
	20	6.326	6.386	5.591	5.522	5.956	7.772
	30	7.584	7.679	6.874	6.779	7.229	6.468
	45	8.726	8.924	8.025	7.956	8.408	5.820
	60	9.567	9.843	8.875	8.771	9.264	5.648
	DR_i[b]	0.026	0.027	0.022	0.022	0.024	11.061
	AUC[c]	410.566	417.088	371.325	367.978	391.739	6.555

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.1.2.2: *Avicel® mixed with magnesium stearate for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.979	1.552	0.516	0.912	0.990	43.120
	2	0.530	0.550	0.443	1.119	0.661	46.789
	4	1.168	1.075	1.150	1.163	1.139	3.787
	5	1.651	1.474	1.356	1.542	1.506	8.204
	6	2.083	1.838	2.275	1.923	2.030	9.492
	10	3.492	2.952	2.895	3.592	3.233	11.143
	20	5.513	4.575	4.465	4.351	4.726	11.265
	30	6.804	5.839	5.720	5.500	5.966	9.655
	45	7.956	7.092	6.822	6.644	7.128	8.162
	60	8.864	8.050	7.729	7.618	8.065	6.979
	DR_i[b]	0.018	0.013	0.020	0.015	0.016	18.801
	AUC[c]	362.687	317.971	308.110	307.529	324.074	8.080
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	1.333	1.097	0.701	1.485	1.154	29.571
	2	0.667	0.590	1.034	0.988	0.820	27.313
	4	1.270	1.513	1.170	0.993	1.237	17.540
	5	1.399	1.872	1.660	1.423	1.588	14.019
	6	1.880	2.118	1.923	2.032	1.988	5.412
	10	2.135	3.181	2.792	2.641	2.687	16.097
	20	3.779	4.323	4.052	4.346	4.125	6.465
	30	5.236	5.896	5.381	5.694	5.552	5.379
	45	6.406	7.193	6.828	6.476	6.726	5.383
	60	7.962	8.186	7.131	8.283	7.891	6.638
	DR_i[b]	0.014	0.019	0.017	0.013	0.015	17.945
	AUC[c]	286.103	321.913	296.335	305.756	302.527	5.029

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.2.1.1: *Avicel® mixed with Pruv® for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.474	1.299	0.769	0.786	0.832	41.211
	2	0.704	1.972	0.798	0.841	1.079	55.442
	4	1.514	2.700	1.531	1.574	1.830	31.737
	5	2.032	3.378	2.049	2.016	2.369	28.406
	6	2.557	3.676	2.473	2.439	2.786	21.364
	10	3.899	4.360	3.612	3.494	3.841	10.030
	20	5.616	5.661	5.252	4.923	5.363	6.444
	30	6.720	6.695	6.432	6.026	6.468	4.986
	45	7.872	7.821	7.449	7.245	7.596	3.961
	60	8.585	8.619	8.246	7.807	8.314	4.543
	DR_i[b]	0.025	0.034	0.023	0.022	0.026	20.566
	AUC[c]	364.474	378.628	346.760	331.243	355.276	5.814
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.819	0.676	0.727	0.794	0.754	8.620
	2	0.706	1.160	0.680	0.731	0.819	27.826
	4	1.463	1.845	1.312	1.371	1.498	16.005
	5	2.007	2.514	1.778	1.812	2.028	16.734
	6	2.481	2.669	2.202	2.236	2.397	9.177
	10	3.764	3.883	3.299	3.274	3.555	8.828
	20	5.464	5.363	4.821	4.745	5.098	7.209
	30	6.635	6.567	5.857	5.823	6.220	7.084
	45	7.728	7.635	6.932	6.907	7.300	6.051
	60	8.551	8.458	7.805	7.805	8.155	4.971
	DR_i[b]	0.023	0.026	0.020	0.020	0.022	13.495
	AUC[c]	358.587	358.558	320.174	318.862	339.046	6.652

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.2.1.2: *Avicel® mixed Pruv® for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.295	0.547	0.362	0.387	0.398	26.879
	2	0.372	0.946	0.331	0.381	0.507	57.712
	4	1.138	1.873	0.970	1.054	1.259	32.988
	5	1.689	2.475	1.478	1.529	1.792	25.872
	6	2.171	2.705	1.893	2.011	2.195	16.353
	10	3.469	3.497	3.047	3.047	3.265	7.713
	20	5.158	4.586	4.550	4.449	4.686	6.829
	30	6.344	5.551	5.567	5.399	5.715	7.457
	45	7.360	6.674	6.767	6.346	6.787	6.229
	60	8.038	7.496	7.472	7.066	7.518	5.309
	DR_i[b]	0.022	0.028	0.019	0.019	0.022	18.855
	AUC[c]	337.203	313.031	303.970	292.150	311.589	6.129
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.496	0.866	0.883	0.816	0.766	23.728
	2	0.500	0.687	0.603	0.636	0.606	13.034
	4	1.181	1.316	1.131	1.190	1.204	6.555
	5	1.681	1.808	1.537	1.597	1.656	7.075
	6	2.222	2.290	1.952	2.061	2.131	7.185
	10	3.435	3.469	3.114	3.023	3.260	6.909
	20	5.031	5.166	4.584	4.398	4.795	7.571
	30	6.083	6.344	5.677	5.398	5.876	7.154
	45	7.115	7.377	6.768	6.505	6.941	5.516
	60	7.835	8.148	7.598	7.294	7.718	4.689
	DR_i[b]	0.021	0.020	0.017	0.018	0.019	10.463
	AUC[c]	327.972	340.591	308.874	297.164	318.650	6.079

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.2.2.1: *Avicel® mixed with Pruv® for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.709	1.231	0.532	0.785	0.814	36.557
	2	0.688	1.744	0.577	0.621	0.907	61.677
	4	1.589	2.252	1.344	1.420	1.651	25.035
	5	2.150	2.803	1.837	1.939	2.182	19.879
	6	2.684	3.227	2.295	2.430	2.659	15.480
	10	4.112	4.047	3.519	3.655	3.833	7.582
	20	5.780	5.248	5.153	5.246	5.357	5.329
	30	6.986	6.570	6.291	6.443	6.572	4.535
	45	7.953	7.614	7.300	7.461	7.582	3.673
	60	8.683	8.411	8.140	8.192	8.357	2.961
	DR_i[b]	0.025	0.028	0.022	0.022	0.024	12.374
	AUC[c]	373.685	362.613	338.374	345.961	355.158	4.497
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.827	1.240	0.894	1.054	1.004	18.332
	2	0.823	1.660	0.764	0.807	1.014	42.555
	4	1.573	2.648	1.362	1.497	1.770	33.430
	5	2.083	2.965	1.804	1.948	2.200	23.769
	6	2.524	3.270	2.261	2.363	2.605	17.540
	10	4.128	3.963	3.351	3.461	3.726	10.145
	20	5.662	5.273	4.874	4.900	5.177	7.168
	30	6.732	6.401	5.809	5.986	6.232	6.667
	45	7.758	7.427	6.851	6.945	7.245	5.865
	60	8.623	8.385	7.708	7.725	8.110	5.734
	DR_i[b]	0.023	0.030	0.020	0.020	0.023	20.714
	AUC[c]	366.043	357.759	319.187	324.934	341.981	6.833

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.2.2.2.2: *Avicel® mixed with Pruv® for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.532	0.565	0.886	0.726	0.677	24.034
	2	0.661	0.712	0.739	0.671	0.696	5.218
	4	1.454	1.539	1.345	1.311	1.412	7.373
	5	1.981	2.125	1.770	1.770	1.911	9.090
	6	2.464	2.667	2.168	2.177	2.369	10.207
	10	3.638	3.758	3.241	3.182	3.455	8.285
	20	5.204	5.221	4.713	4.578	4.929	6.740
	30	6.451	6.367	5.800	5.597	6.054	6.941
	45	7.461	7.427	6.960	6.664	7.128	5.394
	60	8.158	8.250	7.852	7.479	7.935	4.388
	DR_i[b]	0.024	0.025	0.019	0.020	0.022	14.081
	AUC[c]	345.346	346.549	319.013	307.099	329.502	5.951
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.608	0.776	0.675	0.785	0.711	11.949
	2	0.620	1.531	0.603	0.629	0.846	54.025
	4	1.294	2.243	1.243	1.277	1.514	32.106
	5	1.820	2.710	1.727	1.769	2.007	23.448
	6	2.303	3.370	2.202	2.227	2.526	22.358
	10	3.553	4.216	3.342	3.325	3.609	11.579
	20	5.170	5.603	4.966	4.823	5.141	6.608
	30	6.241	6.740	6.138	6.070	6.297	4.819
	45	7.325	7.800	7.215	7.122	7.366	4.090
	60	8.123	8.648	8.055	8.072	8.225	3.453
	DR_i[b]	0.021	0.031	0.020	0.020	0.023	23.593
	AUC[c]	338.539	373.118	331.113	327.806	342.644	6.072

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.1.1.1: *Tablettose® mixed with magnesium stearate for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	1.161	0.908	1.060	1.102	1.058	10.244
	2	0.584	0.693	0.609	0.787	0.668	13.720
	4	1.173	1.808	1.376	1.546	1.476	18.215
	5	1.810	2.930	2.192	2.269	2.300	20.223
	6	2.583	3.477	2.983	2.992	3.009	12.159
	10	4.270	5.019	4.433	4.458	4.545	7.190
	20	6.182	6.693	6.267	6.022	6.291	4.557
	30	7.325	7.751	7.419	6.961	7.364	4.412
	45	8.372	8.501	8.389	7.888	8.287	3.288
	60	9.096	9.182	9.063	8.654	8.999	2.613
	DR_i[b]	0.020	0.033	0.025	0.025	0.026	19.977
	AUC[c]	391.242	414.678	396.352	378.692	395.241	3.778
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.544	0.916	0.764	1.060	0.821	26.871
	2	0.310	0.566	0.464	0.567	0.477	25.388
	4	0.351	0.581	0.521	0.598	0.513	21.957
	5	0.453	0.666	0.606	0.666	0.598	16.803
	6	0.657	0.835	0.759	0.793	0.761	10.025
	10	1.233	1.479	1.428	1.216	1.339	9.996
	20	2.386	2.945	2.767	2.233	2.583	12.767
	30	3.736	4.661	4.305	3.507	4.052	12.990
	45	5.587	6.328	5.895	5.222	5.758	8.143
	60	6.975	7.335	6.977	6.483	6.943	5.039
	DR_i[b]	0.004	0.004	0.004	0.003	0.004	10.374
	AUC[c]	219.685	254.607	238.012	208.318	230.156	8.855

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.1.1.2: *Tablettose® mixed with magnesium stearate for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.570	0.772	0.722	0.916	0.745	19.202
	2	0.285	0.481	0.455	0.507	0.432	23.182
	4	0.284	0.437	0.411	0.462	0.399	19.928
	5	0.300	0.470	0.420	0.445	0.409	18.395
	6	0.351	0.462	0.453	0.487	0.439	13.666
	10	0.588	0.597	0.572	0.589	0.587	1.813
	20	0.987	0.877	0.860	0.826	0.888	7.831
	30	1.404	1.268	1.208	1.064	1.236	11.372
	45	2.116	2.098	1.827	1.565	1.902	13.705
	60	3.058	3.244	2.676	2.354	2.833	14.035
	DR_i[b]	0.001	0.001	0.001	0.001	0.001	23.536
	AUC[c]	89.399	89.355	79.665	71.822	82.560	10.293
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.426	0.527	0.502	0.620	0.519	15.461
	2	0.301	0.437	0.335	0.345	0.355	16.375
	4	0.292	0.454	0.284	0.352	0.345	22.655
	5	0.301	0.420	0.292	0.318	0.333	17.790
	6	0.326	0.403	0.275	0.318	0.330	16.078
	10	0.453	0.436	0.300	0.360	0.387	18.263
	20	0.648	0.547	0.394	0.419	0.502	23.554
	30	0.954	0.767	0.496	0.462	0.669	34.875
	45	1.378	1.081	0.691	0.699	0.962	34.479
	60	1.854	1.429	0.903	0.945	1.283	35.023
	DR_i[b]	0.001	0.002	0.001	0.001	0.001	55.699
	AUC[c]	59.180	49.181	32.428	33.492	43.570	29.655

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.1.2.1: *Tablettose® mixed with magnesium stearate for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.761	1.342	1.231	0.855	1.047	26.964
	2	0.740	1.144	1.297	0.766	0.987	28.119
	4	1.030	1.476	1.639	1.039	1.296	23.876
	5	1.382	1.794	2.017	1.330	1.631	20.273
	6	1.896	2.197	2.403	1.725	2.055	14.750
	10	3.231	3.727	3.541	2.965	3.366	10.007
	20	5.278	5.751	5.263	4.970	5.315	6.079
	30	6.656	6.974	6.357	6.492	6.620	4.020
	45	7.876	8.014	7.456	7.815	7.790	3.055
	60	7.985	8.122	7.590	7.857	7.888	2.874
	DR_i[b]	0.015	0.016	0.019	0.013	0.016	14.852
	AUC[c]	348.129	367.235	342.438	338.911	349.178	3.615
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.753	0.565	0.975	1.359	0.913	37.398
	2	0.313	0.389	0.485	0.641	0.457	30.944
	4	0.336	0.354	0.482	0.603	0.444	28.041
	5	0.311	0.353	0.465	0.560	0.422	26.631
	6	0.302	0.396	0.508	0.559	0.441	26.111
	10	0.438	0.618	0.713	0.747	0.629	21.988
	20	0.712	1.157	1.243	1.261	1.093	23.592
	30	1.209	1.860	1.946	2.057	1.768	21.569
	45	2.407	3.393	3.265	3.470	3.134	15.693
	60	3.993	5.015	4.809	5.007	4.706	10.296
	DR_i[b]	0.000	0.002	0.001	0.000	0.001	87.444
	AUC[c]	94.767	131.437	131.904	139.561	124.417	16.167

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.1.2.2: *Tablettose® mixed with magnesium stearate for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.744	0.633	0.684	0.881	0.735	14.529
	2	0.390	0.423	0.483	0.501	0.449	11.565
	4	0.379	0.388	0.448	0.448	0.416	8.997
	5	0.362	0.396	0.491	0.422	0.418	13.020
	6	0.362	0.439	0.525	0.448	0.443	15.022
	10	0.413	0.508	0.687	0.508	0.529	21.664
	20	0.516	0.687	1.055	0.610	0.717	32.910
	30	0.662	0.978	1.450	0.867	0.989	33.764
	45	1.055	1.450	2.118	1.201	1.456	32.309
	60	1.467	1.956	2.865	1.698	1.997	30.662
	DR_i[b]	0.001	0.002	0.003	0.001	0.002	54.392
	AUC[c]	47.075	63.251	91.624	56.053	64.501	29.852
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.479	0.599	0.300	0.778	0.539	37.317
	2	0.303	0.397	0.259	0.416	0.344	21.805
	4	0.310	0.354	0.250	0.362	0.319	16.025
	5	0.302	0.362	0.208	0.405	0.319	26.757
	6	0.293	0.405	0.267	0.405	0.343	21.215
	10	0.285	0.388	0.319	0.431	0.355	18.537
	20	0.362	0.507	0.396	0.482	0.437	15.830
	30	0.362	0.551	0.507	0.576	0.499	19.169
	45	0.516	0.747	0.738	0.688	0.672	16.012
	60	0.627	0.902	1.107	0.808	0.861	23.177
	DR_i[b]	0.001	0.002	0.001	0.001	0.001	19.064
	AUC[c]	25.611	36.524	34.321	35.614	33.017	15.204

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.2.1.1: *Tablettose® mixed with Pruv® for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.437	0.667	0.633	0.565	0.575	17.696
	2	0.601	2.515	0.765	0.670	1.138	80.896
	4	1.559	3.430	1.773	1.747	2.127	41.090
	5	2.230	3.709	2.316	2.453	2.677	25.923
	6	2.763	4.052	2.866	3.071	3.188	18.506
	10	4.029	4.813	3.979	4.330	4.288	8.935
	20	5.846	6.098	5.803	5.959	5.927	2.225
	30	7.035	6.916	6.693	7.223	6.967	3.186
	45	7.827	7.715	7.662	7.887	7.773	1.319
	60	8.565	8.411	8.351	8.574	8.475	1.319
	DR_i[b]	0.027	0.040	0.027	0.029	0.031	20.039
	AUC[c]	371.403	389.125	363.609	379.708	375.961	2.917
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.684	0.582	0.881	0.966	0.778	22.644
	2	0.406	0.457	0.510	0.630	0.501	19.144
	4	0.985	1.156	0.943	1.243	1.082	13.065
	5	1.518	1.809	1.407	1.776	1.627	12.065
	6	2.008	2.359	1.905	2.257	2.132	9.927
	10	3.231	3.575	2.940	3.403	3.287	8.229
	20	4.911	5.110	4.491	4.844	4.839	5.327
	30	6.048	6.151	5.507	5.996	5.925	4.829
	45	7.164	7.139	6.990	6.489	6.945	4.518
	60	7.904	7.870	7.306	7.815	7.724	3.640
	DR_i[b]	0.017	0.021	0.015	0.019	0.018	14.578
	AUC[c]	325.005	331.736	304.907	316.449	319.524	3.624

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.2.1.2: *Tablettose® mixed Pruv® for 4 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.284	0.292	0.577	0.326	0.370	37.656
	2	0.160	0.160	0.237	0.186	0.186	19.514
	4	0.821	1.791	1.365	1.172	1.287	31.430
	5	1.184	2.269	2.082	1.822	1.839	25.756
	6	1.713	2.489	2.806	2.160	2.292	20.391
	10	2.319	2.984	2.785	2.790	2.719	10.398
	20	3.686	4.217	3.379	3.789	3.768	9.194
	30	4.740	5.128	4.152	4.707	4.682	8.572
	45	5.791	6.087	5.136	5.825	5.710	7.090
	60	6.592	6.912	5.894	6.710	6.527	6.773
	DR_i[b]	0.016	0.028	0.027	0.022	0.023	22.545
	AUC[c]	256.888	283.614	240.260	265.047	261.452	6.892
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.535	0.569	0.686	0.728	0.629	14.624
	2	0.329	0.379	0.380	0.405	0.373	8.572
	4	0.437	0.680	0.412	0.445	0.493	25.329
	5	0.730	1.267	0.621	0.688	0.827	35.926
	6	1.167	1.471	0.898	1.108	1.161	20.375
	10	2.282	2.200	1.795	2.198	2.119	10.348
	20	3.912	3.677	3.281	3.861	3.683	7.765
	30	5.218	5.091	4.453	5.117	4.970	7.020
	45	6.254	6.438	5.765	6.137	6.148	4.622
	60	7.172	7.316	6.684	7.004	7.044	3.855
	DR_i[b]	0.009	0.013	0.006	0.007	0.009	37.307
	AUC[c]	274.260	275.840	243.373	269.080	265.638	5.693

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.2.2.1: *Tablettose® mixed with Pruv® for 8 minutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
0.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.493	0.585	0.635	0.803	0.629	20.642
	2	0.513	1.024	0.572	0.699	0.702	32.509
	4	1.358	2.189	1.384	1.719	1.662	23.329
	5	1.974	2.664	1.999	2.369	2.251	14.626
	6	2.513	3.060	2.504	2.916	2.748	10.306
	10	3.788	4.209	3.746	4.233	3.994	6.589
	20	5.636	5.797	5.460	5.906	5.699	3.416
	30	6.759	6.827	6.549	6.986	6.780	2.675
	45	7.878	7.945	7.534	7.996	7.838	2.664
	60	8.654	8.705	8.259	8.688	8.576	2.481
	DR_i[b]	0.024	0.031	0.024	0.028	0.027	12.683
	AUC[c]	364.046	376.054	351.614	377.772	367.371	3.307
1.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.928	0.602	0.803	0.928	0.815	18.895
	2	0.398	0.547	0.414	0.457	0.454	14.696
	4	0.830	2.086	0.797	0.814	1.132	56.231
	5	1.444	2.722	1.351	1.351	1.717	39.110
	6	1.949	3.278	1.856	1.915	2.250	30.527
	10	3.182	3.641	3.056	3.048	3.232	8.658
	20	4.812	4.664	4.611	4.510	4.649	2.709
	30	5.859	5.657	5.749	5.665	5.732	1.640
	45	7.003	6.784	6.851	6.650	6.822	2.149
	60	7.846	7.719	7.644	7.459	7.667	2.110
	DR_i[b]	0.016	0.033	0.015	0.015	0.020	45.748
	AUC[c]	318.227	320.466	309.648	303.542	312.971	2.501

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Table C.3.2.2.2: *Tablettose® mixed with Pruv® for 8 mininutes at 69rpm. Dissolution data represents four repetitions.*

% w/w Lub	Sampling time (min)	C1[a]	C2[a]	C3[a]	C4[a]	Average	%RSD
1.5	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.535	0.543	0.560	0.702	0.585	13.463
	2	0.346	0.480	0.354	0.414	0.398	15.585
	4	0.437	0.705	0.462	0.496	0.525	23.367
	5	0.663	1.083	0.722	0.772	0.810	23.128
	6	0.999	1.704	1.041	1.100	1.211	27.357
	10	1.896	2.745	1.955	2.014	2.153	18.489
	20	3.458	4.140	3.366	3.458	3.606	9.959
	30	4.738	5.085	4.420	4.630	4.718	5.894
	45	5.892	6.103	5.597	5.849	5.860	3.541
	60	6.785	6.870	6.482	6.768	6.727	2.509
	DR_i[b]	0.007	0.014	0.008	0.008	0.009	34.446
	AUC[c]	252.183	276.372	241.304	251.790	255.412	5.816
2.0	0	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.476	0.535	0.669	0.761	0.610	21.091
	2	0.262	0.371	0.380	0.406	0.355	17.936
	4	0.311	0.362	0.328	0.395	0.349	10.715
	5	0.462	0.412	0.378	0.445	0.424	8.753
	6	0.730	0.596	0.562	0.630	0.630	11.514
	10	1.527	1.292	1.191	1.317	1.332	10.588
	20	2.962	2.643	2.475	2.584	2.666	7.850
	30	4.225	3.880	3.553	3.562	3.805	8.376
	45	5.671	5.260	4.814	4.714	5.115	8.611
	60	6.541	6.322	5.842	5.691	6.099	6.543
	DR_i[b]	0.005	0.003	0.002	0.003	0.003	32.037
	AUC[c]	231.575	214.600	197.826	197.814	210.454	7.674

[a] *Corrected sample concentration ($\mu g.cm^{-3}$)*

[b] *DR_i = initial dissolution rate ($\mu g.cm^{-3}.min^{-1}$)*

[c] *AUC = area under the curve ($\mu g.min.cm^{-3}$)*

Annexure D

FRICTION PARAMETERS

Table D.1.1.1: *Friction parameters of Avicel® tablets without any lubricants or mixing present (baseline formula).*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.285	3.755	2.246	1.114	723.300	6.330	12.120	263.100	2.183	0.530	0.225
2	9.225	3.531	2.481	1.046	713.600	6.280	12.130	226.800	1.895	0.568	0.223
3	9.342	3.695	2.626	1.100	731.700	6.420	12.130	263.100	2.151	0.574	0.229
4	9.314	3.795	2.405	0.837	728.500	6.390	12.120	256.200	2.106	0.641	0.168
5	9.393	3.577	2.847	1.260	727.300	6.440	12.130	225.600	1.839	0.542	0.273
6	9.387	3.372	2.494	0.861	744.900	6.550	12.130	225.100	1.804	0.599	0.200
7	9.281	3.400	2.305	1.008	730.900	6.430	12.130	248.400	2.027	0.534	0.228
8	9.391	3.359	2.445	0.769	742.900	6.560	12.140	230.500	1.843	0.626	0.179
9	9.283	3.350	2.823	0.655	735.800	6.530	12.140	224.300	1.801	0.712	0.152
10	9.436	3.394	2.145	0.580	720.800	6.320	12.120	254.200	2.113	0.681	0.128
11	9.387	3.377	2.915	0.640	755.100	6.650	12.120	232.500	1.836	0.720	0.150
12	9.194	3.211	1.963	0.445	723.200	6.370	12.140	249.300	2.052	0.718	0.104
13	9.336	3.234	2.490	0.566	739.700	6.520	12.120	241.500	1.946	0.708	0.135
14	9.296	3.345	2.863	0.957	742.300	6.600	12.120	241.100	1.919	0.606	0.226
15	9.181	3.301	3.288	0.756	745.800	6.570	12.130	223.100	1.782	0.711	0.179
Average	9.315	3.446	2.556	0.840	733.720	6.464	12.128	240.320	1.953	0.631	0.187
SD	0.077	0.183	0.343	0.237	11.331	0.113	0.008	14.571	0.140	0.072	0.047
RSD	0.822	5.300	13.426	28.258	1.544	1.749	0.064	6.063	7.168	11.476	25.434

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.1.1: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 0.5% w/w magnesium stearate for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.605	3.648	2.700	0.876	821.000	7.190	12.130	143.800	1.050	0.607	0.206
2	9.512	3.603	2.600	0.884	800.900	7.050	12.110	148.700	1.109	0.597	0.207
3	9.679	3.587	2.862	1.194	815.700	7.110	12.110	160.200	1.184	0.519	0.285
4	9.609	3.583	2.447	0.932	813.700	7.190	12.110	135.700	0.992	0.549	0.224
5	9.486	3.924	2.816	1.345	808.600	7.120	12.100	149.100	1.102	0.509	0.294
6	9.639	3.848	2.330	1.087	818.700	7.130	12.120	152.000	1.120	0.506	0.242
7	9.503	3.790	2.856	1.119	819.900	7.200	12.110	148.700	1.086	0.561	0.255
8	9.691	3.739	3.183	1.329	813.800	7.110	12.120	154.000	1.138	0.532	0.304
9	9.608	3.695	2.939	1.120	815.400	7.120	12.130	146.300	1.078	0.562	0.259
10	9.541	3.652	2.575	1.030	811.700	7.080	12.110	156.900	1.165	0.546	0.240
11	9.341	3.686	2.272	0.680	827.200	7.340	12.110	150.600	1.079	0.636	0.161
12	9.697	3.597	2.786	0.866	801.400	7.000	12.120	159.400	1.196	0.620	0.201
13	9.711	3.970	3.388	0.700	823.900	7.190	12.100	154.900	1.133	0.745	0.151
14	9.614	3.587	2.723	0.891	810.500	7.100	12.120	155.300	1.149	0.602	0.211
15	9.440	3.671	2.765	0.950	798.000	7.100	12.110	139.300	1.031	0.599	0.220
Average	9.578	3.705	2.749	1.000	813.360	7.135	12.114	150.327	1.107	0.579	0.231
SD	0.106	0.125	0.294	0.200	8.494	0.079	0.009	7.001	0.057	0.062	0.044
RSD	1.107	3.383	10.704	19.991	1.044	1.111	0.075	4.657	5.129	10.627	19.255

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.1.2: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.0% w/w magnesium stearate for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.232	3.606	3.062	0.354	874.700	7.400	12.110	155.700	1.106	0.985	0.085
2	9.282	3.574	3.132	0.149	867.600	7.430	12.110	155.300	1.099	0.994	0.034
3	9.187	3.770	3.466	0.107	879.900	7.480	12.110	149.600	1.051	0.995	0.022
4	9.356	3.693	2.923	0.165	868.500	7.390	12.100	154.900	1.103	0.994	0.036
5	9.417	3.678	3.225	0.190	868.000	7.420	12.110	150.000	1.063	0.992	0.043
6	9.216	3.655	3.411	0.149	873.600	7.530	12.120	148.300	1.034	0.993	0.033
7	9.208	3.496	2.746	0.227	873.500	7.410	12.120	153.200	1.086	0.991	0.054
8	9.196	3.624	3.162	0.227	877.900	7.450	12.130	154.500	1.088	0.990	0.053
9	9.315	3.595	3.374	0.188	877.300	7.500	12.130	153.600	1.075	0.991	0.044
10	9.452	3.501	3.032	0.117	875.400	7.470	12.120	156.500	1.100	0.995	0.026
11	9.172	3.516	3.507	0.119	878.800	7.490	12.120	153.600	1.077	0.994	0.027
12	9.457	3.754	3.301	0.131	880.000	7.480	12.120	156.100	1.096	0.995	0.028
13	9.287	3.586	3.243	0.114	867.000	7.400	12.130	158.100	1.121	0.995	0.025
14	9.254	3.517	3.394	0.132	865.600	7.400	12.130	155.300	1.101	0.994	0.030
15	9.451	3.577	3.505	0.128	864.800	7.380	12.140	154.500	1.098	0.994	0.028
Average	9.299	3.609	3.232	0.166	872.840	7.442	12.120	153.947	1.087	0.993	0.038
SD	0.104	0.087	0.224	0.065	5.438	0.047	0.011	2.723	0.023	0.003	0.016
RSD	1.113	2.404	6.940	38.954	0.623	0.629	0.088	1.769	2.113	0.281	43.077

TS = Tensile strength; R = coefficient of lubrication; μ_W *= friction coefficient during ejection phase*

Table D.2.1.3: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.5% w/w magnesium stearate for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.553	3.799	3.409	0.243	875.800	7.510	12.130	116.900	0.817	0.901	0.055
2	9.620	3.646	3.056	0.363	879.000	7.520	12.110	125.900	0.880	0.830	0.087
3	9.551	3.774	3.053	0.161	878.100	7.490	12.110	125.900	0.884	0.928	0.035
4	9.536	3.829	2.386	0.197	871.400	7.420	12.100	125.400	0.889	0.890	0.043
5	9.653	3.658	3.101	0.157	878.300	7.480	12.110	122.200	0.859	0.928	0.035
6	9.501	3.768	3.111	0.235	876.000	7.460	12.110	125.400	0.884	0.896	0.053
7	9.487	3.643	2.463	0.120	887.600	7.590	12.100	121.800	0.844	0.933	0.026
8	9.531	3.756	3.327	0.185	870.600	7.420	12.100	123.800	0.878	0.924	0.041
9	9.538	3.739	3.020	0.235	864.700	7.360	12.110	121.800	0.870	0.893	0.052
10	9.421	3.615	3.435	0.134	866.700	7.420	12.100	124.600	0.884	0.946	0.030
11	9.651	3.727	3.014	0.224	898.400	7.660	12.100	126.700	0.870	0.892	0.052
12	9.493	3.758	2.897	0.123	869.800	7.420	12.090	124.600	0.884	0.944	0.026
13	9.462	3.546	3.438	0.113	901.800	7.660	12.100	127.500	0.876	0.953	0.026
14	9.286	3.565	3.673	0.316	871.100	7.430	12.100	121.800	0.862	0.877	0.076
15	9.385	3.616	3.258	0.149	868.800	7.400	12.110	125.900	0.894	0.937	0.033
Average	9.511	3.696	3.109	0.197	877.207	7.483	12.105	124.013	0.872	0.912	0.045
SD	0.098	0.088	0.349	0.073	10.947	0.092	0.009	2.715	0.020	0.033	0.018
RSD	1.031	2.391	11.208	37.162	1.248	1.224	0.076	2.189	2.281	3.617	41.029

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.1.4: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 2.0% w/w magnesium stearate for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.418	3.584	2.843	0.143	867.600	7.410	12.100	113.600	0.807	0.930	0.032
2	9.468	3.798	2.768	0.135	864.000	7.360	12.100	114.000	0.815	0.937	0.028
3	9.455	3.534	3.030	0.114	864.400	7.380	12.120	108.300	0.771	0.948	0.025
4	9.334	3.527	2.970	0.097	865.100	7.430	12.100	110.700	0.784	0.956	0.021
5	9.480	3.438	3.237	0.145	859.700	7.340	12.100	111.100	0.796	0.935	0.034
6	9.289	3.460	3.357	0.116	846.300	7.230	12.100	108.700	0.791	0.953	0.026
7	9.528	3.437	2.925	0.082	844.800	7.230	12.100	106.200	0.773	0.963	0.017
8	9.359	3.497	2.906	0.078	856.700	7.330	12.110	107.900	0.774	0.966	0.016
9	9.390	3.519	3.786	0.087	840.400	7.200	12.100	107.100	0.783	0.970	0.018
10	9.381	3.217	3.052	0.048	857.100	7.320	12.110	108.300	0.778	0.982	0.009
11	9.209	3.372	3.250	0.059	860.700	7.340	12.110	111.100	0.796	0.978	0.011
12	9.268	3.456	3.312	0.068	843.000	7.230	12.120	107.900	0.784	0.975	0.013
13	9.259	3.396	3.317	0.110	865.400	7.410	12.110	115.600	0.820	0.954	0.025
14	9.454	3.380	2.946	0.124	849.900	7.290	12.130	109.500	0.788	0.940	0.028
15	9.374	3.186	2.763	0.122	847.000	7.240	12.120	112.000	0.813	0.935	0.029
Average	9.378	3.453	3.097	0.102	855.473	7.316	12.109	110.133	0.791	0.955	0.022
SD	0.092	0.146	0.277	0.031	9.349	0.076	0.010	2.756	0.016	0.017	0.008
RSD	0.985	4.219	8.952	29.980	1.093	1.034	0.082	2.503	2.016	1.797	35.043

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.2.1: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 0.5% w/w magnesium stearate for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.448	3.599	3.114	0.783	855.000	7.300	12.110	170.000	1.224	0.632	0.190
2	9.292	3.665	2.941	0.812	845.600	7.240	12.110	164.700	1.196	0.619	0.192
3	9.384	3.655	3.347	0.656	851.000	7.290	12.110	165.500	1.193	0.700	0.156
4	9.518	3.614	3.364	0.598	857.800	7.390	12.110	162.200	1.154	0.674	0.145
5	9.216	3.889	3.822	0.467	852.400	7.320	12.120	168.300	1.208	0.789	0.103
6	9.284	3.527	3.133	0.506	844.500	7.280	12.100	154.900	1.119	0.710	0.123
7	9.332	3.521	2.662	0.377	857.400	7.350	12.100	165.100	1.182	0.812	0.092
8	9.278	3.527	3.173	0.315	839.000	7.250	12.110	162.600	1.179	0.859	0.075
9	9.380	3.649	3.064	0.285	848.800	7.330	12.120	161.000	1.154	0.863	0.066
10	9.394	3.635	3.270	0.292	843.500	7.270	12.110	165.500	1.197	0.842	0.067
11	9.365	3.667	3.961	0.421	858.100	7.390	12.120	161.000	1.144	0.754	0.100
12	9.492	3.477	3.308	0.435	854.000	7.340	12.100	163.000	1.168	0.769	0.108
13	9.419	3.718	3.221	0.221	844.600	7.240	12.110	165.100	1.199	0.911	0.049
14	9.303	3.546	3.299	0.161	841.900	7.220	12.110	161.800	1.178	0.919	0.036
15	9.320	3.705	3.151	0.288	845.100	7.290	12.110	162.600	1.173	0.857	0.065
Average	9.362	3.626	3.255	0.441	849.247	7.300	12.110	163.553	1.178	0.781	0.104
SD	0.084	0.103	0.315	0.198	6.288	0.053	0.007	3.512	0.027	0.097	0.048
RSD	0.899	2.842	9.666	44.811	0.740	0.725	0.054	2.148	2.295	12.415	46.326

TS = Tensile strength; R = coefficient of lubrication; μ_W =friction coefficient during ejection phase

Table D.2.2.2: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.0% w/w magnesium stearate for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.310	3.592	3.052	0.196	856.400	7.300	12.120	132.800	0.956	0.913	0.044
2	9.664	3.533	3.505	0.116	864.600	7.380	12.140	125.400	0.891	0.948	0.025
3	9.487	3.587	2.750	0.149	852.900	7.250	12.130	132.000	0.956	0.943	0.033
4	9.411	3.644	2.949	0.054	851.000	7.260	12.130	134.000	0.969	0.981	0.009
5	9.327	3.483	3.021	0.172	860.700	7.330	12.140	127.900	0.915	0.925	0.040
6	9.465	3.538	3.160	0.132	843.000	7.220	12.130	125.400	0.912	0.949	0.029
7	9.542	3.449	3.483	0.157	873.500	7.430	12.130	125.900	0.889	0.916	0.037
8	9.365	3.562	3.479	0.070	859.300	7.380	12.130	126.300	0.898	0.973	0.014
9	9.420	3.449	3.334	0.075	857.600	7.270	12.130	116.000	0.837	0.973	0.015
10	9.335	3.572	3.360	0.103	860.400	7.370	12.130	126.300	0.899	0.956	0.022
11	9.341	3.607	3.521	0.146	866.700	7.420	12.130	125.000	0.884	0.943	0.033
12	9.349	3.573	3.262	0.082	848.000	7.230	12.140	121.800	0.883	0.970	0.016
13	9.355	3.671	3.480	0.086	867.300	7.440	12.120	126.700	0.895	0.966	0.017
14	9.388	3.552	2.956	0.087	860.600	7.400	12.140	126.700	0.898	0.967	0.018
15	9.412	3.662	3.465	0.106	859.600	7.410	12.140	128.700	0.911	0.960	0.022
Average	9.411	3.565	3.252	0.115	858.773	7.339	12.132	126.727	0.906	0.952	0.025
SD	0.096	0.069	0.252	0.042	7.855	0.078	0.007	4.390	0.033	0.021	0.011
RSD	1.015	1.922	7.755	36.046	0.915	1.060	0.056	3.464	3.669	2.217	42.263

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.2.3: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.5% w/w magnesium stearate for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.378	3.852	3.246	0.160	880.500	7.510	12.100	102.200	0.716	0.938	0.034
2	9.411	3.566	3.342	0.155	884.800	7.540	12.100	104.600	0.730	0.927	0.036
3	9.676	3.871	3.312	0.158	880.000	7.510	12.100	103.400	0.724	0.930	0.034
4	9.416	3.564	3.180	0.211	888.800	7.580	12.120	100.900	0.699	0.870	0.051
5	9.423	3.599	3.430	0.138	890.600	7.660	12.130	100.500	0.689	0.935	0.032
6	9.414	3.159	2.688	0.144	864.100	7.380	12.100	98.500	0.702	0.928	0.036
7	9.406	3.633	3.042	0.148	886.400	7.570	12.100	99.300	0.690	0.917	0.034
8	9.490	3.661	3.266	0.159	878.500	7.550	12.110	101.300	0.705	0.931	0.036
9	9.271	3.659	3.339	0.171	894.800	7.700	12.110	96.000	0.655	0.917	0.040
10	9.361	3.607	3.178	0.141	865.500	7.450	12.110	93.600	0.660	0.943	0.032
11	9.475	3.476	3.301	0.137	885.700	7.610	12.110	95.200	0.658	0.933	0.032
12	9.493	3.639	3.070	0.125	884.200	7.580	12.100	97.200	0.675	0.939	0.028
13	9.423	3.633	3.072	0.149	893.700	7.630	12.100	102.600	0.707	0.939	0.034
14	9.396	3.489	3.130	0.137	876.700	7.530	12.100	100.900	0.705	0.945	0.032
15	9.531	3.552	3.312	0.117	898.400	7.670	12.100	107.100	0.735	0.947	0.027
Average	9.438	3.597	3.194	0.150	883.513	7.565	12.106	100.220	0.697	0.929	0.034
SD	0.091	0.164	0.181	0.022	9.785	0.085	0.009	3.666	0.026	0.019	0.006
RSD	0.960	4.548	5.677	14.712	1.108	1.120	0.075	3.658	3.662	2.018	16.262

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.2.2.4: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 2.0% w/w magnesium stearate for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.313	3.256	3.520	0.097	867.300	7.400	12.130	88.300	0.626	0.951	0.022
2	9.164	3.422	3.467	0.081	863.100	7.450	12.110	83.400	0.588	0.962	0.017
3	9.298	3.316	2.893	0.094	859.800	7.360	12.130	85.800	0.612	0.957	0.021
4	9.246	3.350	3.309	0.058	876.800	7.520	12.130	87.900	0.613	0.976	0.012
5	9.352	3.408	2.877	0.079	865.600	7.360	12.120	87.400	0.624	0.968	0.017
6	9.462	3.379	3.592	0.062	863.300	7.370	12.130	90.700	0.646	0.976	0.012
7	9.476	3.291	3.088	0.055	867.900	7.450	12.120	90.700	0.639	0.976	0.011
8	9.399	3.498	3.103	0.060	878.200	7.510	12.150	86.200	0.601	0.974	0.012
9	9.453	3.106	2.942	0.045	871.700	7.470	12.130	91.500	0.643	0.985	0.008
10	9.211	3.438	3.512	0.086	845.700	7.320	12.130	88.300	0.633	0.963	0.018
11	9.234	3.309	2.796	0.069	863.400	7.410	12.140	86.600	0.613	0.972	0.014
12	9.369	3.340	3.598	0.062	871.400	7.500	12.130	85.400	0.598	0.975	0.013
13	9.423	3.448	3.366	0.079	858.300	7.320	12.140	90.700	0.650	0.969	0.016
14	9.692	3.360	3.638	0.088	856.800	7.370	12.150	82.900	0.589	0.957	0.019
15	9.300	3.346	3.116	0.073	853.900	7.330	12.130	84.200	0.603	0.966	0.015
Average	9.359	3.351	3.255	0.073	864.213	7.409	12.131	87.333	0.619	0.968	0.015
SD	0.133	0.094	0.296	0.015	8.652	0.070	0.011	2.757	0.021	0.009	0.004
RSD	1.421	2.807	9.096	21.074	1.001	0.940	0.087	3.157	3.314	0.942	26.412

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.1.1: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 0.5% w/w Pruv® for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.556	3.743	2.620	1.003	774.900	6.710	12.150	205.100	1.602	0.586	0.215
2	9.418	3.703	2.943	1.160	768.000	6.670	12.120	201.900	1.590	0.579	0.251
3	9.543	3.836	3.033	0.941	758.800	6.570	12.130	196.500	1.570	0.662	0.193
4	9.431	3.677	2.579	0.653	775.700	6.690	12.140	215.300	1.688	0.704	0.141
5	9.378	3.471	2.560	0.878	777.600	6.720	12.120	204.700	1.600	0.602	0.203
6	9.485	3.442	2.403	0.938	763.500	6.630	12.120	209.200	1.657	0.558	0.216
7	9.318	3.454	2.893	0.846	769.800	6.660	12.130	212.900	1.678	0.652	0.195
8	9.269	3.586	2.638	0.989	777.800	6.730	12.140	211.300	1.646	0.587	0.222
9	9.406	3.642	2.686	0.889	770.100	6.670	12.130	208.800	1.643	0.629	0.195
10	9.366	3.446	2.523	0.802	766.300	6.640	12.140	217.400	1.717	0.628	0.184
11	9.493	3.366	2.847	0.805	763.900	6.610	12.130	201.400	1.599	0.652	0.189
12	9.236	3.464	3.201	0.813	766.400	6.660	12.120	209.200	1.650	0.693	0.187
13	9.365	3.307	2.797	0.989	763.400	6.610	12.130	201.000	1.596	0.583	0.237
14	9.287	3.269	2.667	0.758	765.200	6.630	12.130	200.600	1.588	0.647	0.183
15	9.580	3.321	2.960	0.563	785.300	6.780	12.140	217.000	1.678	0.741	0.136
Average	9.409	3.515	2.757	0.869	769.780	6.665	12.131	207.487	1.633	0.633	0.196
SD	0.107	0.173	0.219	0.148	7.125	0.054	0.009	6.509	0.045	0.052	0.031
RSD	1.135	4.923	7.960	17.038	0.926	0.816	0.075	3.137	2.725	8.263	15.693

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.1.2: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.0% w/w Pruv® for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.334	3.094	2.477	0.732	760.900	6.570	12.110	219.000	1.752	0.621	0.185
2	9.399	3.191	2.311	0.940	754.400	6.490	12.140	212.900	1.720	0.531	0.229
3	9.334	3.244	2.699	0.728	755.000	6.530	12.130	205.500	1.652	0.663	0.174
4	9.311	3.054	2.939	0.717	762.500	6.590	12.120	214.100	1.707	0.672	0.184
5	9.419	3.247	2.233	0.874	763.600	6.580	12.120	218.600	1.745	0.544	0.212
6	9.211	3.104	2.654	0.658	760.800	6.560	12.150	224.700	1.795	0.677	0.165
7	9.381	3.149	2.845	0.719	766.400	6.610	12.140	213.300	1.692	0.668	0.179
8	9.360	2.989	2.827	0.596	765.300	6.590	12.130	229.200	1.825	0.704	0.156
9	9.404	3.063	2.553	0.549	753.700	6.490	12.130	214.500	1.735	0.708	0.137
10	9.259	3.067	2.498	0.525	754.800	6.450	12.130	232.100	1.889	0.719	0.130
11	9.210	3.014	2.538	0.687	761.600	6.560	12.130	229.600	1.837	0.644	0.178
12	9.281	2.927	2.884	0.590	762.200	6.580	12.140	212.500	1.694	0.709	0.157
13	9.280	3.011	2.631	0.629	757.500	6.540	12.120	226.400	1.818	0.677	0.162
14	9.387	3.048	2.821	0.621	752.000	6.490	12.130	212.100	1.715	0.701	0.157
15	9.286	2.910	2.793	0.542	746.100	6.380	12.120	228.000	1.877	0.728	0.140
Average	9.324	3.074	2.647	0.674	758.453	6.534	12.129	219.500	1.763	0.664	0.170
SD	0.068	0.101	0.211	0.118	5.655	0.063	0.010	8.189	0.072	0.059	0.027
RSD	0.733	3.295	7.977	17.488	0.746	0.964	0.085	3.731	4.095	8.902	15.684

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.1.3: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.5% w/w Pruv® for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.594	3.799	3.049	0.684	805.800	6.940	12.110	205.100	1.554	0.727	0.149
2	9.060	3.675	2.340	0.958	821.500	7.240	12.100	184.300	1.339	0.550	0.226
3	9.559	3.564	2.847	0.629	778.900	6.660	12.100	210.000	1.659	0.726	0.140
4	9.642	3.594	3.430	0.773	804.000	6.890	12.120	201.900	1.539	0.713	0.177
5	9.395	3.795	2.720	1.207	788.300	6.760	12.090	210.400	1.639	0.544	0.259
6	9.621	3.490	3.058	0.641	800.900	6.860	12.110	193.300	1.481	0.726	0.150
7	9.461	3.517	2.852	0.693	780.500	6.700	12.110	190.000	1.491	0.701	0.157
8	9.801	3.460	2.902	1.058	797.800	6.830	12.120	191.200	1.470	0.562	0.250
9	9.442	3.404	2.568	0.812	787.400	6.830	12.120	206.300	1.587	0.614	0.195
10	9.452	3.462	2.960	0.691	798.500	6.890	12.100	206.300	1.575	0.700	0.164
11	9.423	3.548	2.833	1.145	812.700	7.020	12.110	203.100	1.521	0.539	0.272
12	9.287	3.542	3.322	0.869	815.900	7.030	12.120	198.200	1.481	0.675	0.206
13	9.336	3.416	2.262	0.781	798.500	6.890	12.120	200.200	1.526	0.589	0.188
14	9.351	3.533	2.904	0.958	803.600	6.910	12.120	210.800	1.602	0.611	0.224
15	9.208	3.307	2.686	0.753	806.900	6.950	12.130	205.900	1.555	0.644	0.188
Average	9.442	3.540	2.849	0.843	800.080	6.893	12.112	199.880	1.535	0.641	0.196
SD	0.186	0.136	0.315	0.184	12.299	0.141	0.011	9.344	0.078	0.073	0.042
RSD	1.971	3.830	11.061	21.773	1.537	2.049	0.089	4.675	5.115	11.325	21.579

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.1.4: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 2.0% w/w Pruv® for 4 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.546	3.225	2.713	0.934	769.900	6.580	12.110	183.500	1.466	0.578	0.228
2	9.390	3.397	2.881	0.740	774.400	6.560	12.110	195.300	1.565	0.685	0.170
3	9.480	3.210	3.133	0.932	789.200	6.700	12.110	197.800	1.552	0.619	0.233
4	9.376	3.448	3.236	0.453	791.000	6.740	12.110	197.400	1.540	0.814	0.104
5	9.433	3.348	3.192	1.351	780.600	6.640	12.130	195.300	1.544	0.523	0.322
6	9.616	3.398	2.606	0.952	783.700	6.700	12.110	192.900	1.514	0.568	0.225
7	9.325	3.277	3.083	0.820	781.800	6.680	12.120	193.700	1.523	0.663	0.200
8	9.461	3.121	3.082	0.867	779.300	6.650	12.100	185.500	1.468	0.630	0.221
9	9.286	3.265	3.030	0.865	784.800	6.680	12.110	190.000	1.495	0.643	0.212
10	9.152	3.296	3.022	0.551	790.300	6.780	12.110	182.600	1.416	0.758	0.134
11	9.369	3.144	3.325	0.687	778.800	6.660	12.100	192.500	1.521	0.717	0.173
12	9.433	3.243	2.555	0.585	779.800	6.660	12.110	200.200	1.580	0.699	0.142
13	9.457	3.231	3.160	0.354	778.000	6.660	12.100	185.500	1.465	0.841	0.085
14	9.312	3.236	3.281	0.679	769.100	6.520	12.100	194.100	1.566	0.730	0.163
15	9.368	3.003	3.053	0.886	784.400	6.700	12.110	187.600	1.472	0.610	0.237
Average	9.400	3.256	3.023	0.777	781.007	6.661	12.109	191.400	1.512	0.672	0.190
SD	0.112	0.115	0.236	0.243	6.624	0.067	0.008	5.692	0.047	0.090	0.060
RSD	1.186	3.544	7.804	31.331	0.848	1.006	0.066	2.974	3.130	13.420	31.746

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.2.1: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 0.5% w/w Pruv® for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.344	3.397	2.724	0.749	762.200	6.580	12.130	223.900	1.786	0.663	0.173
2	9.337	3.272	3.144	0.712	760.900	6.610	12.130	221.900	1.762	0.693	0.171
3	9.255	3.259	2.850	0.854	760.600	6.640	12.120	213.300	1.687	0.646	0.208
4	9.164	3.063	3.040	0.998	762.500	6.600	12.120	206.300	1.642	0.541	0.258
5	9.120	3.123	2.918	0.672	760.400	6.540	12.120	224.700	1.805	0.674	0.167
6	9.535	3.103	2.590	1.087	753.600	6.560	12.140	205.900	1.646	0.478	0.275
7	9.395	3.175	2.543	0.879	757.300	6.510	12.130	229.600	1.851	0.628	0.215
8	9.292	3.357	2.369	0.694	759.200	6.520	12.120	223.900	1.804	0.689	0.160
9	9.407	3.005	2.925	0.915	756.000	6.490	12.120	226.800	1.836	0.578	0.237
10	9.314	3.226	2.800	0.714	768.000	6.660	12.130	208.400	1.642	0.642	0.175
11	9.424	3.275	2.596	0.850	771.300	6.640	12.130	230.500	1.822	0.627	0.206
12	9.346	3.191	2.678	0.693	749.700	6.480	12.120	213.700	1.732	0.723	0.167
13	9.633	3.224	2.999	0.657	759.100	6.600	12.120	213.300	1.698	0.688	0.160
14	9.239	3.064	2.262	0.570	749.800	6.520	12.120	214.500	1.728	0.717	0.144
15	9.256	3.175	2.800	0.594	757.500	6.580	12.130	220.600	1.760	0.740	0.146
Average	9.337	3.194	2.749	0.776	759.207	6.569	12.125	218.487	1.747	0.648	0.191
SD	0.132	0.110	0.247	0.149	5.836	0.057	0.006	8.244	0.071	0.071	0.041
RSD	1.418	3.455	8.999	19.192	0.769	0.869	0.053	3.773	4.093	11.007	21.258

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.2.2: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.0% w/w Pruv® for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.390	2.993	2.765	0.683	741.300	6.330	12.120	205.500	1.705	0.652	0.172
2	9.381	3.042	3.080	0.892	753.600	6.420	12.120	226.000	1.849	0.540	0.225
3	9.434	3.087	2.880	0.594	758.900	6.480	12.140	214.500	1.736	0.705	0.148
4	9.223	3.086	2.537	0.592	754.900	6.430	12.130	221.900	1.811	0.737	0.146
5	9.568	2.858	2.855	0.823	758.600	6.470	12.140	221.900	1.799	0.527	0.222
6	9.260	2.839	2.801	0.543	757.200	6.480	12.140	218.200	1.766	0.709	0.146
7	9.464	3.094	2.982	0.560	757.000	6.450	12.130	221.100	1.799	0.737	0.138
8	9.355	2.857	3.377	0.552	754.000	6.460	12.130	220.600	1.792	0.722	0.147
9	9.427	2.842	3.140	0.827	744.000	6.380	12.120	205.100	1.689	0.578	0.222
10	9.247	2.974	2.973	0.585	768.600	6.640	12.130	215.300	1.702	0.669	0.155
11	9.352	2.849	3.549	0.753	763.200	6.510	12.140	215.300	1.734	0.600	0.205
12	9.334	3.033	2.881	0.726	758.500	6.490	12.130	207.200	1.676	0.669	0.185
13	9.302	2.924	2.547	0.476	747.600	6.380	12.120	214.900	1.769	0.750	0.122
14	9.293	2.960	2.583	0.576	754.400	6.470	12.140	201.900	1.636	0.717	0.149
15	9.345	2.962	3.210	0.691	755.000	6.460	12.120	210.000	1.708	0.661	0.179
Average	9.358	2.960	2.944	0.658	755.120	6.457	12.130	214.627	1.745	0.665	0.171
SD	0.091	0.095	0.293	0.124	6.908	0.070	0.008	7.266	0.059	0.073	0.034
RSD	0.971	3.209	9.968	18.781	0.915	1.087	0.070	3.385	3.394	10.919	19.875

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.2.3: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 1.5% w/w Pruv® for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.620	3.646	2.819	1.079	768.300	6.610	12.150	192.000	1.522	0.618	0.234
2	9.565	3.588	2.495	0.847	772.600	6.680	12.120	186.700	1.468	0.616	0.188
3	9.605	3.604	2.616	1.288	771.300	6.610	12.100	205.900	1.639	0.522	0.285
4	9.524	3.665	2.746	0.795	763.600	6.580	12.100	194.100	1.552	0.735	0.171
5	9.756	3.558	2.446	0.694	760.400	6.540	12.120	179.800	1.444	0.698	0.152
6	9.579	3.417	2.717	0.767	771.100	6.650	12.100	188.400	1.491	0.692	0.178
7	9.544	3.469	2.902	0.956	762.900	6.530	12.100	203.900	1.643	0.619	0.216
8	9.482	3.415	2.769	0.794	765.400	6.580	12.100	203.100	1.624	0.676	0.183
9	9.453	3.477	2.978	0.930	774.000	6.620	12.110	204.300	1.622	0.597	0.212
10	9.453	3.397	2.740	0.990	766.900	6.670	12.110	195.700	1.542	0.612	0.233
11	9.396	3.488	2.891	0.511	776.300	6.700	12.100	196.500	1.543	0.779	0.116
12	9.433	3.359	2.948	1.217	763.800	6.570	12.120	194.100	1.552	0.596	0.286
13	9.552	3.278	2.723	0.971	767.000	6.590	12.120	201.000	1.602	0.525	0.234
14	9.564	3.331	3.090	0.832	762.600	6.560	12.100	201.900	1.619	0.659	0.196
15	9.550	3.296	2.650	0.836	755.400	6.490	12.100	191.200	1.550	0.641	0.197
Average	9.538	3.466	2.768	0.901	766.773	6.599	12.110	195.390	1.561	0.639	0.205
SD	0.089	0.125	0.177	0.197	5.617	0.059	0.014	8.834	0.063	0.070	0.046
RSD	0.933	3.609	6.383	21.917	0.733	0.891	0.117	4.521	4.028	10.996	22.194

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase

Table D.3.2.4: *Friction parameters of Avicel® tablets. Filler/binder is mixed with 2.0% w/w Pruv® for 8 minutes 69 rpm.*

Tablet	Axial force (Bar)		Radial force (dBar)		Mass (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (N)	Calculated parameters		
	Compress	Eject	Compress	Eject					TS (MPa)	R	μ_W
1	9.636	3.159	3.137	0.725	792.600	6.710	12.100	196.100	1.538	0.636	0.184
2	9.495	3.315	3.138	0.983	769.900	6.550	12.140	192.900	1.544	0.593	0.232
3	9.265	3.301	3.077	0.525	796.800	6.780	12.130	192.000	1.486	0.772	0.127
4	9.342	3.271	2.606	0.795	772.200	6.590	12.140	192.900	1.535	0.692	0.191
5	9.324	3.225	3.074	0.744	781.500	6.690	12.130	194.100	1.523	0.692	0.184
6	9.293	3.130	3.016	0.779	802.700	6.860	12.130	196.100	1.500	0.602	0.204
7	9.320	3.123	2.696	0.582	781.900	6.670	12.130	194.900	1.534	0.739	0.147
8	9.439	3.112	2.864	0.733	771.400	6.570	12.130	185.500	1.482	0.684	0.184
9	9.258	3.294	3.392	0.707	791.200	6.810	12.130	188.400	1.452	0.691	0.174
10	9.311	3.216	3.348	0.718	790.900	6.700	12.130	183.900	1.441	0.691	0.178
11	9.172	3.030	3.340	0.778	808.100	6.920	12.130	199.000	1.509	0.661	0.212
12	9.077	3.192	3.144	0.918	798.400	6.880	12.130	185.500	1.415	0.553	0.237
13	9.443	3.200	3.417	0.564	773.300	6.570	12.120	192.000	1.535	0.759	0.137
14	9.140	2.966	2.839	0.580	786.400	6.710	12.140	180.200	1.408	0.738	0.155
15	9.113	3.087	3.252	0.994	802.600	6.880	12.140	187.100	1.426	0.574	0.265
Average	9.308	3.175	3.089	0.742	787.993	6.726	12.130	191.680	1.489	0.672	0.187
SD	0.152	0.102	0.249	0.144	12.563	0.124	0.010	4.319	0.049	0.068	0.038
RSD	1.631	3.209	8.074	19.442	1.594	1.850	0.082	2.253	3.264	10.090	20.416

TS = Tensile strength; R = coefficient of lubrication; μ_W = friction coefficient during ejection phase