

Powder characteristics and tableting of nevirapine prepared by a novel process

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AIM AND OBJECTIVES

The science of powders in the pharmaceutical industry is a specialised field and the particle size of a powder may influence its bulk performance, its tableting properties and handling. During the synthesis process of an API, the crystal form is dependent on the solvent being used in the final stage of recrystallisation. Usually, the particle size is too large for use as is, in which case milling would be the next step in the production line-up. Milling of APIs can result in polymorphic phase transformations, contamination, and costly product losses through dust. Solid state chemistry of a given API and the physico-chemical properties thereof are thus critical during the pre-development phase.

This study investigated the feasibility of particle size reduction of nevirapine through rapid crystallisation (form IV) and a subsequent phase transformation (form I).

The objectives of this study thus were:

- To successfully prepare nevirapine polymorphic form IV and the subsequent transition into form I;
- To characterise the novel nevirapine powder;
- To compare the properties of the novel nevirapine powder with that of commercially available, nevirapine raw material. The properties to be investigated included: particle size, morphology, bulk density, tapped density, powder flow, powder dissolution and solubility;
- To investigate the different options available for tableting, i.e. direct compression or wet granulation; and
- To compare the tablet properties with regards to monograph tableting specifications, such as hardness, friability, disintegration, dissolution and weight variation.

ABSTRACT

Powder Characteristics and Tableting of Nevirapine Prepared by a Novel Process

The science of powders in the pharmaceutical industry is a specialised field and the particle size of a powder may influence its bulk performance, its tableting properties and handling. During the synthesis process of an API, the crystal form is dependent on the solvent being used in the final stage of recrystallisation. Usually, the particle size is too large for use as is, in which case milling would be the next step in the production line-up. Milling of APIs can result in polymorphic phase transformations, contamination, and costly product losses through dust. The understanding of the physico-chemical properties of a given API is critical during the pre-development phases of dosage forms.

This study investigated the feasibility of particle size reduction of nevirapine through rapid crystallisation (metastable, intermediary form IV), followed by desolvation and a subsequent phase transformation. The powder obtained by this novel method was characterised and compared with commercially available, nevirapine powder. The following properties of the two nevirapine powders were investigated: 1) Particles size and size distribution, 2) Particle shape and surface, 3) Powder flowability, using angle of repose, critical orifice diameter, Carr's compressibility index and the Hausner ratio, and 4) Solubility and dissolution rate. Tablets were also manufactured during this study by means of wet granulation from the two nevirapine powders. The tablets were subjected to the following tablet tests: 1) Friability, 2) Crushing strength/hardness, 3) Disintegration, 4) Dissolution, and 5) Weight variation.

Based on the results obtained from the powder and tablet studies, the following conclusions were reached. Nevirapine raw material may be suitable for tablet manufacturing, either through direct compression, or through a method involving processing prior to tablet compression, i.e. granulation. Novel nevirapine powder posed flowability problems and would only be suitable for use if its flow properties could be improved by a granulation process. However, novel nevirapine powder

may be the preferred API, due to its properties that could aid the dissolution of the final product. The results have shown that those tablets that had been produced from the novel nevirapine powder had several advantages over those, produced from the nevirapine raw material, such as better mechanical strength and dissolution properties.

This study showed that small changes in the powder characteristics could significantly affect its subsequent processing. The change in the powder properties of nevirapine had proven this statement. There were significant differences in the flowabilities and solubilities of the two nevirapine powders, as well as between their respective tablet properties. Novel nevirapine powder had poor flowability, while offering better solubility values. Its poor flowability rendered the production of tablets by direct compression practically impossible. The tablets produced from the novel nevirapine powder showed advantageous properties.

Further studies are, however, recommended in order to improve the flowability of the fine, novel, nevirapine powder and to further establish its promising potential to produce effective tablets without prior milling, as is currently being practiced.

UITTREKSEL

Die Poeiereienskappe en Tabletering van Nevirapien Berei Deur 'n Nuwe Proses

Die wetenskap van poeiers is 'n gespesialiseerde veld binne die farmaseutiese industrie. Die gedrag van 'n poeier in grootmaat, sy tableteringseienskappe, sowel as die hantering daarvan word grootliks deur die deeltjiegrootte beïnvloed. Tydens die sintese-proses van 'n aktiewe bestanddeel, is die kristalvorm van 'n geneesmiddel van die oplosmiddel wat gebruik word gedurende die finale stap van rekristallisering, afhanklik. Gewoonlik is die deeltjiegrootte, soos verkry vanaf rekristallisering, te groot vir gebruik tydens formulering. Die gevolg is die insluiting van vermalings as die volgende stap in die produksie-lyn. Die vermalingsproses kan tot polimorfiese fase-veranderings, kontaminering, sowel as tot groot produkverliese weens die ontstaan van stof, aanleiding gee. Met inagneming van hierdie feite kan vermalings van geneesmiddels dus 'n duur proses wees. Begrip van die fisies-chemiese eienskappe van 'n geneesmiddel speel dus 'n kritiese rol gedurende die vroeë ontwikkelingsfasies van doseervorme.

Gedurende hierdie studie is die haalbaarheid van die verkleining van die deeltjiegrootte van nevirapien, deur middel van vinnige rekristallisering (metastabiele tussenganger, vorm IV), gevolg deur desolvasie en 'n fase-oorgang (hierna die "nuwe nevirapienpoeier"), ondersoek. Die poeier wat deur bogenoemde proses verkry is, is gekarakteriseer en met die kommersieel-beskikbare nevirapienpoeier vergelyk. Die volgende eienskappe van die twee nevirapienpoeiers is ondersoek: 1) Deeltjiegrootte en deeltjiegrootte-verspreiding, 2) Poeierdeeltjie-vorm en sodanige oppervlakte-eienskappe, 3) Vloeibaarheid van die poeier is deur middel van die hoek van rus, die tegniek van kritiese deursnee van 'n opening, Carr se indeks vir saampersbaarheid en die Hausner-verhouding bepaal, en 4) Oplosbaarheid en dissolusie-tempo. Die proses van nat granulering is gebruik vir die vervaardiging van tablette. Die tablette is gevolglik met behulp van die volgende metodes getoets: 1) Bepaling van brosheid of breeksterkte, 2) Tablethardheid, 3) Disintegrasie, 4) Dissolusie, en 5) Massavariasie.

Die resultate vanuit al die bogenoemde toetse verkry het tot die volgende gevolgtrekkings aanleiding gegee. Nevirapiengrondstof behoort geskik te wees vir die vervaardiging van tablette deur die proses van direkte samepersing, of deur eers die poeiereienskappe voor tabletsamepersing te verander, deur 'n proses soos granulering. Die nuwe nevirapienpoeier het oor swak vloei-eienskappe beskik en sou slegs vir tableting geskik kon wees, indien hierdie eienskappe deur middel van 'n granuleringsproses verbeter sou kon word. Nogtans sou die nuwe nevirapienpoeier verkies word, omdat dit die dissolusie van die finale produk kan bevoordeel. Die resultate het getoon dat die tablette wat vanuit die nuwe nevirapienpoeier vervaardig is oor verskeie voordele beskik het, vergeleke met die tablette wat vanuit die nevirapiengrondstof gemaak is. Die tablette wat met die nuwe nevirapienpoeier vervaardig is, het beter meganiese sterkte, sowel as beter dissolusie-eienskappe getoon.

Hierdie studie het getoon dat klein veranderinge in die poeiereienskappe van 'n geneesmiddel 'n noemenswaardige effek op die daaropvolgende prosessering kan hê. Die verandering in die poeiereienskappe van nevirapien het hierdie stelling gestaaf. Daar was noemenswaardige verskille in die vloei- en oplosbaarheid van die twee nevirapienpoeiers, sowel as in die relevante tableteienskappe. Die nuwe nevirapienpoeier het swak vloei-eienskappe getoon, maar terselfdertyd het dit beter oplosbaarheid gewys. Die swak vloei-eienskappe van die nuwe nevirapienpoeier het die produksie van tablette deur middel van direkte samepersing prakties onmoontlik gemaak. Die tablette vanuit die nuwe nevirapienpoeier vervaardig, het verskeie voordelige eienskappe getoon.

Verdere studies word egter aanbeveel, met die doel om die vloei-eienskappe van die fyn, nuwe nevirapienpoeier te verbeter, sowel as om die belowende potensiaal daarvan om die vervaardiging van verbeterde tablette te bewerkstellig, sonder die insluiting van 'n voorafgaande vermalingsproses, soos wat huidig die praktyk is, te vestig.

CHAPTER 1

Properties of Pharmaceutical Powders and Tablets

1.1 Introduction

Particle technology refers to the science related to particles and powders (Rhodes 2008). Particles and powders are often described as bulk solids (Rhodes 2008). A powder is a solid substance composed of small particles or finely dispersed solid particles. The British Pharmacopoeia (BP) (2009) defines different types of powder, according to its coarseness or fineness properties and this classification is presented in Table 1.1. The differentiation is based on information computed from laser diffraction particle analysis.

Table 1.1: Classification of powder according to its measure of fineness (British Pharmacopoeia 2009)

Classification of powders by fineness	
Descriptive terms	x_{50} (μm)
Coarse	> 355
Moderately fine	180 – 349
Fine	125 – 179
Very fine	< 125

From the above classification, it is necessary to consider some of the principles of micromeritics in the characterisation of powders. Micromeritics is the science and technology of small particles (Wikipedia 2010). Pharmaceutical micromeritic topics include particle size and size distribution, particle shape, particle texture and packing geometry. Other properties of powders are surface area, porosity, density and powder flowability (Wikipedia 2010).

In pharmaceuticals, powder is encountered in almost every process. Although the pharmaceutical industry has many different dosage forms available, the active

pharmaceutical ingredient (API) is usually in a powder form prior to formulation. The characteristics of a powder affects the formulation processes of a dosage form, as well as the after formulation stages, i.e. dissolution and drug bioavailability testing. This is the reason why formulation scientists are now “...concerned not only with chemical purity but also with those other characteristics of pharmaceutical materials which may influence safety, efficacy, formulation and processing of medicines” (Beckett, Stenlake 1988).

In addition to chemical, biological and other studies, it is a prerequisite that an intensive study must be conducted to investigate the powder properties of the drug, before it is being processed into a medicine. Acquiring information regarding powder properties can give the formulator the power to rationally design formulations and predict the quality of the dosage form. Failure to ensure that the powder possesses adequate technical properties could result in a number of problems, which could affect the tablet weight, cause dose and colour variation, inconsistent physico-mechanical properties, capping and lamination, and adhesion and sticking (Staniforth, Aulton 2007b).

1.2 Powder properties

The behaviour of a powder largely depends on its particulate properties, including particle size distribution, particle morphology, particle texture and moisture content, among other parameters. Knowledge of these properties is important in the description or assessment of powders.

1.2.1 Particle size and size distribution

Particle size is an important, definitive property of a powder. Information about the particle size and particle size distribution of pharmaceutical powders is essential to pharmaceutical scientists. Most powders are therefore defined on the principle of particle size distribution. The discrete particles in a powder are not always uniform and of the required size. Often there are many varying particle sizes. Significant particle size variances can have deleterious consequences during the formulation processes. As a result, there is an increased demand by regulatory authorities for

pharmaceutical dosage forms to be prepared from a powder of uniform particle size. The International Pharmacopoeia (IP) states that “...in process control during tablet production should include the particle size of the active ingredient(s)” (World health organization 2006).

When determining particle size, a powder particle is often considered approximate to a sphere, which can then be characterised by determining its particle diameter. The dimension is referred to as the equivalent particle size of the particle, since it is measured based on a hypothetical sphere (Staniforth, Aulton 2007a). In order to be able to compare the characteristics of two or more powders, consisting of particles with many different equivalent particle sizes, the powders must be quantified into size distributions. Size distribution can be subdivided into different size ranges. A frequency distribution graph can then be constructed by plotting the number of particles in a given size range. The ideal resulting curve shows normal distribution behaviour, with the standard deviation measuring the distribution around the mean. Standard deviation is an indication of the uniformity of particle size within a sample (Brittain 1995).

Most powders encountered in pharmaceutical preparations, however, do not exhibit “ideal normal distribution” behaviour, but rather shows skewed distribution tendencies. Skewed distribution can be normalised by plotting frequency *versus* logarithm of the particle size, to give a log normal distribution (Brittain 1995).

Particle size influences numerous factors, from the type of dosage form to be formulated to the ability of the dosage form to release the drug, following administration. Formulation factors that are often influenced by particle size include powder flow, mixing, granulation, compression, capsule filling and dosage uniformity. The particle size of the active ingredient(s) is of primary significance in determining the rate and extent of dissolution, and hence its bioavailability. This is often the case with drugs that are poorly soluble in aqueous media, in which case the dissolution rate is a rate-limiting step in the absorption process (Conway 2008). By reducing particle size, the effective surface area is increased, which successfully improves the dissolution rate of the API. The effects of particle size on the dissolution and absorption rates are illustrated in Figure 1.1. The solubility and the bioavailability of griseofulvin, a class II drug (low solubility/high permeability), for example, was

reported to be largely increased by a particle size reduction (Jounela, Pentikäinen et al. 1975). Particle size irregularities in a dosage form may also be reflected in differences observed in clinical responses, or toxic effects (Beckett, Stenlake 1988).

A realisation of the importance of particle size has encouraged pharmaceutical industries to take several measures to carefully control the particle sizes of an API, within the range that would generally yield a good balance of bioavailability and processability. In an attempt to achieve such balance, several methods of size reduction are often employed. Size reduction is a process of modifying powder particles size, without chemically changing the compound. Traditional methods of size reduction include milling, fluid energy micronisation, trituration and grinding, and solvation and desolvation (Habib 2001). It should be noted that drug substances are susceptible to polymorphic and chemical transformation when they undergo size reduction by most of the traditional methods (refer to section 1.3). Digoxin, spironolactone, and estradiol are some of the drugs being reported to undergo polymorphic transformation during physical size reduction processes (Zhou, Porter et al. 2009).

Many techniques are used for the characterisation of particle size. The choice depends on the size range to be examined. Light diffraction is the most widely used technique, both in pharmaceutical industries and in research institutions. This method is widely accepted, due to its capability to analyse a broad particle size range and its ease of use. Microscopy, however, is the most reliable and efficient method, because it can provide direct observation of the particles under consideration and is capable of measuring particles of 0.3 μm or larger. Sieving analysis, which is the simplest method of particle size analysis, is applicable where the majority of the particles are larger than 75 μm . Other methods include a sedimentation method, which is based on the determination of the particle size from the particles' sedimentation velocity in a gravitational field, whilst resistive pulse techniques (electrical zone sensing) are used for particles larger than several micrometers in diameter, as well as optical methods (i.e. optical blockage technique, photon correlation spectroscopy and light scattering method) and elutriation methods. Irrespective of the particle size analysis method employed, in order to

acquire meaningful data, representative samples of the bulk powder must be analysed (Allen 2003).

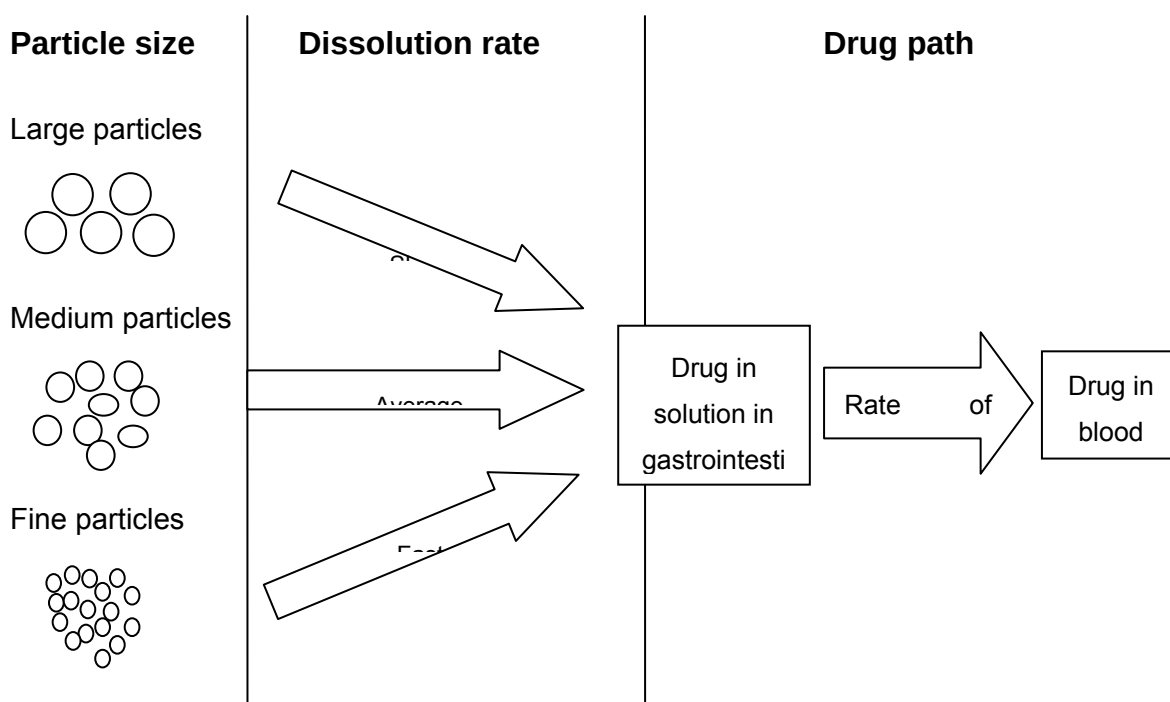


Figure 1.1: Illustration of the effect of particle size on the drug dissolution rate and the path of a drug following oral administration (Alderborn 2007).

1.2.2 Particle morphology: Shape and surface characteristics

Particle shape significantly influences the behaviour of a powder and its subsequent processing. It affects the particle size determination, the way that the powder flows and therefore mixing, as well as the physical stability of solid dosage forms. Although spherical particles exhibit the highest measure of flowability and are therefore mixed effortlessly, they also segregate more easily than non-spherical particles, in the event of large particle size variances. Irregular, or needle shaped particles may become interlocked, thus reducing the tendency to segregate after powder mixing has been completed (Twitchel 2007).

Particles in powders may assume different shapes and can for example be described as spherical, elongated, acicular, angular, etc., as listed in Table 1.2. Even though these terms do not describe the pattern of relationships among all of

the points that constitute the external boundaries, and despite conveying little quantitative information, they are still commonly used, because they are less complex (Washington 2005).

The surface characteristics of a particle are as important as its shape. Particle surface characteristics determine the way that particles behave when they come into contact with other substances. Twichel (2002) states that “...the texture of particles may also influence powder flowability, as particles with very rough surfaces will be more cohesive and have greater tendency to interlock than smooth-surfaced particles.” Surface characteristics may be described as cracked, smooth, porous, rough, or pitted (British Pharmacopoeia 2009).

Microscopy is used to provide information regarding particle shape and surface characteristics, with scanning electron microscopy (SEM) being the most widely used technique. SEM is an ideal instrument for this purpose, especially when the descriptions from the observations can be clearly identified and distinguished with photomicrographs.

Table 1.2: Particle shapes with corresponding descriptions (Steele 2004)

Shape	Description
Acicular	Elongated, needle-like prism.
Angular	Sharp edged, roughly polyhedral.
Anhedral	Poorly formed, external crystal faces not developed.
Bladed	Like a wedge or knife blade, flattened acicular.
Cubic	Cube shaped.
Dendritic	Tree-like growths, branched crystalline.
Equant (round or angular)	All boundaries are approximately equal in length.
Fibrous	Elongated, slender clusters of thread-like crystals.
Octahedral	Shaped like an octahedron, eight-sided (two pyramids base to base).
Prismatic	Elongated crystal of columnar-like-prism.
Tabular	Flat, rectangular, with a pair of parallel faces.

1.2.3 Powder flow

Powder flowability is the ability of powder to flow in a desired manner in a specific piece of equipment (Prescott, Barnum 2000). Provided that the effect of the equipment is neglected, powder flowability simply means the ability of the powder to flow. This 'simple' definition is well accepted when distinguishing between powders. In this study, powder flowability referred to the later explanation. Powder flowability is an indispensable property of an API in the production of tablets and capsules, warranting it to be assessed during pre-formulation. Many pharmaceutical processes depend on the flowability of the powder. These include:

- **Mixing:** Free flowing powder is easily mixed at minimum energy consumption.
- **Filling of tablet die and capsule dosators:** Powder flow dictates the tablet weight uniformity and consistency in terms of physico-mechanical properties.
- **Tablet ejection:** 'Non-flowing' powders require great force to friction during ejection.
- **Blending:** In this case the quality of the resulting blend depends on the type of blender used and on the flow behaviour of the powder during the blend cycle (Prescott, Barnum 2000).

Powder flow is strongly related to the physical properties of the discrete particles constituting the powder. These include interparticle forces, particle size and particle size distribution, particle density, particle shape and roughness, packing geometry and moisture content. In general, more fine particles exhibit poor flowability, due to strong interparticle forces, whilst particles of different shapes behave differently during powder flow testing (refer to section 3.2). Particles with a smooth texture also flow with ease, due to the lack of interlocking among the particles. The flow pattern, or the behaviour being adopted by a powder, is dictated by a combination of these powder characteristics, as well as environmental conditions (e.g. relative humidity), rather than by a single factor (Burch, Cocks et al. 2008).

1.2.3.1 Characterisation of powder flow

Powder flow influences many pharmaceutical processes and therefore requires that formulation scientists should have an in-depth knowledge regarding the flow properties of the powder active ingredient. The assessment of powder flowability is

time consuming, but the benefit of accurately characterising powder flow prior to commencing with formulation, by far outweighs this disadvantage (Prescott, Barnum 2000). There are several methods that may be employed in the characterisation of powder flow, for example angle of repose, hopper flow rate, critical orifice diameter, the Carr compressibility index and the Hausner ratio, as described below. The method of choice for the characterisation of powder flow depends on the ability of the scientist to use it effectively. It is also advantageous to use multiple, standardised test methods to characterise various aspects of powder flow (Linoya, Gotoh et al. 1991).

a. Angle of repose

The angle of repose is a characterisation method being used to determine pharmaceutical powder flow, but it is also used in other branches of science to characterise or to compare powders. It is defined as the “...angle from the horizontal plane to the free surface of the pile of powder under the critical stress in the gravitational field” (Linoya *et al.*, 1991). There are two main types of angles of repose, namely the static and dynamic angles. The angle of repose can be determined by a fixed cone method, fixed base cone method, tilting table method and a rotating cylinder, as shown in Figure 1.2.

The angle of repose is derived by measuring the height and the base of the cone of powder and by calculating the angle of repose (α) with the tangent equation (Twitchel 2007).

$$\tan(\alpha) = \frac{\text{height}}{0.5 \text{ base}} \quad \text{Equation 1.1}$$

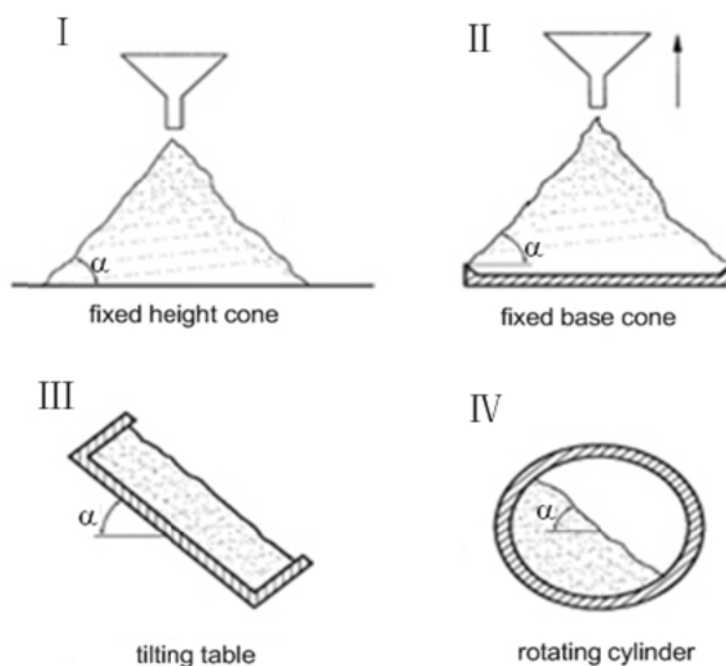


Figure 1.2: Measurement methods employed to determine the static and dynamic angles of repose of powders (Geldart, Abdullah et al. 2006).

The angle of repose of a powder is formed when the powder is passed through a funnel-like container. When conducting a fixed height cone angle of repose test, it is recommended that the base must be fixed and free of vibration and that a funnel must be maintained at a height of 2 - 4 cm from the top of the powder pile as it forms. Powder having a small angle of repose is regarded as having excellent flow characteristics (British Pharmacopoeia 2009). The measure of flowability and corresponding characterisation descriptions are listed in Table 1.3.

Table 1.3: Powder flowability and characterisation scale (British Pharmacopoeia 2009)

Flow character	Angle of repose (°)	Compressibility index (%)	Hausner ratio
Excellent	25 – 30	≤ 10	1.00 – 1.11
Good	31 – 35	11 – 15	1.12 – 1.18
Fair	36 – 40	16 – 20	1.19 – 1.25
Passable	41 – 45	21 – 25	1.26 – 1.34

Poor	46 – 55	26 – 31	1.35 – 1.45
Very poor	56 – 65	32 – 37	1.46 – 1.59
Very, very poor	≥ 66	≥ 38	≥ 1.60

b. Flow rate

Determining flow rate through an orifice is a direct and simple method to measure the rate at which a powder discharges. This method is useful only with materials that have the capacity to flow and is it thus impractical for cohesive materials. Flow rate can be measured as a mass or volume of powder flowing from a container, calculated against time. Measurement can be made in discrete or continuous increments. A number of experimental variables must be taken into account when using this method. These variables include:

- The type of container (cylinder, funnel, hopper from production equipment) and container material used (metal, glass, plastic).
- The diameter and shape of the orifice.
- The diameter and height of the powder bed. The flow rate is virtually independent of the powder head, provided that the height of the powder bed (the “head” of the powder) is much larger than the diameter of the orifice.
- The method used to measuring powder flow rate. Flow rate can be measured continuously by using an electronic balance. (British Pharmacopoeia 2009).

c. Carr’s compressibility index and Hausner ratio

The Carr’s compressibility index and the Hausner ratio are closely related and are popular methods for predicting powder flow characteristics. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder. When characterising powder flow with these methods, powder of a known volume is filled into a cylinder and repeatedly tapped for a pre-determined duration (British Pharmacopoeia 2009). The volume after tapping is measured and the compressibility index (C) and Hausner ratio are calculated, using the following formulas:

$$\text{Compressibility index} = 100 \times \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right] \quad \text{Equation 1.2}$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{Equation 1.3}$$

Powders with high capacity to flow have a low compressibility index and Hausner ratio. The generally accepted scale of flowability by compressibility index and Hausner ratio is given in Table 1.3. The BP recommends that a 250 mL volumetric cylinder with a test sample weight of 100 g should be used and that a conclusion should be made, based on an average of three determinations (British Pharmacopoeia 2009).

d. Critical orifice diameter

This method was developed in 1980 by Albert Gioia. He studied the importance of the critical orifice diameter method and implemented this flowability measurement method, because of its simplicity and relevance in capsule filling (Ghugare, Dongre et al. 2010). This method of powder flow characterisation is not recommended in either the BP, or the USP (United States Pharmacopoeia), but it has been well applied in research environments and pharmaceutical industries. The device consists of a cylinder with a series of interchangeable discs of different diameter orifices and a stainless steel cylinder (sample holder). The discs and the sample holder are separated by a mobile shutter. Critical orifice diameter is the size of the smallest orifice of the discs through which the powder freely discharges when the shutter is opened (Staniforth, Aulton 2007b). "Critical orifice diameter is a direct measure of powder cohesion and arch strength." (Staniforth, Aulton 2007b.) There is no official scale of flowability for critical orifice diameter through which to distinguish between poor and good flowing powders. However, it is well accepted that the smaller the critical orifice diameter, the better the flow (Staniforth, Aulton 2007b).

e. Shear cell method

The shear cell method can provide adequate data regarding the flowability of the material when used effectively. This method relates the flow of powder with the equipment used, and as such it can be helpful in the engineering of pharmaceutical equipment. There are three basic method types for shear cell analysis, namely cylindrical shear cell, annular shear cell and rotational plate cell (plate type). The BP recommends that the results of powder flow characterisation, using shear cell methodology, should include a complete description of the equipment and methodology used (British Pharmacopoeia 2009).

1.2.3.2 *Reasons for poor powder flow*

There are several factors that can contribute to poor powder flow.

- **Particle size:** Powders, comprising mainly of small particles, are often associated with poor flow, whereas those with larger particles are associated with acceptable flow.
- **Particle shape and surface:** Well rounded, spherical particles are associated with a powder of good quality. The particle surface determines the ability of the particles to interlock, which can result in poor powder flowability.
- **Moisture content:** Low moisture content in the formulation or analysis area is desirable for better powder flow. High moisture content reduces interparticulate distances and increases surface tension between the particles, with ultimate reduction in powder flowability (Teunou, Fitzpatrick 1999). Reports have indicated that powder flowability is inversely proportional to its moisture content. This relationship is more dominant in powders consisting of small particles (Teunou, Fitzpatrick 1999, Zou, Brusewitz 2002).

1.2.3.3 *Alteration of powder flow*

Due to the prerequisite for using fine particles in the formulation of dosage forms, pharmaceutical powders are often cohesive, having a poor flowing capacity. This requires the enhancement of their flowability, which is accomplished by altering the physical properties of the discrete particles forming the powder. Particle size can be changed by means of granulation, moisture content by means of drying, particle shape and texture by means of spray-drying and by controlling the production methods (such as crystallisation conditions), and more commonly by the addition of

a glidant to the formulation (i.e. talc, maize starch, magnesium stearate) (Staniforth, Aulton 2007b).

1.3 Polymorphism and its relationship to powder properties

1.3.1 Introduction to polymorphism

Polymorphism is the ability of a substance to exist in more than one distinct crystal form. “Polymorphs are different crystalline forms of the same pure substance, in which the molecules have different arrangements and/or conformations of the molecules.” (Grant 1999). Since polymorphism is related to the packing arrangements and/or conformations of the molecules, this characteristic is only exhibited by a substance when in its solid form. A substance in the liquid and gaseous states would hence behave identically (Saunders, Gabbott 2011).

Polymorphs may display different chemical and physical properties, such as solubility, dissolution rate, hygroscopicity, stability, melting point, crystal shape and size. Acetaminophen, for example, exhibits polymorphism and can exist as the monoclinic or orthorhombic forms. The monoclinic form is stable under ambient conditions, whereas the orthorhombic form has a higher density (Grant 1999).

1.3.2 Preparation of polymorphs

The preparation process of a specific polymorphic form of a compound is of specific pharmaceutical importance. The nature of the crystal structure, as assumed by a given compound upon crystallisation, exerts profound effects on the solid state properties of that polymorphic form (Adeyeye, Brittain 2008). The controlling of the preparation process is therefore incredibly important during the pre-formulation stages, as to ensure that a suitably stable, polymorphic form is prepared. The most common method for preparing a polymorph is the recrystallisation of a given substance from a variety of solvents, under different crystallisation conditions (i.e. temperature and humidity). A single solvent or a mixture of solvents may be used. In order to induce the nucleation and growth of different possible polymorphs, pharmaceutical scientists usually subject a given drug substance to various solvents,

or mixtures of solvents and to a variety of crystallisation conditions. It is important to ensure that recrystallisation is carried out from a truly clear solution, in order to minimise seed crystals. It is also important to use highly pure materials to avoid artefacts. The presence of impurities may further alter the crystal habit and its growth rate (Libbrecht 2008, Sangwal 1996).

Grinding is a particle size reduction method and may result in a polymorphic transformation in certain materials, and as such it is sometimes used in the generation of certain polymorphic forms. Solid phase transformations of APIs, caused by mechanical stress, are more frequently associated with the formation of amorphous states, rather than 'true' polymorphs (Rodríguez-Spong, Price et al. 2004) Sublimation is a direct transition of a compound from the solid to the gaseous phase, without passing through the liquid phase. The reverse process is called deposition. Approximately two thirds of organic compounds undergo both processes (Guillory 1999). Sublimation is an endothermic phase transition and thus occurs when heat is applied. During sublimation, crystals may form on cooler surfaces that are in close proximity to the organic compound when it melts, in those instances where no crystals formed at temperatures below the melting point. The formation of a polymorphic form depends on the temperature at which sublimation occurs. The size and form of the crystal is largely influenced by both the sublimation temperature and the distance of the collecting surface from the material undergoing sublimation (Guillory 1999). Sublimation usually produces very high quality crystals. Panagopoulou-Kaplani and Malamataris (2000) identified a new, insoluble polymorphic form of glibenclamide through sublimation, by spreading a portion of quickly cooled melt on a petri dish, covered with a watch glass that served as a condenser. Heat was gradually applied and the temperature increased from 130°C to 160°C over a period of six hours (Panagopoulou-Kaplani & Malamataris, 2000).

Vapour diffusion crystallisation requires two solvents, or a solvent mixture in which the sample is soluble in one solvent, but insoluble in the other, with the two solvent systems being miscible. In this method, a solution of the solute in a solvent in which it is soluble is placed in a small, open container. This system is then placed inside a large, tightly closed container that contains a small volume of solvent in which the sample is insoluble. Crystals form as the vapour from the solvent in the large

container diffuses into the solution in the small container. This method is frequently applied in the preparation of single crystals (Guillory 1999).

1.3.3 Pharmaceutical importance of polymorphism

Polymorphism is a research field that is very important to the pharmaceutical industry and to pharmaceutical regulatory authorities, since many APIs exhibit polymorphic behaviour. Since polymorphic forms affect the API's stability, bioavailability and manufacturability, knowledge of polymorphism is essential for the manufacturer in order to produce an API form that is suitable for formulation purposes (Bernstein 2002).

1.3.3.1 Stability

Polymorphism can influence an API's stability, either through a direct effect on chemical reactivity and therefore the drug's basic chemical stability, or *via* instability of the polymorphic form itself (Florence 2009). The differences (i.e. physical stability of the dosage form, solubility, etc.) between a stable and a metastable polymorphic form are thus of pharmaceutical interest, since a stable polymorph, for example, of a given drug is typically used for the formulation of suspensions, whereas a metastable form may sometimes be used in the formulation of tablets and capsules (Haleblian, McCrone 1969, Singhal, Curatolo 2004).

1.3.3.2 Manufacturability

Since particle size, particle shape and powder density are dependent on polymorphism, among other factors, polymorphism can affect powder flowability and compressibility. It is also important to consider the possibility of polymorphic transformations that may occur during manufacturing (Snider, Addicks et al. 2004).

1.3.3.3 Bioavailability

The rate of dissolution and therefore the bioavailability of a solid substance are influenced by polymorphism. This is especially applicable to water insoluble

compounds, since their bioavailabilities may largely be dependent upon their rates of dissolution (Bernstein 2002, Florence, Attwood 2006).

1.3.4 Characterisation of polymorphs

A number of analytical techniques are employed in the characterisation of polymorphs. Some of these methods include X-ray diffraction (XRD), thermal analysis (TA), hot stage microscopy, infrared (IR) spectrometry and solid state nuclear magnetic resonance (NMR). Despite the importance of all these methods, thermal analysis and powder XRD methods receive much more attention, since they already provide invaluable information on their own (Craig 2006).

1.3.5 Crystal habit and its pharmaceutical importance

Structurally, a polymorph can be described in terms of its external appearance (crystal habit) and/or internal structural units (unit cells). Crystal habit is described by its length, width, thickness, and surface appearance (roughness, smoothness and porosity). Crystal habit does not necessarily reflect the internal structure of a compound, whereas polymorphs of same internal structure may assume different crystal habits, and hence they may exhibit different physico-mechanical properties (Sunagawa 2003, Swarbrick 2004).

1.3.6 Relationship between polymorphism and powder properties

When discussing powder properties and polymorphism, there are several similarities that can be established. Almost all pharmaceutical powders are of a particular polymorphic form, and a change in the polymorphic form of an API during preparation, can directly influence its powder characteristics. There are several methods of preparing polymorphs, as discussed in section 1.3.2. The specific method of preparation of a polymorph can also influence certain powder properties. The use of a 'rapid expansion of supercritical carbon dioxide solutions' (RESS) method, for example, in the preparation of carbamazepine, resulted in micronised particles of less than 3 μm (Gosselin, Thibert et al. 2003).

A change in the crystal habit of polymorphs, due to changes in preparation, may also affect the particle shapes of the resulting powder. Such changes may cause essential variations during tablet formulation. This was demonstrated by ibuprofen, when such changes influenced the compressibility, flow rate, bulk density and tableting behaviour of the prepared ibuprofen crystals (Garekani, Sadeghi et al. 2001).

The instability of certain polymorphic forms can also influence powder properties and can a metastable polymorph transform into a known stable polymorph, but present with different powder characteristics. When metastable form IV nevirapine, for example, transforms into the stable form I nevirapine, it presents as a very fine powder, without being mechanically ground (Stieger, 2009). The influences of such changes on the nevirapine API were being investigated during this study (Garekani, Sadeghi et al. 2001, Rasenack, Müller 2002).

1.4 Conclusion

Solid state studies of an API are prerequisite to any formulation study. The knowledge of polymorphism helps a pharmaceutical scientist to be aware of phase transitions that may occur during the manufacturing process. Also, to have a successful compaction of powders, an understanding and knowledge of the properties of powders are essential. During the tableting process, the particle size and mechanical properties of powders play an important role.

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CHAPTER 2

Overview Tablet Production and Properties

2.1 Introduction

The oral route is proven, the most common route of drug administration and among oral dosage forms, tablets are the most popular. A tablet may be defined as an oral solid dosage form, consisting of a blend of one or more active ingredients and excipients, compressed together into a compact entity. Tablets are formed by the compression of uniform volumes of a blended powder within a confined space. The compression process consists of three steps, namely die filling, tablet formation and tablet ejection (Alderborn 2007). Excipients are substances capable of modifying the behaviour of the active ingredient, in order to achieve ease of preparation and quality, or an acceptable finished product. The most common excipients being used in tablet formulation are diluents, binders, disintegrating agents, glidants and lubricants. Excipients may also include colouring and flavouring agents, depending on the organoleptic properties of the active pharmaceutical ingredient (API) (Alderborn 2007).

2.2 Desirable properties of tablets

Pharmaceutical dosage forms should meet specific physical, chemical and biological properties and tablets are no exception. Desirable properties of tablets and the associated tests for the purpose of ascertaining these properties are as follows:

- A tablet should be mechanically strong and resistant to shock and fracture from handling, packaging and shipping procedures prior to use.

Tests: Crushing strength (hardness) and friability tests (Alderborn 2007, Rudnic, Schwartz 2006, Banker, Anderson 1986, British Pharmacopoeia 2009).

- Tablets must be uniform in weight and dose content. This is to ensure that the right amount of drug is taken with each tablet.

Tests: Weight variation and content uniformity tests (Alderborn 2007, Rudnic, Schwartz 2006, Banker, Anderson 1986, British Pharmacopoeia 2009).

- The drug should be released from the tablet when in contact with the gastrointestinal fluid, in a controlled and reproducible manner. The tablet serves as a vehicle for drug delivery and therefore it should be able to release the drug at its intended site of action. Failure of the tablet to release the drug at its intended location will render the drug useless.

Tests: Disintegration and dissolution tests (Alderborn 2007, Rudnic, Schwartz 2006, Banker, Anderson 1986, British Pharmacopoeia 2009).

- Tablets should be chemically, physically and microbiologically stable over the lifetime of the product. Any form of instability may render the drug ineffective or deleterious to the user.

Tests: Stability studies (Alderborn 2007, Rudnic, Schwartz 2006, Banker, Anderson 1986, British Pharmacopoeia 2009).

The above tests are discussed in detail in Chapter 6.

2.3 Tablet compression process

There are two types of tablet presses, i.e. the single punch and the rotary presses, as described in section 2.4. Both systems operate with an identical mechanism of tablet formation. Tablets are prepared by the compression of powder and/or granules (drug(s)/API(s) and excipient(s)) within a closed compartment (die cavity) by an upper and lower punch. This causes the particles to cohere into a porous, solid mass (tablet) of defined geometry (Alderborn 2007). The tablet compression process is a sequential process that can be divided into three steps, namely die filling, tablet formation and tablet ejection, as depicted in Figure 2.1.

2.3.1 Die filling

During this stage, the lower end of the die is closed by the lower punch. The upper end is open to allow powder or granules to flow into the die. The flow of powder or granules is usually accomplished by gravitational flow from a hopper, by means of the die table into the die (Alderborn 2007).

2.3.2 Tablet formation

This stage is characterised by the two punches coming into close proximity, and thus forcing the powder or granules into a compact tablet/disc. The upper punch descends and enters the die, while the lower punch may be stationary or moving towards the upper punch, depending on the type of tablet press used. This is followed by the decompression phase during which the upper punch reverts to its original position (Alderborn 2007).

2.3.3 Tablet ejection

This is the final stage of tablet formation and is characterised by the removal of the tablet from the die. The lower punch rises until its tip reaches the top of the die that allows the tablet to be pushed away (Alderborn 2007).

2.4 Tablet presses

As mentioned, the two types of tablet presses are the single punch and rotary presses. The basic unit of both presses is called a station, consisting of a die and an upper and lower pair of punches. They both operate on the same mechanism. A particulate solid is compressed within the die by a collective pressing action of the two punches. The die and the punches hence determine the shape (i.e. round, spherical, oval, square, triangular, rectangular) and diameter ($\frac{3}{16}$, $\frac{7}{32}$, $\frac{1}{4}$, $\frac{9}{32}$, $\frac{5}{16}$, $\frac{11}{32}$, $\frac{7}{16}$, $\frac{1}{2}$, $\frac{9}{16}$, $\frac{5}{8}$, $\frac{11}{16}$, $\frac{3}{4}$ in) of the tablet. The tablet weight is determined by the volume of the die cavity (Rudnic, Schwartz 2006). In addition to the above two press systems, in research and project development environments, hydraulic presses are used to determine the tableting properties of powders, in order to predict upscaling possibilities and for mass tablet manufacturing (Alderborn 2007, Rudnic, Schwartz 2006).

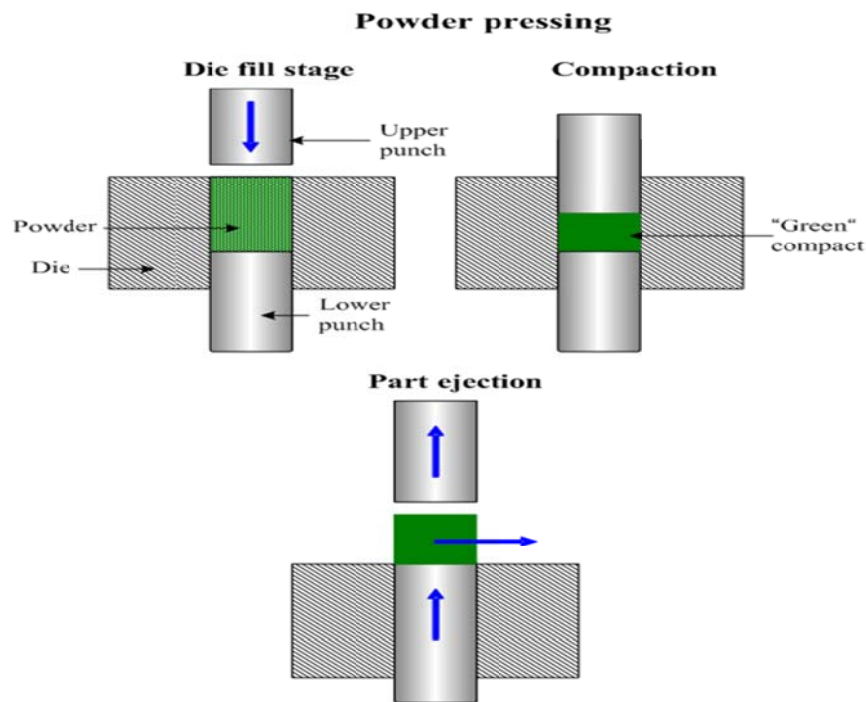


Figure 2.1: Diagrammatic representation of the three tablet compression stages (Mechanical Engineering: Online Guide 2010)

2.4.1 Single punch tablet press

The single punch tablet press is the simplest tablet press available. It consists of a single die and a pair of punches. During the compression process, the lower punch remains at a predetermined position and also controls the amount of powder that flows into the die. Pressure is applied by the upper punch as it descends towards the lower punch. It is incapable of producing a multitude of tablets, as is needed for commercial purposes, but is it mainly used during the early stages of tablet formulation development and in small scale production, such as for clinical trials (Alderborn 2007).

2.4.2 Rotary tablet press

The rotary press is a complex system that is very suitable for large scale, industrial use. It has multiple dies and sets of punches that revolve continuously during operation, as illustrated in Figure 2.2 (Alderborn 2007). The amount of dies and sets

of punches may vary from three, in a small rotary press, to sixty or more in large presses (Alderborn 2007).

The rotary press is also referred to as a multistation press and was specifically designed to increase tablet output. Large rotary presses can produce over 10 000 tablets per minute. In contrast to the single punch press, all of the punches (lower and upper) are in motion during the compression process. The primary use of this press is for up-scaling during the final stages of the product formulation process (Alderborn 2007).

2.5 Tablet manufacturing methods

There are three basic methods of tablet manufacturing, namely direct compression, wet granulation and dry granulation. The steps employed in these three methods are summarised in Table 2.1. Their differences lie in the processing or pre-compaction operations, hence prior to tablet compression. These operations include particle size reduction, powder mixing, particle size enlargement and powder drying. Particle size enlargement operations are generally referred to as granulation, but preferably and where possible, direct compression should be implemented, as it is less time and energy consuming (Alderborn 2007).

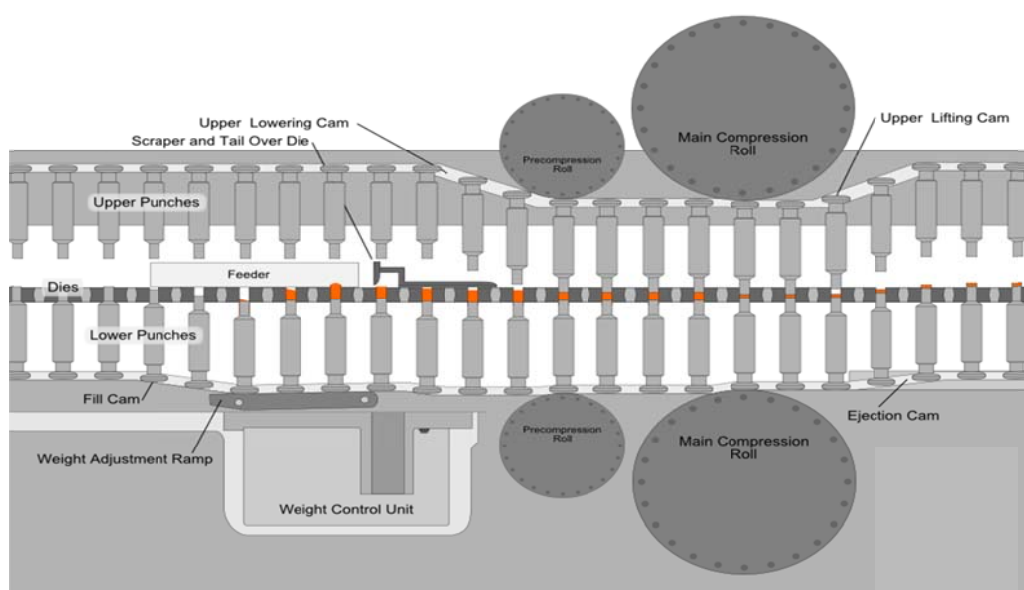


Figure 2.2: Punch tracks of a rotary tablet press, depicting the multiple sets of punches and dies (Wikimedia commons 2008).

Table 2.1: Steps involved in the different methods of tablet manufacturing (Bandelin 1989)

Wet granulation	Dry granulation	Direct compression
Milling of drugs and excipients.	Milling of drugs and excipients.	Milling of drugs and excipients.
Mixing of milled powders.	Mixing of milled powders.	Mixing of all excipients.
Preparation of granulation fluid and mixing with powder mixture to form wet mass.	Compression into slugs.	Tablet compression.
Coarse screening of the wet mass.	Screening of slugs.	
Drying of moist granules.	Mixing with lubricants and disintegrating agents.	
Screening dry granules with lubricants and disintegrating agents.	Tablet compression.	
Tablet compression.		

2.5.1 Direct compression

Direct compression is defined as a manufacturing process during which the powder blend of the active ingredient(s) and suitable excipient(s) are directly compressed into tablets, without prior modification by granulation methods. Direct compression is ideally used for fairly soluble drugs that are processed from coarse particles and small quantities of strong, potent drugs that may be mixed with relatively coarse excipient particles. A powder considered for direct compression should exhibit good flowability, compactability, friction and adhesion properties. This is often not the case and additives, capable of imparting the characteristics required for compression and flow, have to be added (Alderborn 2007, Rudnic, Schwartz 2006).

2.5.1.1 Advantages of direct compression

The advantages of direct compression include that it is simple, efficient and very cost effective, since it requires only two manufacturing steps, namely powder blending

and compression. Additionally, it requires the use of less machinery/equipment and manpower during the formulation process. As this method does not incorporate heat and moisture, product stability may be improved. The drug dissolution rate of a tablet, manufactured by direct compression, may also be faster, due to quick tablet disintegration into its primary drug particles (Alderborn 2007, Rudnic, Schwartz 2006).

2.5.1.2 *Disadvantages of direct compression*

Many drugs are commonly micronised to aid their rates of dissolution and bioavailability (Shangraw 1989). This often negatively impacts on the basic requirement for direct compression, namely the flow of the powder drug. Often compressibility problems are experienced with the active ingredient and segregation problems with the blend, making the method technically demanding. The direct compression method is further associated with dust, hence posing a health risk to the people working in operation and a risk to the cleanliness of the plant (Alderborn 2007).

2.5.2 Granulation

Granulation is a particle size enlargement process, which combines the discrete particles of powder into larger agglomerates, called granules. Granulation is mainly performed to produce suitable feed material for further pharmaceutical processing. The objective of granulation is to improve powder flow and handling, to decrease dustiness, and to prevent segregation of the constituents of the product. Granulation is classified into two types, i.e. wet and dry granulation (Alderborn 2007).

2.5.2.1 *Wet granulation*

Wet granulation is the most widely used granulation method in the pharmaceutical industry. The steps associated with wet granulation are summarised in Table 2.1. The primary steps involve dry mixing of the powder constituents and wetting of the powder blend (usually containing the active ingredient(s), binder and filler) with a granulating fluid. In the traditional wet granulation method, the resultant wet mass is

forced through a sieve to produce wet granules, which are then dried (Alderborn 2007). The dry granules are passed through a smaller sieve, resulting in small granules ready for compression with the extragranular excipients, usually a disintegrant and a lubricant (Bandelin 1989).

The granulation fluid (solvent) must be non-toxic and preferably volatile to reduce the drying period through evaporation. It may be used in its pure form or as a solution of the binder to allow uniform distribution of the binder. Although water is the most preferred granulation fluid, due to its biological and chemical compatibility with many pharmaceutical materials, it is not always ideal to use, as it may cause hydrolysis of susceptible ingredients. Where water is unsuitable, organic solvents, such as ethanol and isopropanol, are used as granulating fluids. The wet granulation method can lead to the extended exposure of the drug to moisture and heat, due to the incorporation of the granulation fluid and a long drying period, which may negatively affect drug stability (Bandelin 1989).

2.5.2.2 *Dry granulation*

The application of dry granulation is often superseded by wet granulation. However, the method is employed where wet granulation is unsuitable, due to the inherent properties of the powder material. Wet granulation methods are, for example, unsuitable for thermolabile and moisture sensitive materials (Peck, Soh et al. 2008). During dry granulation, the powder blend is processed into granules, without the addition of a granulation fluid, in which case drying is hence eliminated. Methods of dry granulation include slugging and roller compaction. In slugging, the powder blend is compressed into large tablets, called slugs (Peck, Soh et al. 2008). These slugs are then milled into granules and sieved to obtain powder feed of a desired size distribution. In roller compaction, the powder blend is passed through two counter-rotating rolls to produce a sheet of solid mass. This solid mass is then milled into granules of desired size distribution and then finally compressed into tablets, together with other excipients (Peck, Soh et al. 2008).

2.5.2.3 *Advantages of granulation*

Granulation allows for the rectification of the flaws of the direct compression method and offers advantages that circumvent the disadvantages of the direct compression method. Advantages of granulation include the following:

- Improved powder flow and less segregation.
- Improved compressibility and compactability.
- Less weight and drug content variations.
- Increased hydrophilicity of surfaces (Augsburger, Vuppala 2005).
- Less dust reduces the health risk to operational workers, whilst a cleaner plant poses a lower risk to cross contamination (Alderborn 2007).

2.5.2.4 *Disadvantages of granulation methods*

Although granulation is implemented to counteract the problems associated with direct compression, it is not without flaws. Its disadvantages are usually technical in nature and are as follows:

- It is a complex method (associated with multiple steps), making validation and control difficult.
- It is not ideal for moisture (exception to dry granulation) and heat sensitive drugs.
- It is not cost effective and requires large manufacturing spaces and supplementary equipment.
- It is time consuming and technically demanding.
- Granulation is associated with loss of material during various stages of processing (Augsburger, Vuppala 2005).

2.6 Tablet components

The key component of a tablet is its active pharmaceutical ingredient (API). The API determines the purpose for which the tablet is formulated. Tablets, as previously stated, consist of an API(s) and excipients. Excipients facilitate tablet formulation and other related stages of tablet production, up to the point of drug release from the tablet after oral administration. Excipients therefore determine how a tablet would

achieve its intended purpose. Excipients are categorised according to their intended main functions and may affect the properties of a powder or the tablet, or in the events that their functions overlap, excipients are described as multifunctional (Alderborn 2007).

2.6.1 Excipient properties

Excipients should possess certain properties for it to be considered pharmaceutically acceptable. These properties are the following:

- It must be chemically and biologically inert (non-reactive).
- It must be non-hygroscopic.
- It must possess good biopharmaceutical properties (e.g. it should be water soluble).
- It must possess good mechanical properties (.g. compactability or compressibility).
- It must have a pleasant taste and acceptable colour.
- It must be compatible with the active ingredient and other excipients (Banker, Anderson 1986; Alderborn 2007).

There is no excipient currently available that possesses all of these properties. In fact, only few possess more than one of these properties, which explains the dominance of certain excipients in practice (Banker, Anderson 1986).

2.6.2 Types of excipients

2.6.2.1 Filler (*diluent*)

A filler or diluent is an excipient that is used for the purpose of increasing the bulk volume/weight of the tablet to a size, suitable for compression and handling. It has a limited influence on the formulation process. Fillers are also used in the production of placebos that are mainly used for research purposes and in many contraceptive packages. Common fillers include cellulose, glucose, lactose, mannitol and sucrose (Alderborn 2007, Banker, Anderson 1986).

2.6.2.2 *Binder*

One of the desirable properties of granules and tablets is mechanical strength. The attainment of the required mechanical strength can be ensured by the addition of a binder. Binders can be added as a dry component (i.e. a dry binder) or in solution (i.e. a solution binder). Common solution binders include cellulose derivatives, e.g. hydroxypropyl methylcellulose, polyvinylpyrrolidone, starch and gelatin. Commonly used dry binders include microcrystalline cellulose and cross linked polyvinylpyrrolidone (Alderborn 2007, Banker, Anderson 1986).

2.6.2.3 *Disintegrant*

A disintegrant is a substance that facilitates the breakup of a tablet into small fragments, and subsequently into its primary particles, when in contact with a liquid (Banker, Anderson 1986). After deaggregation into the primary particles, the drug is in solution in the gastrointestinal fluid and ready for systemic absorption. The disintegration process of a tablet is depicted in Figure 2.3. During formulation, a disintegrant can be added prior to (intragranulation) or after (extragranulation) granulation. The common trend involves the addition of a disintegrant both as an intragranulation and an extragranulation portion (50/50) (Conway 2008). Common disintegrants being used include cellulose, cross linked polyvinylpyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose and starch (Alderborn 2007, Banker, Anderson 1986).

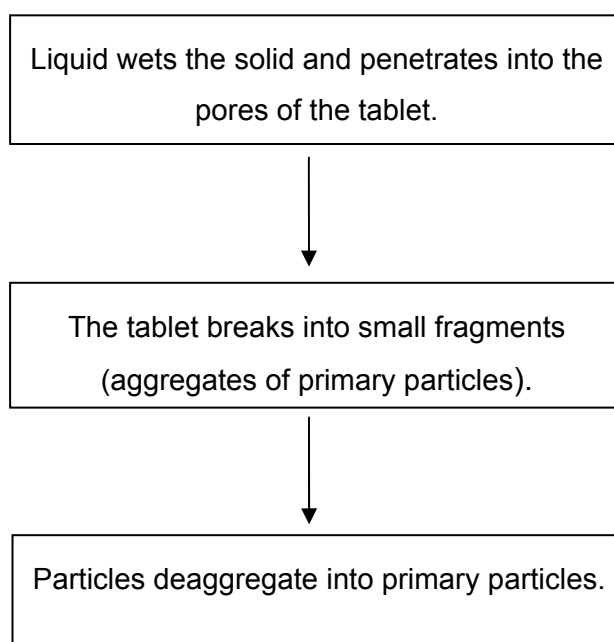


Figure 2.3: The basic steps in the disintegration of a tablet into its primary particles, ready for systemic absorption.

2.6.2.4 *Lubricant*

A lubricant is added to almost all tablet formulations to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. The concentration of lubricant in a tablet formulation is often limited to 1%, due to its adverse effects, such as the retardation of the disintegration and dissolution of tablets. The most commonly used lubricant is magnesium stearate (Alderborn 2007, Banker, Anderson 1986).

2.6.2.5 *Glidant*

Glidants are used to improve the flowability of the powder. This is of particular importance during tablet production at a high speed and during direct compression. They may also be added to a formulation for granulation, before tableting. Common glidants include talc and colloidal silica (Alderborn 2007).

2.7 Technical tablet defects

Tablets are manufactured with the ultimate objective of producing a pharmaceutical product that is free from both functional and visual defects. In practice, this is not always achieved, since various problems may occur (Banker, Anderson 1986). Problems being encountered during tablet manufacturing have increased, due to the growing complexity of the manufacturing processes and because of a higher demand for quality by pharmaceutical authorities. The detection of any occurring problems during production is also difficult and may be subjected to try and error processes. Primarily, the source of a problem can arise in the formulation stage, or in the compression stage, or in both stages. The most important technical defects that are encountered during the tableting procedure include capping and lamination, sticking or adhesion, mottling and weight variation (Banker, Anderson 1986).

2.7.1 Capping and lamination

Capping is the partial or complete separation of the upper or lower segments of a tablet from the main body. Lamination is the separation of a tablet into two or more distinct layers within the tablet structure. Lamination is a precursor to capping, since it involves the occurrence of layers in a compact, parallel to the punch face (Santos, Sousa 2008). Capping and/or lamination may happen during tablet ejection from the tablet press, or during tablet handling and can be detected through friability tests. Capping and lamination may occur due to the following factors:

- **Air entrapment:** Entrapped air among the particles or granules in a tablet has been associated with capping and lamination (Santos, Sousa 2008).
- **Excessive die wall pressure:** During compression/compaction, die wall pressure is produced and may exceed that which can be relieved by elastic recovery. Excess die wall pressure can cause a crack that propagates and initiates the fracture of the compacted powder, thus presenting itself in the form of tablet capping and/or lamination upon ejection from the die. Tablet capping and lamination can be eliminated by pre-compression, slowing the tableting rate, and by reducing the final compression pressure (Banker, Anderson 1986).
- **Concave punches:** Curved punches may produce tablets that cap. This can be eliminated by the use of flat punches (Banker, Anderson 1986).
- **Other sources:** Moisture content of the feed, old and poorly finished dies and the incorrect setup of the tablet press (Alderborn 2007, Banker, Anderson 1986, Santos, Sousa 2008).

2.7.2 Picking and sticking

Picking is when the surface material from a tablet is sticking to and being removed from the tablet's surface by a punch. Picking can cause serious problems with engraved or embossed punches, by diminishing the design. Sticking is when tablet material adheres to the die wall, which may render the tablet too difficult to eject from the press. Additional force is then required to remove the tablet, which can cause chipping of the tablet's edges. Formulation adjustments are necessary to eliminate

these problems, such as the addition or increase of an anti-adherent(s) to the powder formulation. Non-formulation adjustment may include the use of punches with tips plated with chrome that gives a smooth and non-adherent surface (Santos, Sousa 2008).

2.7.3 Mottling

Mottling is defined as the uneven colouration of tablets, or the non-uniformity of colour over the tablet surface (Alderborn 2007). This problem is uncommon for tablets that are produced from uniformly coloured excipients, or where no colorant is used. Mottling may be caused by a difference in colour between the active ingredient and the excipients, or rarely due to the degradation of one of the ingredients, in which case spot zones appear across the surface of the tablets. Another cause may be the poor distribution of the colorant, especially during direct compression (Banker, Anderson 1986).

2.7.4 Weight variation

Weight variation analysis is a compulsory requirement, with specific recommendations, as indicated in Table 2.2. Tablet weight is predominantly affected by powder related factors, such as particle size variation, powder flow and particle segregation. Non-powder related factors are tablet press conditions, tableting rate and die filling processes. The weight of the compressed tablet is determined by the amount of feed into the die prior to compression, and therefore the die filling process has a direct influence on the tablet weight and possible weight variation (Banker, Anderson 1986). Tablet weight may change during production, due to changes in the feed pressure. The best way to overcome this unpredictable change is by including tablet weight variation tests as part of the in-process, quality control procedures (Santos, Sousa 2008).

Table 2.2: Average tablet mass and corresponding percentage deviation allowed
(British Pharmacopoeia 2009)

Tablet formulation	
Average mass	Percentage deviation allowed
≤ 80 mg	$\pm 10\%$
> 80 mg and < 250 mg	$\pm 7.5\%$
≥ 250 mg	$\pm 5\%$

2.8 Conclusion

It is well known that tablets are one of the most important pharmaceutical dosage forms available. This is due to the advantages they offer when compared with other dosage forms. Tableting does not simply involve the compression of the active ingredient. The production of tablets is an engineered process, involving the selection of the right amounts of ingredients and suitable excipients and of a method of production suited to the active ingredient and its intended use.

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CHAPTER 3

Nevirapine: An Overview

3.1 Introduction

The human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS). It remains a serious concern in both research circles and in social life. Statistics in 2004 (Greene, 2004) showed that every six seconds, a next person was being infected with this pathogenic, human retrovirus, whereas another person died as a result of AIDS or associated opportunistic infections every ten seconds (Greene, 2004). Nevertheless, the current therapeutic interventions of combination therapies (highly active antiretroviral therapy (HAART)) seize hope in the treatment of HIV-1 (Neofytos & Squires, 2008). HAART consists of nucleoside, reverse transcriptase inhibitors (NRTIs), non-nucleoside, reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). NRTIs and NNRTIs both inhibit the viral reverse transcriptase, whilst PIs inhibit protease, an HIV enzyme essential for the production of mature, progeny virions. Currently FDA approved HIV drugs are listed in Table 3.1.

This study was conducted on nevirapine. Nevirapine is a potent, non-nucleoside, reverse transcriptase inhibitor, used in combination therapies for the treatment of HIV infection and AIDS. Nevirapine was in 1996 the first FDA approved, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Medicinal products containing nevirapine are available as an oral therapy (tablet and suspension) for the treatment of HIV-1 infection.

3.2 Physico-chemical properties of nevirapine

Chemically, nevirapine falls in the dipyridodiazepones class of compounds. Its chemical name is 11-cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2',3'*e*][1,4]diazepin-6-one. The chemical structure of nevirapine is illustrated in Figure 3.1. Nevirapine is a white, or almost white, crystalline powder. Nevirapine has a molecular formula, C₁₅H₁₄N₄O, with a molecular weight of 266.30. Nevirapine is a weak base with a pK_a value of 2.8. Nevirapine is a hydrophobic unit and is

practically insoluble in water. It is sparingly soluble, or slightly soluble in methylene chloride and slightly soluble in lower alcohols. It is, however, highly soluble at a pH <3. Its aqueous solubility decreases with an increase in pH to approximately 0.1 mg/ml at neutral pH (Merck Index, 2001).

Nevirapine does not exhibit isomerism, but it exhibits polymorphism and is known to exist in the hemihydrate and anhydrous forms (European Medicine Agency, 2004). Several nevirapine crystalline forms have recently been discovered and others have been patented (Reguri & Chakka, 2006; Caira *et al.*, 2007; Stieger *et al.*, 2009).

Table 3.1: Currently FDA approved HIV chemotherapeutic agents (Neofytos & Squires, 2008)

Class	Generic name
Nucleoside reverse transcriptase inhibitor (NRTI)	Zidovudine Lamivudine Didanosine Zalcitabine Stavudine Abacavir Emtricitabine
Nucleotide reverse transcriptase inhibitor (NtRTI)	Tenofovir disoproxil
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Nevirapine Efavirenz ??Delavirdine
Protease inhibitor (PI)	Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Lopinavir Atazanavir
Viral entry inhibitors	Enfuvirtide

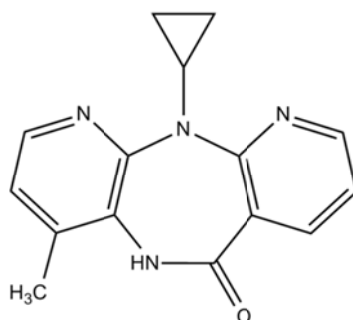


Figure 3.1: Chemical structure of nevirapine (Harms, 2007).

3.3 Synthesis of nevirapine

Nevirapine was discovered by scientists at Boehringer Ingelheim Pharmaceuticals, Inc. (Harms, 2007). Nevirapine is synthesised, as illustrated in Figure 3.2. Synthesis of nevirapine commences with the acylation **(1)** of 3-amino-2-chloro-4-methylpyridine with 2-chloronicotinoyl chloride to form 2,2'-dichloro amide. Then 2'-chlorine is displaced **(2)** by cyclopropylamine. To complete the nevirapine synthesis, ring closure/cyclisation **(3)** is affected through heating under reflux (Harms, 2007).

3.4 Pharmacological properties

3.4.1 Mechanism of action

Nevirapine is the prototypic member of the NNRTI class of antiretroviral compounds. Nevirapine is a potent and selective, non-competitive inhibitor of the reverse transcriptase (RT) enzyme, a crucial step (Figure 3.3, step 4) in the life cycle of HIV. It binds to the HIV, RT enzyme, blocking the ribonucleic acid (RNA) dependent and deoxyribonucleic (DNA) dependent DNA polymerase activities, by causing a disruption of the enzyme catalytic site. It does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase (Witvrouw *et al.*, 2004).

3.4.2 Indication

Nevirapine is indicated for use in combination with other antiretroviral agents for the ongoing treatment of HIV-1 infection in young and adult patients. Nevirapine is also

used in mother to child transmission (MTCT) of HIV prevention programmes (Harms, 2007).

3.4.3 Dosage and administration

The recommended dose of nevirapine is 200 mg daily for the first fourteen days, followed by one 200 mg tablet twice daily. The total daily dose should not exceed 400 mg at any time (Klein & Strubel, 2009).

3.4.4 Side effects and toxicity

Nevirapine appears to be well tolerated. Nevirapine is nevertheless associated with several adverse effects. Skin reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome, characterised by rash, constitutional findings and visceral involvement, are commonly associated with nevirapine treatment. Nevirapine is also associated with severe, or life threatening hepatotoxicity, and characterised by elevated serum gamma-glutamyl transferase. In some cases, fetal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure have been reported (Srivastava *et al.*, 2010). Some other, non life threatening adverse reactions include gastrointestinal disturbances, characterised by diarrhoea and nausea, fever and headaches (European Medicine Agency, 2004).

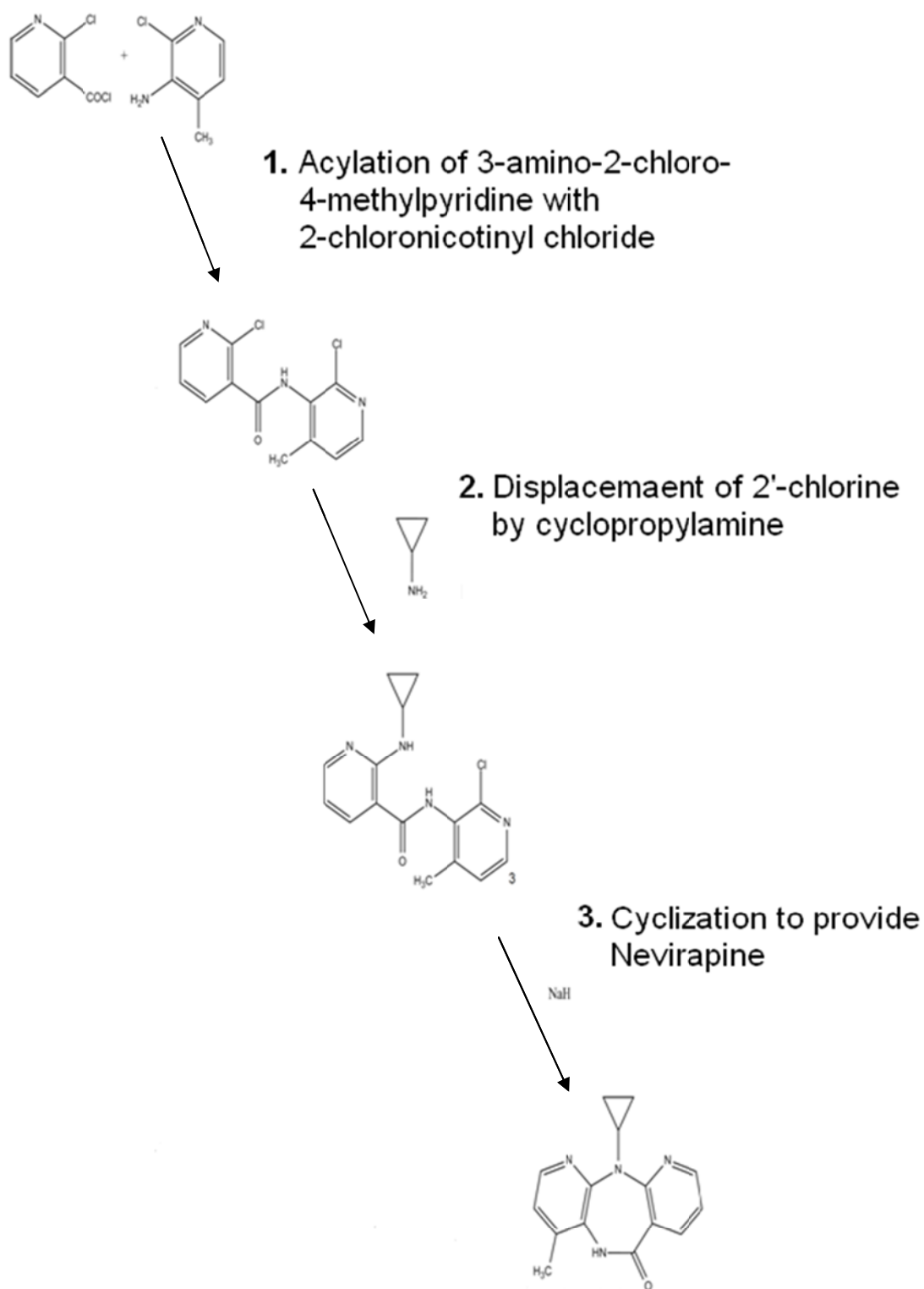


Figure 3.2: Schematic representation of nevirapine synthesis (Harms, 2007).

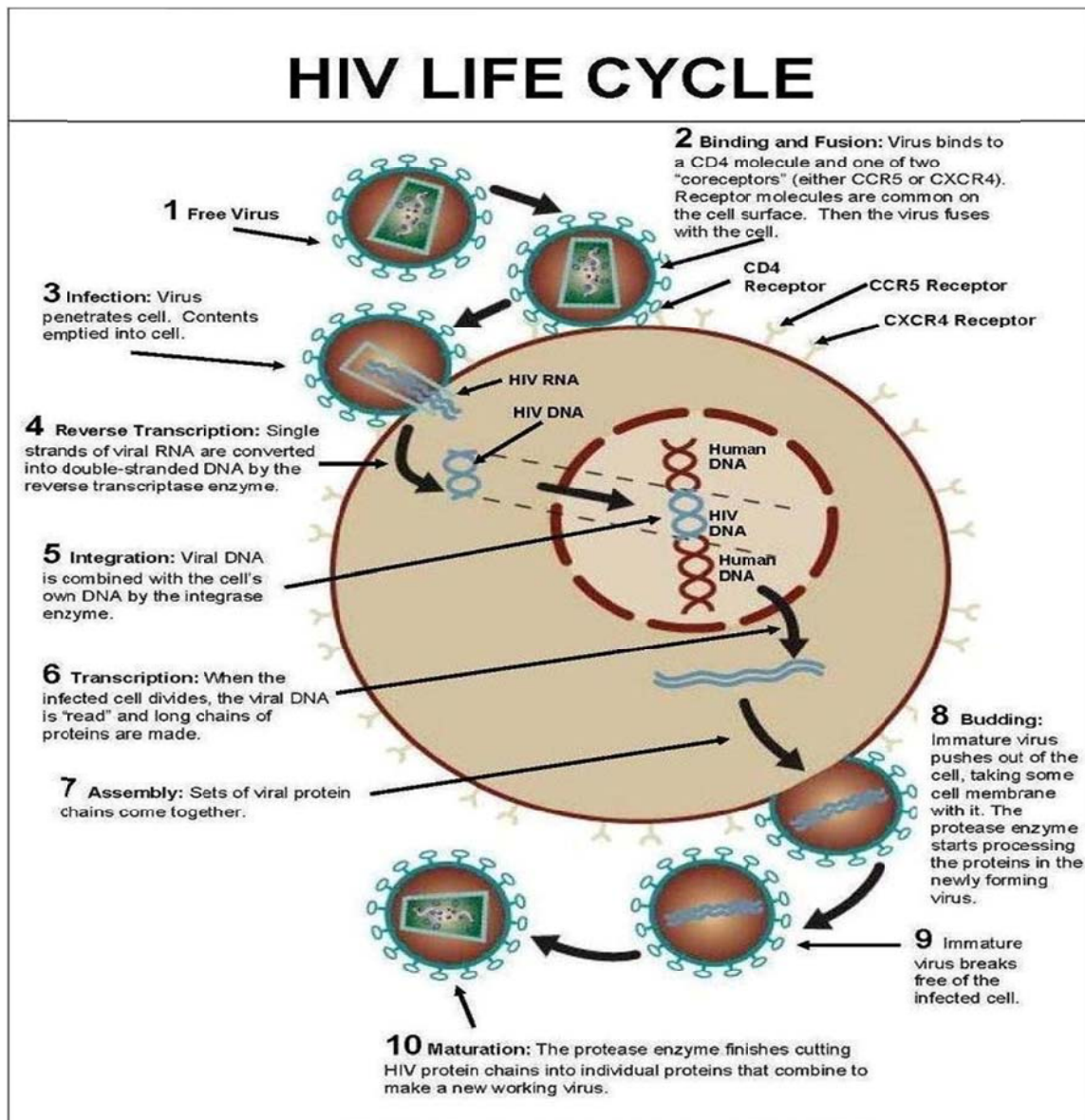


Figure 3.3: Diagrammatic representation of the inhibition of step 4 in the HIV life cycle by NNRTI (Wai, 2009).

3.5 Pharmaceutical aspects

- **Stability:** Nevirapine has proven highly stable, even under stressed conditions, over a period of two years, without showing any signs of degradation (European Medicine Agency, 2004).
- **Solubility and bioavailability:** Nevirapine is insoluble in pure water, but is readily absorbed orally. However, high doses (>50 mg) of nevirapine exhibit characteristics of solubility rate limited absorption, with a resultant decrease in bioavailability (Lamson *et al.*, 1999).

- **Dissolution:** Paradoxically, previous studies on nevirapine had shown that the particle size of nevirapine did not significantly influence drug dissolution (Sarkar *et al.*, 2008). However, the nevirapine tablet dissolution was found to be well correlated with the particle size of the active substance (European Medicine Agency, 2004).
- **Dosage form:** Nevirapine is available in tablet and suspension forms. Nevirapine is also used in fixed dose combinations, along with other antiretroviral drugs (e.g. lamivudine, zidovudine, stavudine). The manufacture of fixed dose combinations poses serious problems, such as dosing regimen challenges, incompatibility, insolubility and instability. Moreover, nevirapine is a poorly soluble, hydrophobic drug that posing even more problems during the manufacture of fixed dose combinations (Sarkar *et al.*, 2008).
- **Tablet manufacturing:** Nevirapine tablets are currently manufactured through wet granulation only, in order to facilitate its dissolution rate (European Medicine Agency, 2004).

3.6 Conclusion

Active pharmaceutical ingredients (APIs), including nevirapine, generally pass through the crystallisation process, before being processed into the desired dosage form, in order to obtain the physically modified form that would give good formulation and drug product performance. API modifications of pharmaceutical concern upon crystallisation include polymorphic form, drug stability, dissolution rate, crystal/particle size, morphology, surface properties, bulk density, and flowability, among others.

This study stemmed from the newly discovered, nevirapine form IV, by Stieger *et al.* (2009). According to this study, nevirapine form IV was highly unstable at room temperature and transformed into form I with ease. What was interesting upon such transformation was that, instead of forming usual agglomerates of raw material, it disintegrated into a finely powdered material.

The focus of this study was on the powder and tableting properties of the resultant, finely powdered material, in comparison with commercially available, anhydrous nevirapine raw material. In this study, the fine nevirapine powder was referred to as the novel nevirapine powder.

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CHAPTER 4

Powder Characterisation Methods and Materials

4.1 Material

The reference material being used in this study was the commercially available, anhydrous nevirapine raw material, manufactured by Anhui Biochem United Pharmaceuticals, China. A fine, anhydrous nevirapine powder was prepared during this study, according to a novel method of preparation by Stieger *et al.*, (2009a), as described next in section 4.2. All reagents used were of analytical grade.

4.2 Preparation of fine, anhydrous nevirapine powder

The novel nevirapine powder was prepared as follows, as described by Stieger *et al.* (2009a). Commercially available, anhydrous nevirapine raw material was dissolved in methanol through heating (at about 100°C), based on the following reference formula:

<u>Ingredient</u>	<u>Quantity</u>
Anhydrous nevirapine	1 g
Methanol	50 mL

The clear solution being prepared was immediately refrigerated (2 -8°C) to produce nevirapine form IV. The nevirapine form IV crystals were removed from the mother liquid and then dried in an oven at an average temperature of 30°C to create novel nevirapine powder. Although the novel nevirapine powder could also have been obtained at ambient conditions, the oven was used to facilitate consistency, since under high humidity conditions, agglomerates may have formed, instead of the fine powder.

Each prepared batch was randomly placed in a half open container and left over night at room conditions, prior to use.

4.3 Authentication of the polymorphic form

Before tests were performed, measures were taken to ensure that the novel, fine nevirapine powder was similar to nevirapine raw material in terms of polymorphic form. This procedure was essential in ruling out any unwanted influences during this study, due to differences in polymorphism. Polymorph similarity was confirmed, using differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRPD). In this study, a DSC-60 Shimadzu instrument (Shimadzu, Kyoto, Japan) was used to determine the melting points and phase transitions at a heating rate of 10°C/min. A PANalytical Empyrean diffractometer (PANalytical, Almelo, Netherlands) was used to generate the X-ray diffractograms. Measurement conditions of target, Cu; voltage, 40 kV; current, 30 mA; divergence slit, 2 mm; antiscatter slit, 0.6 mm; detector slit, 0.2 mm and monochromator scanning speed, 2°/min (step size, 0.025°; step time, 1.0 sec) were used.

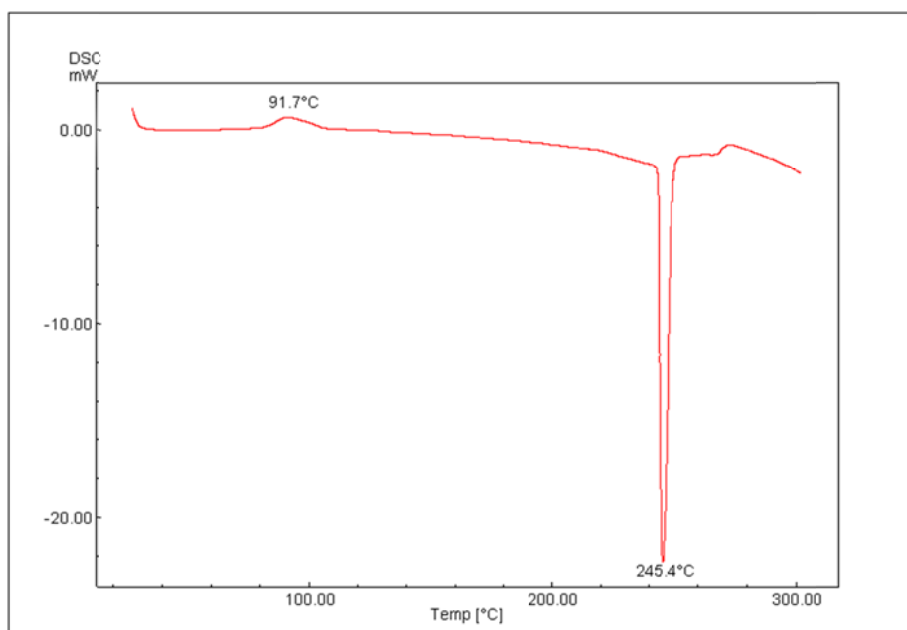


Figure 4.1: DSC thermogram of metastable form IV showing a phase transformation at 91°C (Stieger *et al*, 2009a).

Both the DSC trace (Figure 4.1) and the XRPD diffractogram (Figure 4.2) confirmed the transformation of nevirapine form IV into form I (anhydrous nevirapine). The transformation into the stable form I was also reported to have occurred at ambient

temperature, or when placed in an oven to reduce the transformation time (Stieger *et al.*, 2009a).

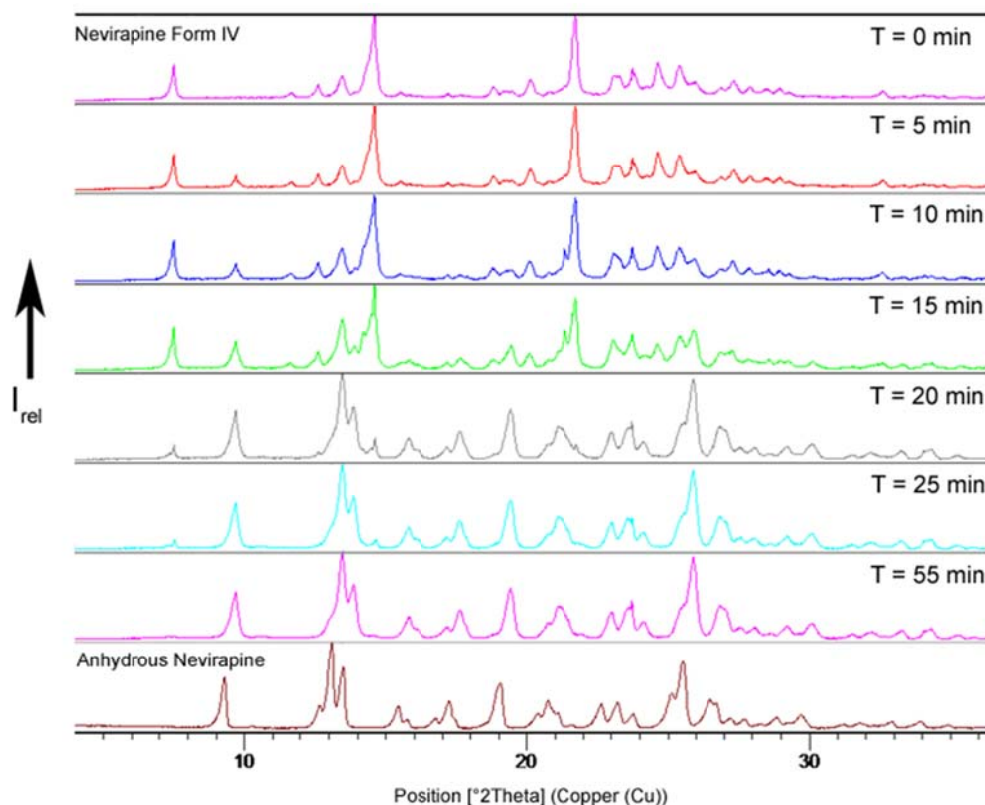


Figure 4.2: XRPD diffractograms of form IV (top) and its transformation into the anhydrous form over time at ambient temperature (Stieger *et al.*, 2009a).

4.4 Powder characterisation

4.4.1 Particle shape and surface characterisation

Particle shape and surface characteristics are inherent properties of powders. They are the determining factors of the properties being displayed by a powder, such as flowability, compaction behaviour and bulk density. A description of the particle shape and surface characteristics conveys much information when associated with photomicrographs, as generated during this study (Chapter 5). The particle shapes and surface characteristics were studied, using an FEI Quanta 200 environmental scanning electron microscope (ESEM) (Philips, Eindhoven, The Netherlands),

operating under high vacuum conditions at 10 kV. The samples were mounted on double sided, conductive, carbon tabs to the ESEM stubs and dusted with an inert gas. The samples were subsequently sputter coated with 20 nm gold:palladium (60:40). An Eiko[®] ion coater (model IB-2, Eiko Engineering, Japan) was used in all coating procedures.

4.4.2 Particle size and particle size distribution

The mean particle size and size distribution were measured by laser diffraction, using the Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK), equipped with a Hydro 2000SM cassette. Distilled water, prepared by a Millipore[™] Milli-Q[®] Ultrapure Water Purification system (USA) was used to aid in the dispersion of all samples.

4.4.3 Bulk density and Tapped density

The difference between bulk and tapped densities of a powder indicates the extent of interparticle interactions and is often used as an index of the ability of the powder to flow. Bulk and tapped densities were determined by using the methods as outlined in the BP (British Pharmacopoeia, 2009). Each sample was passed through a number 18 sieve prior to the determination. Without compacting, approximately 100 g and 60 g of nevirapine raw material and the fine, novel powder, respectively, were introduced into separately pre-weighed, dry 250 mL graduated cylinders and the unsettled initial volumes were recorded. The bulk densities, in g/mL, were calculated according to the following equation:

$$\text{Bulk Density} = \frac{\text{Sample Weight (g)}}{\text{Initial Volume (mL)}} \quad \text{Equation 4.1}$$

For tap density determinations, the cylinders were then vibrated for 60 minutes on a Fritsch[®] Analysette (Type 03.502, Germany) at amplitude of 10 to obtain tapped volumes. The tap densities were calculated according to the following equation:

$$\text{Tap Density} = \frac{\text{Sample Weight (g)}}{\text{Tapped Volume (ml)}} \quad \text{Equation 4.2}$$

All densities were determined as the mean of three measurements.

4.4.4 Powder flow characterisation

Compressibility index, angle of repose, critical orifice diameter and flow rate were used to characterise powder flow. The composite index was computed for these techniques, as discussed below.

4.4.4.1 Compressibility index and Hausner ratio

The bulk and tapped densities were used to calculate Carr's compressibility index and the Hausner ratio in order to provide a measure of the flow properties of the nevirapine samples, using the following formulae.

$$\text{Compressibility index} = 100 \times \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right] \quad \text{Equation 4.3}$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{Equation 4.4}$$

Higher Carr compressibility index and Hausner ratio values represented higher interparticle interactions and hence poor flowability of the powders.

4.4.4.2 Angle of repose

Approximately 200 mL of powder was poured into a funnel that was held at a fixed height (15 cm) above a clean flat base (work bench surface). The funnel used was made of interchangeable brass discs (the same interchangeable brass discs used in

the critical orifice diameter apparatus shown in Figure 4.4) and the size of the orifice used was 8 mm. Pictures of the formed conical heaps were taken with a digital camera and reference lines were drawn on each picture, in order to measure its height and base, as shown in Figure 4.3. The angle of repose (α) was calculated with the following equation:

$$\tan(\alpha) = \frac{\text{height}}{0.5 \text{ base}} \quad \text{Equation 4.5}$$

Results were only considered valid when a symmetrical cone of powder was formed. This test was repeated three times for each powder sample. Lower angle of repose values represented better flow.



Figure 4.3: Powder conical heap with reference lines to enable measurement of its height and base for the angle of repose calculation.

4.4.4.3 *Critical orifice diameter*

Critical orifice diameter is the size of the smallest orifice through which a powder sample can discharge freely. The apparatus, developed by Buys (2006), was employed to determine the critical orifice diameter of the two samples (Figure 4.4). The device consisted of a funnel with a series of interchangeable brass discs of different diameter orifices and a stainless steel cylinder (sample holder). The diameter of the orifice of the largest disc was 32 mm and that of the smallest was 1.5 mm. The discs and the sample holder were separated by a mobile shutter. The critical orifice diameter of each sample was determined by placing 100 mL of the sample in the sample holder, with the shutter closed. The shutter was then gently opened. If all of the powder had passed through the orifice of a disc under the influence of gravity, the test was repeated using a disc of smaller diameter. The reduction in disk diameter was continued until no flow was observed. The diameter of the disc, above the one that disallowed any flow, was considered the critical orifice diameter of the sample. Powder flow through a smaller critical orifice diameter indicated better flow. The test was repeated three times for each sample.



Figure 4.4: The apparatus developed by Buys (2006) for use in the determination of the critical orifice diameter.

4.5 Solubility and dissolution rate studies

Since the particulate properties of powders can have a profound impact on the solubility and dissolution rate of a drug (which in turn are key determinants of bioavailability) (see discussion in Chapter 1), solubility and dissolution rate studies were also performed during this study.

4.5.1 Solubility studies

Solubility is simply the maximum amount of solute that can be dissolved in a given amount of solvent, at a specified temperature, to form a solution that is in chemical equilibrium. Drug solubility is an important feature of drugs, especially for drugs having a history of poor solubility, such as nevirapine. Nevirapine has poor aqueous solubility, with a reported water solubility of ~0.1 mg/ml at neutral pH. It is, however, highly soluble at pH values <3 (The Merck index, 2006).

Low soluble compounds sometimes are poorly wettable also, resulting in possible floating on the surface of the solvent. Due to the minimal surface contact, very slow dissolution rates are achieved (Avdeef, 2007), resulting in a possibly low bioavailability of the compound.

Simple alteration of the physical properties, such as changing the particle size of a drug compound, can influence its biopharmaceutical properties. "Particle size can affect the solubility of the compound itself since the free energy of the system increases with decreasing particle size" (Lee *et al.*, 2000). Therefore, the production of the fine nevirapine powder necessitated the determination of its solubility in comparison with the nevirapine raw material.

Solubility determination

The solubility of two samples each of the novel nevirapine powder and the raw material was determined by a UV spectrophotometric method, as developed by Stieger *et al.* (2009b). In this study, it was demonstrated that the spectrum of nevirapine that had dissolved in water, showed a peak of maximum absorbance at 283 nm and when dissolved in 0.1 N HCl, it showed a peak of maximum absorbance at 313 nm. These peaks were used to determine the solubility of the samples in the two solvents used. The water used was prepared with a Millipore™ MilliQ® Ultrapure Water Purification system (USA). Solubility was determined at $37 \pm 2^\circ\text{C}$. A Shimadzu UV-1800 (Shimadzu, Kyoto, Japan) UV spectrophotometer was used in the solubility studies.

Construction of a standard curve: Nine concentrations of each batch of nevirapine (6.0, 5.0, 4.0, 2.0, 1.0, 0.5, 0.25, 0.125 and 0.0625 mg/100 ml) were prepared in

each of the two solvents, in order to construct two standard curves. The standard curves were then used to convert the UV-absorbencies of the solubility samples to their corresponding concentration values in the two respective solvents.

Preparation of the solutions: Each batch of nevirapine was introduced into six 20 mL amber test tubes (in excess) and filled with the solvent. The test tubes were fixed to a rotating axis (54 rpm) and submerged in a warm water bath (at $37 \pm 2^\circ\text{C}$) for a period of 24 hours. After 24 hours, the solutions were filtered through hydrophilic PVDF 0.45 μm (Millipore Millex-HV) membranes to remove the residues. The filtrates were diluted for suitable determination with a UV spectrophotometer. Dilutions were prepared as follows:

- Dilution of nevirapine in water: 5 to 10 mL.
- Dilution of nevirapine in 0.1 N HCl: 1 to 100 mL.

After dilution, the concentrations of the filtrates were determined.

4.5.2 Powder dissolution studies

For poorly soluble drugs, dissolution is the most important step in the absorption process and knowledge of the dissolution rate of a drug substance is useful in formulation development (Tong, 2000). Dissolution of a drug substance is, among other factors or properties, controlled by the surface area and consequently by the particle size (Lee *et al.*, 2000). Because of the effect of particle size on the dissolution rate, particle size reduction prior to formulation is often employed, to improve the rate and extent of absorption of poorly, water soluble drugs.

Intrinsic dissolution and powder dissolution are dissolution methods that have been employed extensively for the characterisation of drug substances (Tong, 2000). Powder dissolution is useful in determining the effect of particle size on dissolution and is the preferred method for these studies. Intrinsic dissolution is independent of the particle size of the material.

Contrary to theory, previous studies on nevirapine had shown that the particle size of nevirapine did not significantly influence its dissolution (Sarkar *et al.*, 2008). However, “the nevirapine tablet dissolution was found to be correlated with the particle size of the active substance” (European Medicine Agency, 2004).

Powder dissolution determination

The powder dissolution of the two batches of nevirapine was determined, as described by Henwood *et al.* (2001). The dissolution conditions are shown in Table 4.1. The powder sample (100 mg) was rinsed from the glass weighing vessel into a 10 mL test tube with exactly 2 mL of the dissolution medium. Glass beads (50 mg), with a mean size of 0.1 mm, were added to the suspension and the mixture agitated for 60 seconds, using a vortex mixer. Glass beads were added to enhance wettability and to reduce floatation and aggregation problems, which may have ultimately affected the dissolution rates of the two batches. The contents of the test tubes were each transferred into the dissolution medium (900 mL), and the dissolution rate measured.

Dissolution was performed in a water medium at $37 \pm 0.5^\circ\text{C}$. Water was the first choice of medium, since nevirapine was known to dissolve easily in 0.1 N HCl. Previous studies in 0.1 N HCl as dissolution medium, did not show any difference in dissolution rate between nevirapine powders of varying particle size (Sarkar *et al.*, 2008). The water used was prepared with a MilliporeTM MilliQ[®] Ultrapure Water Purification system (USA). The apparatus used was USP type II apparatus set at 75 rpm. Samples were withdrawn at specific time intervals of 10, 20, 30, 45, 60, 90 and 120 minutes and filtered through hydrophilic PVDF 0.45 μm (Millipore Millex-HV) membranes to remove any residues, before being quantified by UV-spectrophotometry at 283 nm. With every withdrawal (7 mL), an equally corresponding volume of freshly prepared dissolution medium was added to keep the medium volume constant. The dissolution parameters are summarised in Table 4.1.

Table 4.1: Summary of the dissolution parameters used

Dissolution conditions	
Sample	Nevirapine raw material or nevirapine novelpowder (100 mg) and 50 mg of glass beads
Dissolution medium	Water (900 mL – final volume)
Temperature	$37 \pm 0.5^\circ\text{C}$
Apparatus	USP type II apparatus set at 75 rpm

Detection/quantification	UV spectrophotometry at 283 nm
Withdrawal intervals	10, 20, 30, 45, 60, 90 and 120 minutes
Withdrawal volume	7 mL per each interval
Dilution	5 to 25 mL with dissolution medium
Number of determinants	6 samples for each batch of nevirapine powder

4.6 Conclusion

The preparation of the nevirapine novel powder was performed as described by Stieger *et al* and authentication of the powder revealed polymorphic similarity between the nevirapine novel powder and nevirapine raw material. Investigations were undertaken to characterise the powder properties of the two samples and the results are presented in chapter 5.

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CHAPTER 5

Powder Characterisation Test Results and Discussion

5.1 Introduction

Powders were characterised with respect to their particle sizes, particle shapes and surface characteristics. The particle size, particle shape and surface properties of particles can significantly affect the flowability of the powder and its subsequent processing into dosage forms. In this chapter, the particle sizes and shapes, and surface characteristics of the two batches of nevirapine powders are discussed and related to the results obtained with regards to their powder flow characterisations.

5.2 Particle characterisation

The particle shapes and surface characteristics of the two batches of nevirapine powders were studied based on the SEM photomicrographs taken (Figures 5.1 and 5.2). These micrographs showed that the two batches of nevirapine powder each had distinct particle morphologies and sizes. Commercially available nevirapine raw material (Figure 5.1), which had been subjected to milling, consisted of large, equant, block shaped particles. The novel nevirapine powder consisted of relatively plate-like shaped particles, with irregular edges. Commercially available nevirapine raw material had smooth, compact, particle surfaces, whilst the novel nevirapine powder particles showed cracks on their surfaces. A highly magnified photomicrograph of novel nevirapine powder is presented in Figure 5.3, for the purpose of providing a clearer view of its particle surfaces. The cracks on the surfaces of the novel nevirapine powder are a distinct characteristic of unmilled particles. During milling, the cracks are taken as an advantage to achieve a reduced particle size with less energy consumption. Based on the SEM photomicrographs, it was evident that the particle sizes of the commercially available nevirapine raw material were larger than those of the novel powder. This was well supported by the results from the laser diffraction particle size analysis (Table 5.1).

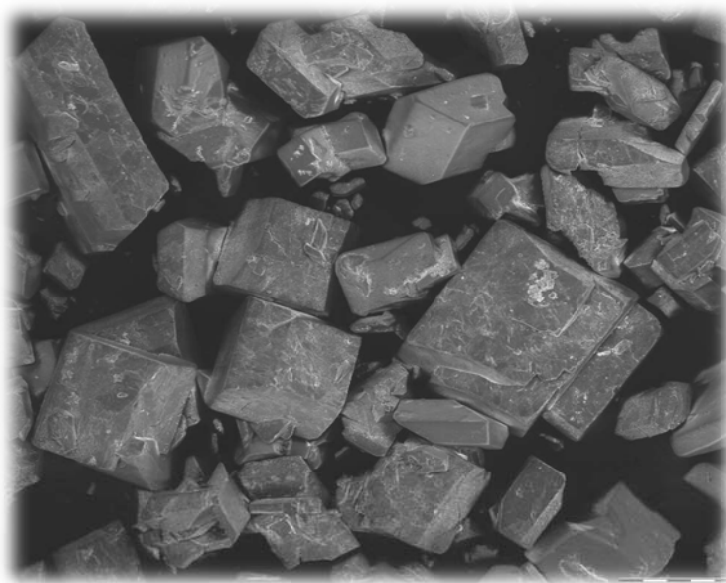


Figure 5.1: SEM photomicrograph of commercially available nevirapine raw material.



Figure 5.2: SEM photomicrograph of fine nevirapine powder (novel method of preparation).

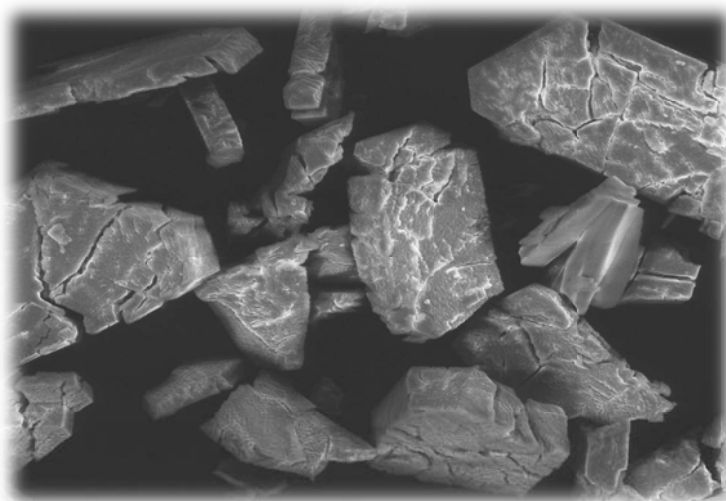


Figure 5.3: SEM photomicrograph of nevirapine powder (novel method of preparation) under high magnification.

The results of the particle sizes and particle size distributions tests are summarised in Table 5.1. It was evident from these results that the two nevirapine powders differed markedly. Novel nevirapine powder had a mean median particle size (D_{50}) of 45.52 μm , approximately one third of that of nevirapine raw material ($D_{50} = 129.04 \mu\text{m}$). Novel nevirapine powder also exhibited a narrow particle size distribution (Figure 5.4). According to the BP classification of powder by fineness (Table 5.2), nevirapine raw material was considered a fine powder, whilst novel nevirapine powder was considered a very fine powder.

Table 5.1: Particle size distributions of nevirapine raw material and of novel nevirapine powder

Material	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)
Nevirapine raw material	30.740167 ± 5.0303449	129.0352 ± 12.55036	286.5667 ± 16.59585
Novel nevirapine powder	19.347667 ± 2.1881401	45.5155 ± 3.266414	93.97783 ± 4.709396

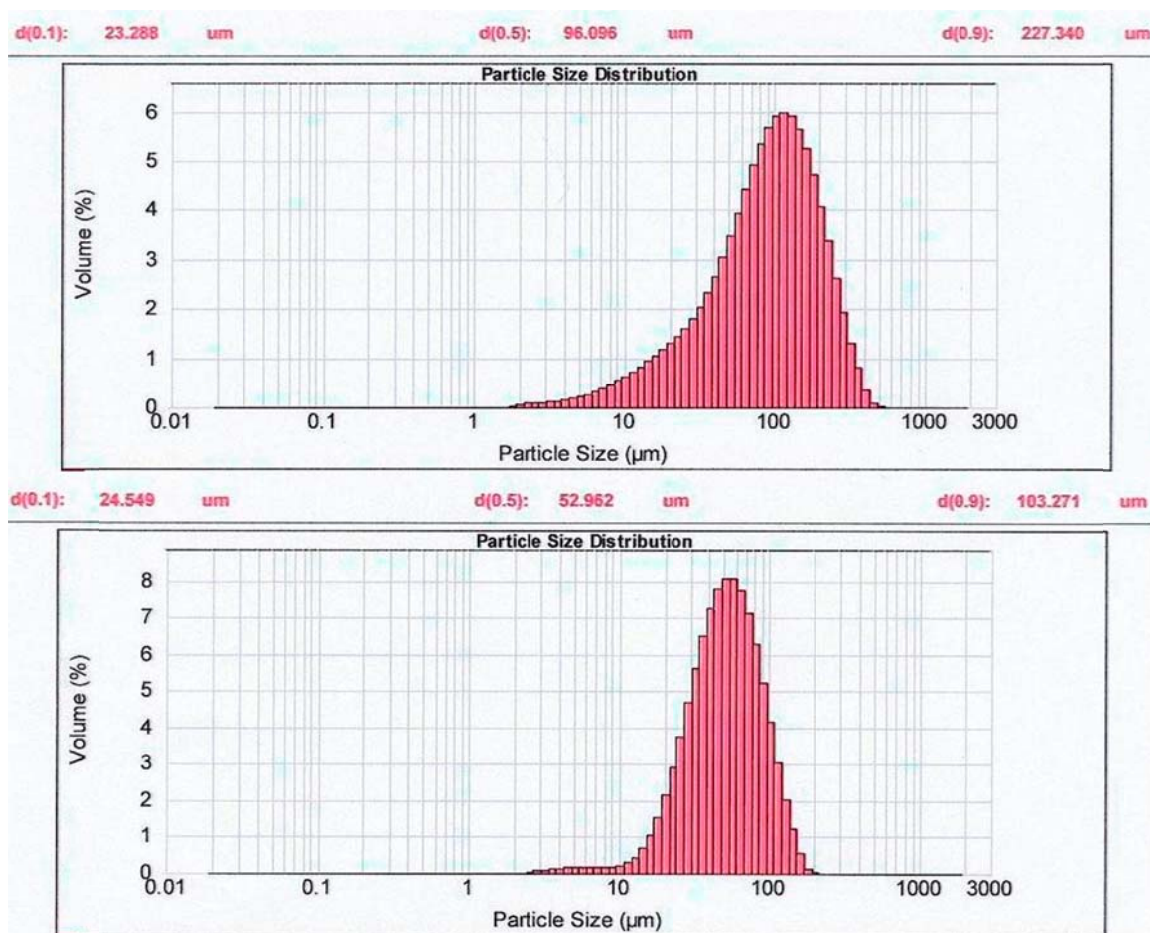


Figure 5.4: Histograms generated from the particle analysis of nevirapine raw material (top) and novel nevirapine powder (bottom).

Table 5.2: Classification of powder according to its measure of fineness (British Pharmacopoeia, 2009)

Classification of powders by fineness	
Descriptive terms	x_{50} (μm)
Coarse	> 355
Moderately fine	180 – 349
Fine	125 – 179
Very fine	< 125

The observed differences between the two nevirapine powder batches are of pharmaceutical importance, as they may have favourable and/or adverse effects on

powder processing and dosage formulation. Possible beneficial effects of the observed characteristics of the novel nevirapine powder include:

- Reduced particle size (and increased surface area) may improve the dissolution rate of nevirapine and hence its bioavailability. This is of utmost importance to this study, as nevirapine is known to be a poorly, water soluble drug, with its dissolution rate being a possible time limiting factor during absorption (Jinno *et al.*, 2006).
- Particles may interlock, due to the irregularities of the particle edges, whereas the narrow particle size distribution may promote powder homogeneity. Both these factors would therefore minimise powder segregation during subsequent handling and tableting (Tang & Puri, 2004).
- In a study of the relationship between the effective interparticulate contact area and the tensile strength of tablets of amorphous and crystalline lactose of varying particle sizes, Sebhatu and Alderborn (1999) demonstrated that tablets, made from smaller particles, were often stronger.

The tablets produced from this novel powder may prove even stronger, since the cracks in its particles could fragment during compaction, leading to a bonding potential of the particle surfaces, which could be higher than what could be predicted from bulk particle deformability (Eriksson & Alderborn, 1995).

- Although the irregular particle edges may offer improved compactability, it might not be the case, due to possible fragmentation during compaction, with a subsequent loss of original shape.
- An improved tablet to tablet content uniformity, by virtue of the increased number of particles per unit weight of the novel nevirapine powder (Lantz, 1990).
- No possible change in polymorphic form, as is often associated with milling.
- Overall, this novel method of preparing fine nevirapine powder may offer several economic advantages in terms of time and costs, compared to traditional methods of particle size reduction techniques. Currently, nevirapine is milled before being formulated into a finished dosage form, in order to obtain

an acceptable size distribution and to optimise dissolution (European Medicine Agency, 2004).

Possible disadvantages of the characteristics of the novel nevirapine powder (Lantz, 1990) include:

- Flowability may be negatively affected by the small particle sizes and the flaky, plate-like shapes of the particles.
- The material may be hygroscopic and unstable, with possible susceptibility to degradation of the drug, as a result of oxidation or adsorption of unwanted moisture on the increased surface area.
- Small particle size may paradoxically decrease the effective surface area and hence its dissolution and bioavailability. This may occur as a result of an increase in the particle surface energies, which may result in static charge problems that may cause the small drug particles to agglomerate. This phenomenon was observed in aspirin, phenacetin and phenobarbitone (Ashford, 2007).
- The material may become dusty and difficult to handle.

5.3 Powder flow characterisation

Traditional methods of pharmaceutical powder flow characterisation, as described in section 4.6, were employed to determine the flowability of the two samples of nevirapine. The results are presented in Table 5.3. The results correlated well with the beneficial and adverse effects being outlined in section 5.2 above.

Table 5.3: Flow parameters of the two samples of nevirapine powder

Material	Densities (g/ml)		Hausner ratio (HR)	Compressibility index (CI)	Critical orifice diameter (COD)	Angle of repose (AoR)
	Bulk	Tapped				

Nevirapine raw material	0.581448 ±0.006761 *	0.604932 ±0.009182	1.040361 ±0.004033	3.878563 ±0.373408	3	17.3058 ±0.144685
Novel nevirapine powder	0.365151 ±0.004651	0.463942 ±0.004164	1.270713 ±0.022118	21.28803 ±1.379494	N/A	N/A
* The average of three (3) measurements ± the standard deviation.						

5.3.1 Compressibility index and Hausner ratio

The Carr's compressibility index and Hausner ratio values for nevirapine raw material were 3.88 and 1.04, respectively (Table 5.3). According to the BPs (British Pharmacopoeia, 2009) scale of flowability in Table 5.4, these values were indicative of excellent powder flow. As for the novel nevirapine powder, the values were 21.29 and 1.27 for Carr's compressibility index and Hausner's ratio, respectively. The different values obtained between nevirapine raw material and novel nevirapine powder were well expected, when taking into consideration their differences in particle properties. Possible future studies could include tests of the nevirapine raw material (previously sieved) and the fine powder having similar particle size distributions, in order to better compare their particle properties.

Table 5.4: BP scale of flowability for Carr's compressibility index and the Hausner ratio (British Pharmacopoeia, 2009)

Flow character	Carr's compressibility index (%)	Hausner ratio
Excellent	≤ 10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very poor	32 – 37	1.46 – 1.59
Very, very poor	≥ 38	≥ 1.60

5.3.2 Critical orifice diameter (COD)

The critical orifice diameter of the nevirapine raw material was found to be 3 mm. As for the novel nevirapine powder, it was impossible to determine the critical orifice diameter. The powder would not pass through the largest disc (32 mm), due to it having formed a cohesive arch (Figure 5.5). The formation of such cohesive mass by the novel powder was attributed to its small particle sizes and plate-like shaped particles, which possibly caused strong particle interlocking. These results emphasised the possible negative impact of a reduced particle size on the flowability of a powder. Based on these results, it could be concluded that nevirapine raw material exhibited better powder flow than the novel nevirapine powder.



Figure 5.5: Cohesive arch formed by novel nevirapine powder during critical orifice diameter determination.

5.3.3 Angle of repose

The angle of repose was determined, using the same apparatus to establish the critical orifice diameter, as described in section 5.3.2 above. The angle of repose for nevirapine raw material was found to be 17.31° (Table 5.3), which correlated well with the other results that indicated that the nevirapine raw material exhibited good flow properties. Since it was impossible to determine the critical orifice diameter of the novel nevirapine powder on this apparatus, due to its poor flow properties, its angle of repose could also not be determined. Apart from indicating the cohesiveness of the novel, fine, nevirapine powder particles, it also demonstrated that the angle of repose test would be suitable for 'free flowing' powders only.

The outcomes from the powder flow characterisation techniques correlated well with the possible advantages and disadvantages of the novel nevirapine powder, as outlined in section 5.2, where it was predicted that the novel nevirapine powder may exhibit flowability difficulties.

The overall results showed that nevirapine raw material had superior flow properties to the novel nevirapine powder. The outcomes of this study showed that the novel nevirapine powder differed markedly from the raw material, probably as a result of the differences in the particle properties of the two powders. Nevirapine raw material consisted of large, equant, block shaped particles with smooth surfaces and hence exhibited good powder flow properties, compared to the novel nevirapine powder (Hoag & Lim, 2008). Contrary, nevirapine had small, irregular, plate-like particles with cracked surfaces and hence showed undesirable flow properties. The poor flow properties of the fine nevirapine powder could also have been attributed to its particle sizes and shapes. Fine particles are usually more affected by surface properties, such as static charges and adsorbed moisture, which would adversely affect a powder's flow. The irregular shapes of the fine nevirapine powder and the associated cracks, hence would have promoted particle interlocking. This may have been responsible for the observed cohesive arch that formed by the novel powder, during the determination of its critical orifice diameter.

5.4 Solubility and powder dissolution studies

The results for the solubility studies of the two nevirapine powders are summarised in Table 5.5. The ultraviolet (UV) spectra of the two batches of nevirapine in the respective solvents are shown in Figure 5.6. The results from this study showed that the solubilities of the two nevirapine powders differed. A 3.1% difference in solubility in water was recorded between the nevirapine raw material and the novel powder, with the latter being more soluble. A 3.9% difference in solubility in 0.1 N HCl was also observed, with the novel nevirapine powder showing a higher solubility again. These differences in solubility were not significant though. However, in light of the poor solubility of nevirapine in water and the fact that solubility is rarely increased by particle size reduction, such a slight difference may prove meaningful in future research.

Table 5.5: Solubility data of nevirapine raw material and the novel nevirapine powder in water and in 0.1 N HCl

Sample	Medium	R ² calibration curve	Equation calibration curve	Solubility * at 37°C (mg/100ml)	% difference in solvent	Relative standard deviation
NVP raw material	Water	R ² = 0.9997	y = 0.267x + 0.0116	12.71	3.1%	0.081
Novel NVP fine powder				13.12		0.052
NVP raw material	HCL	R ² = 0.9997	y = 0.306x + 0.0019	374.89	3.9%	0.066
Novel NVP fine powder				390.03		0.021

* as a function of six (6) determinants.

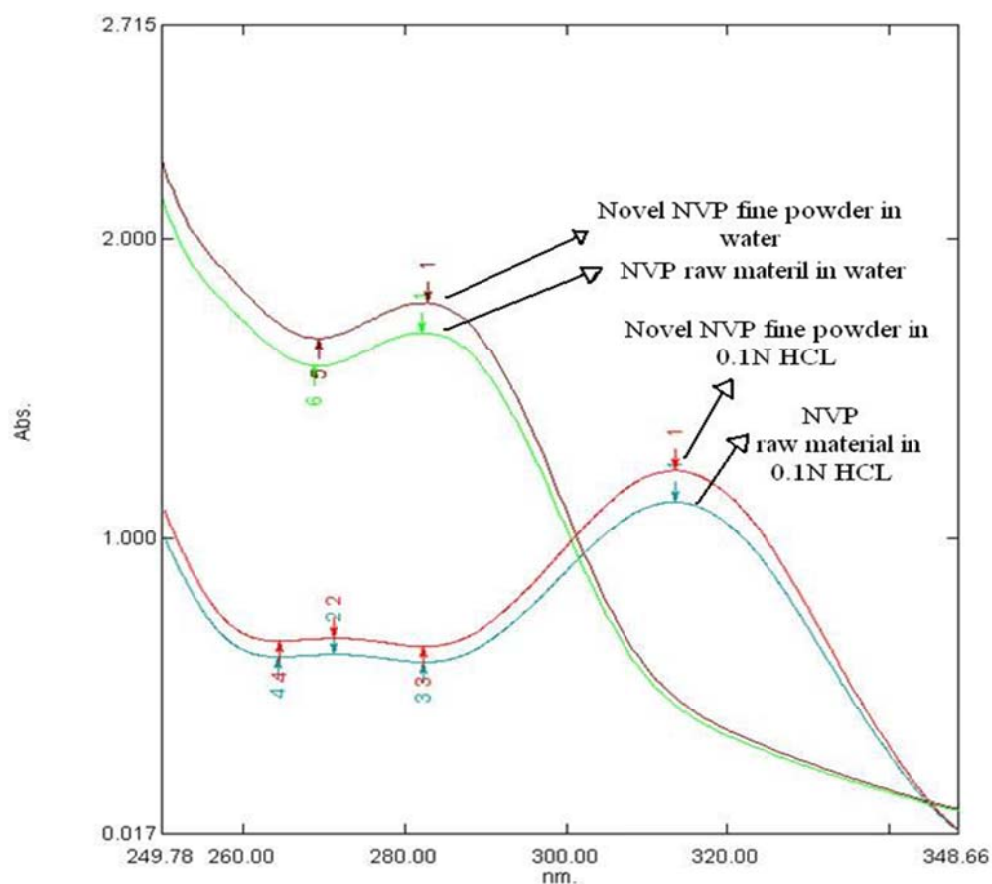


Figure 5.6: UV spectrum of two batches of nevirapine powders in water and in 0.1 N HCl.

The comparison of the powder dissolution profiles of the two batches of nevirapine revealed differences in their dissolution rates (Figure 5.7). The similarity factor ($f_2 = 39$) revealed that neither of the two profiles were equivalent. Novel nevirapine powder exhibited a slightly better dissolution profile than the nevirapine raw material. These results correlated well with the particle size properties of the two batches. The positive agreement between the particle size properties and the observed dissolution profiles suggested that the dissolution of nevirapine would follow the Noyes–Whitney equation and would its dissolution possibly be enhanced by a particle size reduction.

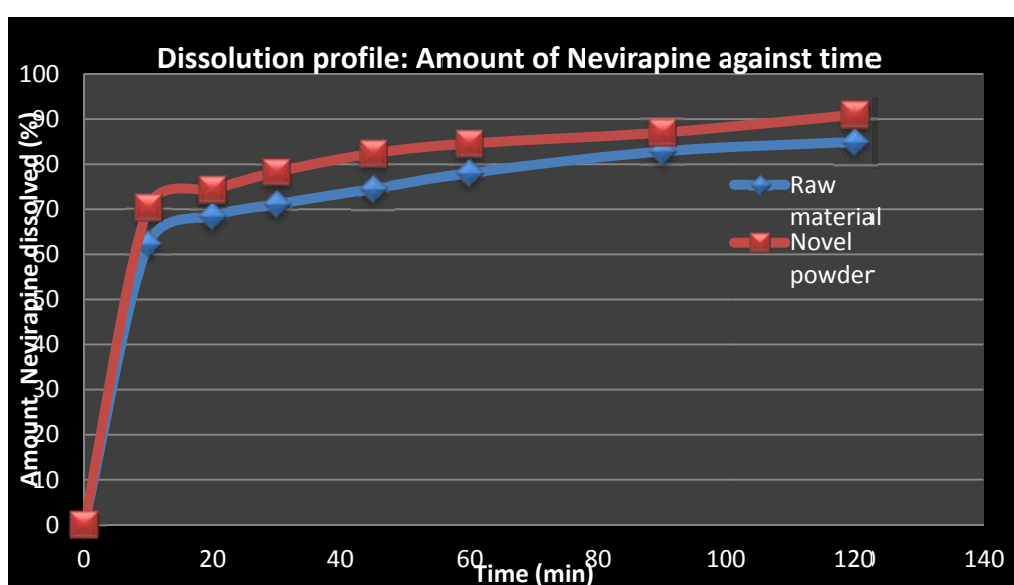


Figure 5.7: Comparison of the dissolution profiles of nevirapine raw material and the novel powder.

5.5 Conclusion

Many pharmaceutical processes depend on the flowability of the powder formulation and as such, powders with better flow are always preferred. From this view, nevirapine raw material could be the preferred material, since it exhibited better flow properties than the fine, novel powder during this study. However, with regards to the poor water solubility of nevirapine raw material, the slightly more soluble, novel nevirapine powder could be preferred in the hope of optimising the dissolution of the final product. Nevirapine raw material may be suitable for both direct compression and granulation methods of tablet manufacturing, whereas the novel nevirapine

powder would only be suitable for use if its flow properties could be improved through a granulation process.

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CHAPTER 6

Tablet Characterisation Methods and Materials

6.1 Introduction

Several pharmaceutical dosage forms are available on the commercial market, of which tablets represent a greater share. This chapter relates to the nevirapine tablets that had been produced during this study and the quality control tests that they were subjected to. The tablets were manufactured by means of wet granulation. Tablets, like other dosage forms, have to adhere to certain acceptable quality standards. In order to ascertain the quality of the manufactured tablets, the following tests were performed during this study:

- Friability,
- Crushing strength,
- Disintegration,
- Dissolution behaviour of the active, and
- Weight variation.

6.2 Tablet compression

Initially it was envisaged that the tablets would be prepared by both direct compression and wet granulation. However, preliminary studies, together with the outcomes of the studies in Chapters 4 and 5, had revealed the undesirable flow properties of the novel fine powder, hence making it unsuitable for direct compression. As a result, only wet granulation was applied during the formulation processes in this study, specifically the traditional wet granulation method. In this study, two different formulations were prepared from each nevirapine powder batch, i.e. the raw material and the novel powder, to produce four nevirapine tablet batches.

(i) *Mixing*

Mixing is an important step in tablet formulation, as it ensures the uniform distribution of all ingredients. Mixing was done, using a Turbula[®] mixer T2C (W.A. Bachofen, Basel, Switzerland), set at 69 rpm for 10 minutes.

(ii) *Compression*

Tablet production involves the compression of loose powder particles into a compact tablet. Tablet compression was performed, using a Cadmach, single stroke, tablet press (Ahmedabad, India), equipped with a 10 mm, flat-with-bevel-edges punch. The die volume was adjusted to produce tablets of theoretical weight of 400 mg each.

(iii) *Granulation fluid*

The granulation fluid was prepared by dissolving the required amount of binder, i.e. Povidone k30, into distilled water. The water was pre-boiled and used while still hot to obtain an optimum solution of the binder. Water was preferred, based on its physiological and chemical compatibility with nevirapine.

(iv) *Pre-conditioning of the material*

All powder materials, prior to use, were subjected to 30°C in an oven for 24 hours, as a pre-conditioning standard.

6.2.1 *Formulation 1 (F1)*

The composition of the tablets being manufactured according to formulation 1 is presented in Table 6.1.

Formulation 1: Formulation process

Nevirapine powder from each of the two batches was each firstly mixed with the filler, i.e. lactose monohydrate (Flowlac[®] 100). This powder mixture was then mixed

with the granulating fluid (prepared as per 6.2(iii) above) to form a wet mass that was forced through a 1 000 µm sieve to form granules. These sieved wet granules were dried in an oven, set at 100°C for 24 hours. The resultant dry granules were then gently forced through a 500 µm sieve to produce granules suitable for compression. These granules were subsequently mixed with the remaining ingredients, i.e. the extragranular disintegrant, croscarmellose sodium (Ac-di-sol®), and the lubricant, magnesium stearate. This mixture was finally compressed into tablets.

Table 6.1: Formulation 1: Summary of the ingredients used

Ingredient	Purpose	% Content	Quantity per tablet (mg)
Nevirapine	Active ingredient	50	200
Lactose monohydrate (Flowlac® 100; Lot: 04492)	Filler	42	168
Povidone k30 (Kollidon® 30; Lot: 8605852240)	Binder	5	20
Croscarmellose sodium (Ac-di-sol®; Lot: T017C)	Extragranular disintegrant	2	8
Magnesium stearate (Lot: 01214)	Lubricant	1	4

6.2.2 Formulation 2 (F2)

The composition of the tablets being manufactured according to formulation 2 is presented in Table 6.2.

Formulation 2: Formulation process

Nevirapine powder from each of the two powder batches was each firstly mixed with the filler, i.e. lactose monohydrate (Flowlac® 100) and with the intragranular disintegrant, i.e. microcrystalline cellulose (Avicel® PH101). The powder mixture was then mixed with the granulating fluid (prepared as per 6.2(iii) above) to form a wet mass that was forced through a 1 000 µm sieve to form granules. These sieved wet granules were dried in an oven, set at 100°C for 24 hours. The resultant dry granules were then gently forced through a 500 µm to produce granules suitable for

compression. The granules were subsequently mixed with the remaining ingredients, i.e. the extragranular disintegrant, croscarmellose sodium (Ac-di-sol®) and the lubricant, magnesium stearate. This mixture was finally compressed into tablets.

Table 6.2: Formulation 2: Summary of the ingredients used

Ingredient	Purpose	% Content	Quantity per tablet (mg)
Nevirapine	Active ingredient	50	200
Lactose monohydrate (Flowlac® 100; Lot: 04492)	Filler	37	148
Povidone k30 (Kollidon® 30; Lot: 8605852240)	Binder	5	20
Microcrystalline cellulose (Avicel® PH101)	Intragranular disintegrant	5	20
Croscarmellose sodium (Ac-di-sol®; Lot: T017C)	Extragranular disintegrant	2	8
Magnesium stearate (Lot: 01214)	Lubricant	1	4

6.3 Tablet evaluation

6.3.1 Weight variation

The weight of a compressed tablet is determined by the pre-set, volumetric fill of the die cavity during tablet compression (Troy, 2006). In practice, the weight of tablets is routinely checked to ensure continuous production of the desired tablet weight. In tablets with a higher content of the active ingredient, weight variation is commonly used to determine content uniformity (Banker & Anderson, 1986).

Procedure: This test was carried out in accordance with the BP (British Pharmacopoeia, 2009). Twenty (20) tablets from each of the four nevirapine batches were individually weighed, using a pre-calibrated, analytical balance (Optical instrument, West Germany). The tablets were randomly selected and dusted prior to weighing and the average weight determined. According to the BP, not more than two of the individual tablet weights should deviate from the average mass by more

than the allowed percentage deviation (Table 6.3), whereas none should deviate by double the allowed percentage deviation. Since the formulated, theoretical weight of the tablets was 400 mg each, a percentage deviation of $\pm 5\%$ was applicable, i.e. 400 mg ± 20 mg.

Table 6.3: Average tablet mass and corresponding percentage deviation allowed (British Pharmacopoeia, 2009)

Tablet formulation	
Average mass	Percentage deviation
≤ 80 mg	$\pm 10\%$
> 80 mg and < 250 mg	$\pm 7.5\%$
≥ 250 mg	$\pm 5\%$

6.3.2 Friability

Friability is the tendency of the tablet to abrade/scrape small particles and fragments from its surface. These may result from stress conditions (i.e. coating, packaging, shipping, handling and other processing conditions) that tablets may be exposed to, before reaching its final destination. The friability test is a measure of the physical ability of the tablet to resist abrasion during such conditions. Tablets that abrade with ease will result in an undesirable, progressive reduction in their weight and in a change in appearance. In addition to ascertaining that tablets would remain virtually intact during these conditions, the friability test gives the opportunity for detecting relative capping, or lamination from the tablet (Seitz & Flessland, 1965; Sotiropoulos *et al.*, 1981).

Procedure: The test was performed in accordance with the BP (British Pharmacopoeia, 2009). Twenty (20) tablets from each of the four nevirapine batches were subjected to a uniform tumbling motion at 25 rpm for 4 minutes, using the Roche® friabilator. The duration of 4 minutes was chosen in order to achieve the required 100 rotations. The tablets were dusted and weighed on the analytical balance, prior to and after executing the test. According to the BP, the tablets should not lose more than 1% of their total weight. The percentage weight loss was calculated using the following formula:

$$\%F = 100 \times \frac{(W_0 - W_1)}{W_0}$$

Equation 6.1

Where:

%F is percentage weight loss;

W_0 is total weight of the 20 tablets before the test; and

W_1 is total weight of the 20 tablets after the test.

6.3.3 Crushing strength

In addition to friability, crushing strength is also used to measure the physical strength of a tablet. Tablets with good physical strength properties can withstand manufacturing processes, such as coating, packaging and printing. Crushing strength is the ability of the tablet to resist fracture (breakage) into pieces, when subjected to external forces. Physical strength of a tablet is controlled by, or is affected by the degree of pressure applied during the compression stage, in addition to the effect of the binder (if included in the formulation) (Beom-Jin, 2008). A crushing strength test measures the force required to cause a tablet to break in a specific plane. The crushing strength tester consists of two platens, one of which moves against the other to apply sufficient force to the tablet to cause it to fracture. The force (in Newton) required to break the tablet is electronically recorded by the tester.

Procedure: To determine the crushing strength of the tablets, 15 tablets from each of the four nevirapine batches were individually placed between the platens of the crushing strength tester (Pharma Test[®], PTB-311, Switzerland). Activation of the test button caused the instrument to break the tablet and to record the crushing strength.

6.3.4 Disintegration

While it is a pharmaceutical prerequisite that tablets should be physically strong in order to withstand coating, packaging, shipping, handling and other processing conditions, it should also be delicate enough to disintegrate suitably after swallowing. A disintegration test is used to determine the ability of a tablet to disintegrate into small particles within a specified time, when immersed in a test medium. Disintegration allows for the individual particles of a tablet to come into contact with the medium, with the ultimate possible dissolution of the active ingredient. Based on this understanding, results from the disintegration test are used to indicate an increase in the surface of the active ingredient exposed to the dissolution medium, thereby increasing the chances of improving dissolution rate. The results should, however, not be overestimated as a measure of bioavailability, since bioavailability is not directly influenced by disintegration. The ability of the tablet to disintegrate is affected by the amount of disintegrant used and the compression conditions. Hence, the more the disintegrant, the easier the tablet would disintegrate.

According to the BP (British Pharmacopoeia, 2009), the test is deemed successful if the resultant particles/agglomerates are small enough to pass through the mesh wire at the base of the disintegration apparatus vessels. Failure of the tablet to meet disintegration requirements can result in disintegration of the dosage form being the rate limiting step in drug bioavailability (Kumar & Tewari, 2006). The USP disintegration apparatus consists of six cylindrical tubes in which a tablet each is introduced. The lower ends of the tubes are closed off by a mesh wire on which the tablets lie, before starting the test. During the disintegration process, the tubes move up and down to ensure continuous agitation.

Procedure: The disintegration times of the tablets were determined in distilled water at $37.0 \pm 0.50^{\circ}\text{C}$, using the Apex disintegration testing apparatus (Apex Construction Ltd, Northfleet Gravesend and Dartford, Kent, U.K). Tablets from each of the four nevirapine batches (3 tests x 6 tablets = 18 tablets per batch) were tested and a tablet introduced into each of the six cylindrical tubes, before initialising the apparatus. Time was kept using a stop watch. The time taken for all of the tablets to disintegrate and pass through the mesh wire was recorded. Each test was repeated

in triplicate. The BP (British Pharmacopoeia, 2009) recommends that conventional tablets should be disintegrated within 15 minutes of initialising the test.

6.3.5 Dissolution

Dissolution is the process during which a solid substance is evenly distributed into the solvent to yield a solution (Kumar & Tewari, 2006). “Drug dissolution is a prerequisite to drug absorption and clinical response for almost all drugs given orally.” (Amidon *et al.*, 1995). The importance of dissolution in pharmaceutical quality control has been discussed in Chapter 1. The dissolution of a drug is affected by many factors, such as its solubility, particle size, polymorphism, and factors related to the formulation parameters (Kumar & Tewari, 2006). Dissolution studies are among the regulatory techniques used in pharmaceutical quality control (Freitag, 2001). The results are used to determine the *in vitro* rate of release of the drug from the dosage form and to predict the *in vivo* rate of release of a drug from the dosage form (Alderborn, 2002). Additionally, dissolution studies can be used to construct and compare the dissolution profiles of different formulations of an active ingredient and with the reference medicinal product. This is often required for the approval of generic drug products (Freitag, 2001). The ultimate aim is to establish/demonstrate similarities or differences between the generic and the reference products (Costa & Sousa-Lobo, 2001). The analyses of the dissolution profiles can be achieved through several methods, e.g. model dependent and model independent methods. However, the most recommended method for dissolution profile comparison is the ‘model independent similarity factor’ (f₂) (Freitag, 2001). The similarity factor (f₂) is calculated according to the following formula:

$$f_2 = 50 + \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} * 100 \right\}, \quad \text{Equation 6.2}$$

Where:

R_t and T_t are the cumulative percentages dissolved at each of the selected n time points of the reference and test product, respectively.

In general, two dissolution profiles are declared similar/equivalent, if f₂ is higher than 50 (50 - 100). This similarity factor has been adopted by the Centre for Drug

Evaluation and Research (of FDA) and by the Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicinal Products (EMA), as a criterion for the assessment of the similarity between two *in vitro* dissolution profiles (Costa & Sousa-Lobo, 2001). The f2 was used in this study also for comparing the dissolution profiles of the four batches of formulated tablets. Dissolution studies can be performed using one of the USP apparatuses (USP apparatus I with a mesh wire basket, USP apparatus II with a paddle, USP apparatus III, USP apparatus IV with a flow through cell, and USP apparatus V, VI and VII). USP apparatus 2 is the most commonly used for tablet dissolution studies.

Procedure: USP apparatus II (paddle) was used to determine the dissolution rates of the four nevirapine tablet batches. Each test was carried out at a temperature of $37 \pm 0.5^{\circ}\text{C}$, with the apparatus set at a rotating speed of 50 rpm. The dissolution medium used for the tablets was 0.1 N HCl, whereas the powder dissolutions were done in water for the purpose of comparing the two nevirapine powder samples. For this dissolution study the specifications, as summarised in Table 6.3 were used. The outcomes were determined, using the UV spectrophotometric method being developed by Stieger *et al.* (2009b).

Table 6.4: Summary of the dissolution parameters used

Dissolution conditions	
Sample	Four batches of formulated nevirapine tablets
Dissolution medium	0.1 N HCl (900 mL – final volume)
Temperature	$37 \pm 0.5^{\circ}\text{C}$
Apparatus	USP type II apparatus set at 50 rpm
Detection/quantification	UV spectrophotometry at 313 nm
Withdrawal intervals	2, 5, 10, 15, 20, 30, 45 and 60 minutes
Withdrawal volume	5 mL per each interval
Procedure	Disperse each tablet into 900 mL of pre-conditioned dissolution medium
Number of determinants	6 tablets for each batch of nevirapine tablets

6.3.5 Conclusion

Tablets for purpose of this were prepared by wet granulation. The tablets were subsequently subjected to tablets tests which included friability, crushing strength, disintegration, dissolution behaviour of the active, and weight variation. The results from these tests are presented in chapter 7.

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CHAPTER 7

Tablet Characterisation Results and Discussion

7.1 Introduction

In Chapter 2, the literature review with regards to tablet properties was discussed, whilst tablet characterisation methods were described in Chapter 6. In this chapter, the outcomes from the tablet characterisation studies being performed, as described in Chapter 6, are presented and discussed. In conclusion, a trend of relationships between the nevirapine powder properties and the tablet characteristics is established.

7.2 Tablet characteristics analysis

Tablet analyses were undertaken in order to compare the tablet properties of those tablets produced from the two nevirapine powder batches (nevirapine raw material and novel powder). Two formulations were prepared for each powder batch (four tablet batches), to help observe any formulation related differences. The two formulations are summarised in Tables 7.1 and 7.2.

Table 7.1: Formulation 1: Summary of the ingredients used

Ingredient	Purpose	% Content	Quantity per tablet (mg)
Nevirapine	Active ingredient	50	200
Lactose monohydrate (Flowlac [®] 100; Lot: 04492)	Filler	42	168
Povidone k30 (Kollidon [®] 30; Lot: 8605852240)	Binder	5	20
Croscarmellose sodium (Ac-di-sol [®] ; Lot: T017C)	Disintegrant	2	8
Magnesium stearate (Lot: 01214)	Lubricant	1	4

Table 7.2: Formulation 2: Summary of the ingredients used

Ingredient	Purpose	% Content	Quantity per tablet (mg)
Nevirapine	Active ingredient	50	200
Lactose monohydrate (Flowlac® 100; Lot: 04492)	Filler	37	148
Povidone k30 (Kollidon® 30; Lot: 8605852240)	Binder	5	20
Microcrystalline cellulose (Avicel® PH101)	Intragranular disintegrant	5	20
Croscarmellose sodium (Ac-di-sol®; Lot: T017C)	Extragranular disintegrant	2	8
Magnesium stearate (Lot: 01214)	Lubricant	1	4

7.2.1 Weight variation

The results from the weight variation test are summarised in Table 7.3. The BP acceptable weight variation guideline is shown in Table 7.4. Not a single tablet from any of the four formulations was out of specification. This was consistent with the BP requirement that not more than two of the individual tablet weights should deviate from the average weight by more than the percentage deviation shown in Table 7.4. As indicated in Chapter 5, preliminary studies on tablet production by direct compression had revealed that the flowability of the feed from the formulation, containing the novel nevirapine powder, posed a problem with regards to its tabletability and would it possibly have produced tablets with large weight variations. The consistencies in the tablet weights showed that the use of the wet granulation method was successful in improving the flowability of the feeds, particularly those of the two formulations containing the novel nevirapine powder.

Table 7.3: Weight variation results of the four batches of nevirapine tablets and the calculated BP acceptable range

Formulation	Weight variation (mg)*	BP acceptable range**
Raw material F1	401.05 ±0.002946	380.9975 – 421.1025

Novel powder F1	407.682 ±0.002715	387.2979 – 428.0661
Raw material F2	406.682 ±0.003386	386.3479 – 427.0161
Novel powder F2	402.15 ±0.002183	382.0425 – 422.2575
* As an average of 20 determinants.		
** Calculated according to BP acceptable weight variation (British Pharmacopoeia, 2009).		

Table 7.4: The BP guideline on weight variation* (British Pharmacopoeia, 2009)

Tablet formulation	
Average mass	Percentage Deviation
≤ 80 mg	10%
> 80 mg and < 250 mg	7.5%
≥ 250 mg	5%
* Not more than 2 of the individual masses must deviate from the average mass by more than the percentage deviation shown.	

7.2.2 Physical strength: Friability and crushing strength

Both friability and crushing strength relate to the physical strength of the tablet and are their results hence discussed simultaneously. Friability and crushing strength tests were performed, as described in Chapter 6. The results from the friability and crushing strength tests for the four formulations are summarised in Table 7.5 and Figure 7.1. The results of the friability tests showed that all of the tablets being produced from both the nevirapine raw material and the novel powder had passed the BP specifications. The BP states that the tablets should not lose more than 1% of their total weight (British Pharmacopoeia, 2009). There was, however, a difference in terms of their percentages of friability. Tablets produced from the novel nevirapine powder had lower percentage friability than those manufactured from the raw material. This difference was consistent among both formulations (F1 and F2). The percentage difference in friability was at least 14% for both formulations. Even though this difference may have been only marginally significant, it showed that those tablets manufactured from the novel nevirapine powder had better physical strength than those made with the nevirapine raw material.

Table 7.5: Friability and crushing strength results of the four batches of nevirapine tablets

Formulation	Friability (%F)	Crushing strength (N)*
Raw material F1	0.97	44.27778 ±3.195687
Novel powder F1	0.83	45.85714 ±3.91952
Raw material F2	0.81	57.83333 ±1.917412
Novel powder F2	0.66	71.86667 ±3.62268
* As an average of 15 tablets.		

The results of the crushing strength tests coincided with those of the friability tests. Those tablets being produced from the nevirapine raw material had crushing strengths of 44.28 N and 57.83 N for F1 and F2, respectively. Tablets produced from the novel nevirapine powder had crushing strengths of 45.86 N and 71.87 N for F1 and F2, respectively. Figure 7.1 shows how a decrease in the percentage friability corresponded with an increase in the crushing strength in the following order: RM F1 ⇒ NP F1 ⇒ RM F2 ⇒ NP F2. The results thus showed that those tablets that had been manufactured from the novel nevirapine powder had a higher crushing strength than those produced from the nevirapine raw material. It was noted that the difference between the two batches of F2 was higher. Microcrystalline cellulose, which was included in F2, is widely used as a binder, among other uses (Kachrimanis *et al.*, 2003). Microcrystalline cellulose can also augment the compactability of formulations (Edge *et al.*, 2000). It is also well recognised that tablets made from smaller particles are often stronger (Sebhatu & Alderborn, 1999; Sun & Grant, 2001). Therefore, the observed higher crushing strengths of those tablets produced from the novel powder in F2, could have been attributed to the possible effects of microcrystalline cellulose complementing the fine particles of the novel powder.

It was predicted in Chapter 5 that one of the possible beneficial effects of the fine, novel nevirapine powder would be the possible production of mechanically stronger tablets. The results from the friability and crushing strength tests confirmed that prediction, when comparing the results of the tablets made from the two nevirapine powders.

7.2.3 Disintegration

After tablet administration, disintegration marks the first step towards the bioavailability of a drug. Therefore, the results from the disintegration tests would be indicative, but not conclusive, of the possible release of the drug from the tablet. To establish whether the tablets, made from the two batches of nevirapine powders, would undergo disintegration after administration, disintegration tests were performed, as described in Chapter 6. The results from these tests are summarised in Table 7.6 and illustrated in Figure 7.2.

All of the tablets from the four batches disintegrated within the prescribed 15 minutes, as per the BP specification. The differences in disintegration between the two batches of each formulation were insignificant.

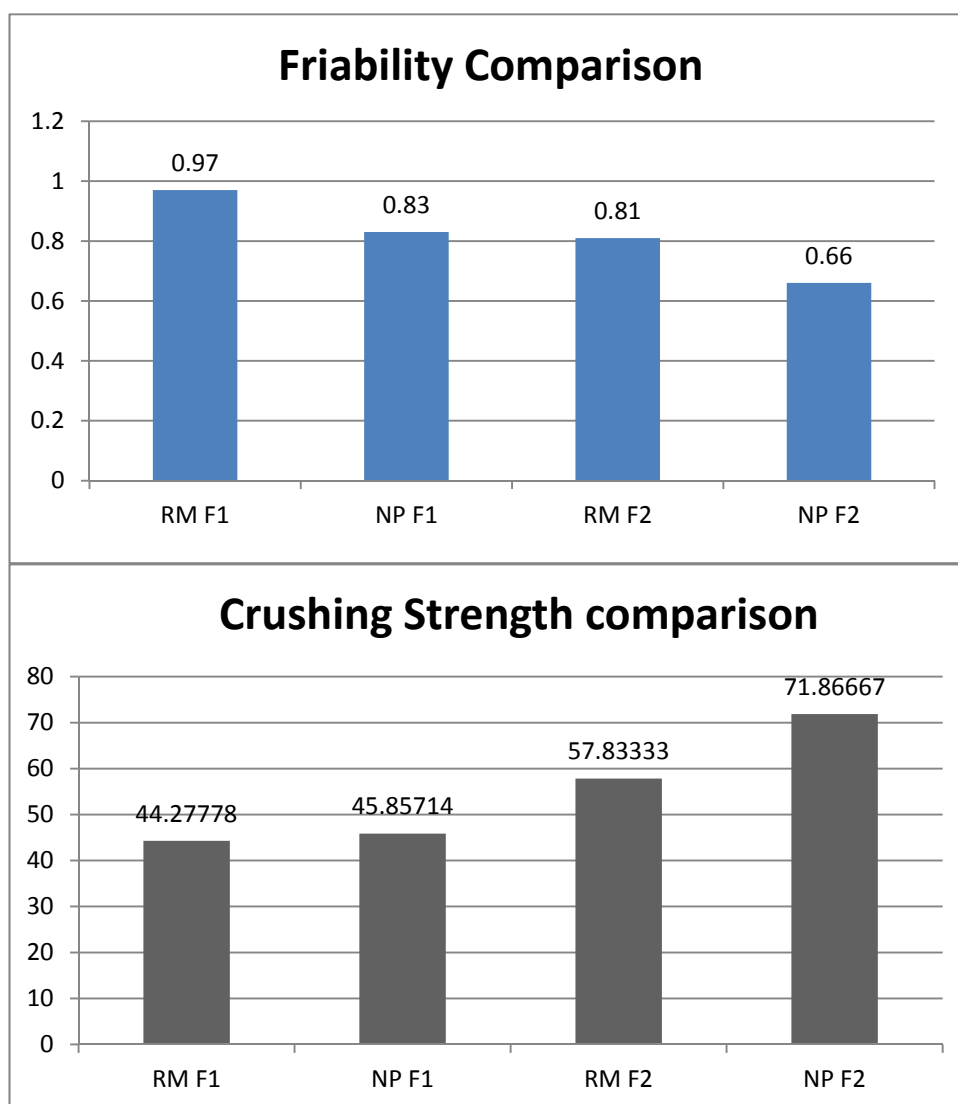


Figure 7.1: Friability and crushing strength comparisons of the four batches of nevirapine tablets.

The different physico-chemical properties of the two nevirapine active ingredients did not seem to have influenced the disintegration properties of both the formulations. This was evidenced by the fact that the disintegration differences being observed did not correspond with the use of either the nevirapine raw material or the novel powder. It is well known that the disintegration time of tablets would increase with an increasing physical strength (Riippi *et al.*, 1998).

It could be expected that, based on the results from the crushing strength, tablets of F2 would exhibit longer disintegration times than those of F1. However, the test outcomes showed the exact opposite, which could have been explained by the

inclusion of the microcrystalline cellulose in F2. Microcrystalline cellulose has three hydroxyl groups in each glucopyranose unit and therefore it can be easily swelled by water. Through this mechanism, microcrystalline cellulose can facilitate rapid disintegration of tablets in water (Obae *et al.*, 1999).

The disintegration differences in the two formulations could further have been attributed to the relationship between disintegration and the compactability of the tablets, especially with the use of croscarmellose sodium in both the tablet formulations. Croscarmellose sodium (Ac-di-sol[®]) produces efficient disintegration of the tablet when the applied pressure increases. This is because under high pressure, croscarmellose sodium has the ability to cause enough pressure in the pores of the tablet (Ferrero *et al.*, 1997).

Table 7.6: Tablet disintegration results of the four batches of nevirapine tablets

Formulation	Disintegration (min)*
Raw material F1	2.32 ±0.141
Novel powder F1	2.11 ±0.066
Raw material F2	1.03 ±0.026
Novel powder F2	1.05 ±0.021
* As an average of 3 determinants.	

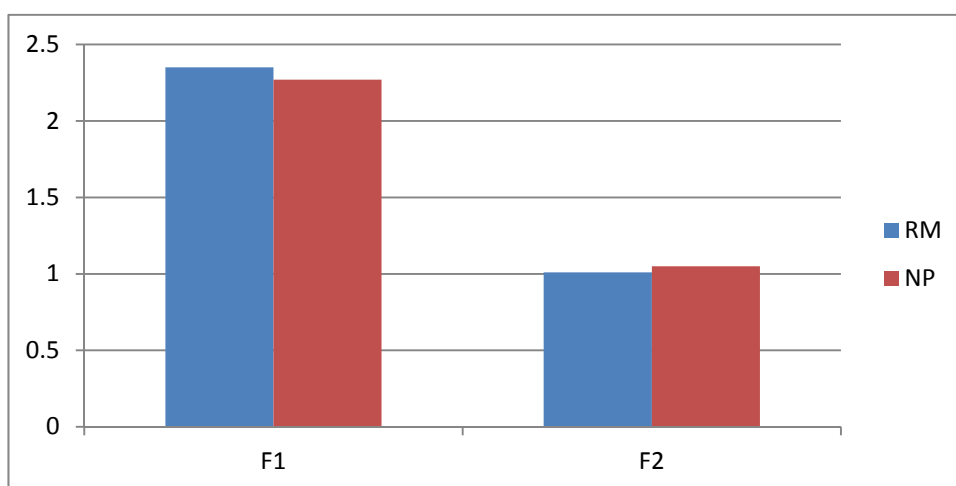


Figure 7.2: Tablet disintegration comparison between the four batches of nevirapine tablets manufactured from the nevirapine raw material and the novel powder.

7.2.4 Dissolution

(i) *Pre-dissolution study*

The UV spectrophotometer had been used before to quantify the dissolution rate of nevirapine powder (Sarkar *et al.*, 2008; Stieger *et al.*, 2009). It was hence used in this study for the purpose of determining the solubilities and dissolution rates of the nevirapine raw material and of the novel powder (Chapters 5 and 6). Before the method was applied, it had to be established with certainty that the excipients in the tablets would have negligible or no effects on the UV results.

To achieve this, three samples (with six determinants for each) were subjected to the UV method. The samples were as follows:

1. All excipients alone (sufficient to represent the excipients present in a 400 mg tablet as per F2).
2. Nevirapine alone (200 mg).
3. Nevirapine plus all excipients (sufficient to produce a 400 mg tablet as per F2).

The samples were each dissolved in a 0.1 HCl medium at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$, until a clear solution was attained. The one sample, consisting of the excipients and the other, consisting of the nevirapine plus the excipients, did not attain a completely clear solution over a 24h period. It was concluded that this would not have statistically meaningful effects on the tablet dissolution timeframe.

The results of the pre-dissolution study are summarised in Table 7.7, whilst the representative spectra are shown in Figure 7.3. From the outcomes, it could be deduced that the difference between the absorbances of nevirapine alone and of the nevirapine plus the excipients of 0.014, was as a result of the absorbance of the excipients alone (Abs = 0.015). Figure 7.3 illustrates that in actual fact, the influence of the excipients on the absorbance was negligible. Nevertheless, mathematical

corrections were used to render it possible to determine the amount of nevirapine in a tablet with accuracy, using this UV method.

Table 7.7: UV absorbance of the pre-dissolution samples

Sample	Absorbance *
Excipients alone	0.015 ±0.000752773
Nevirapine alone	0.679 ±0.00175119
Nevirapine plus all excipients	0.693 ±0.002168

* As an average of 6 (six) determinants.

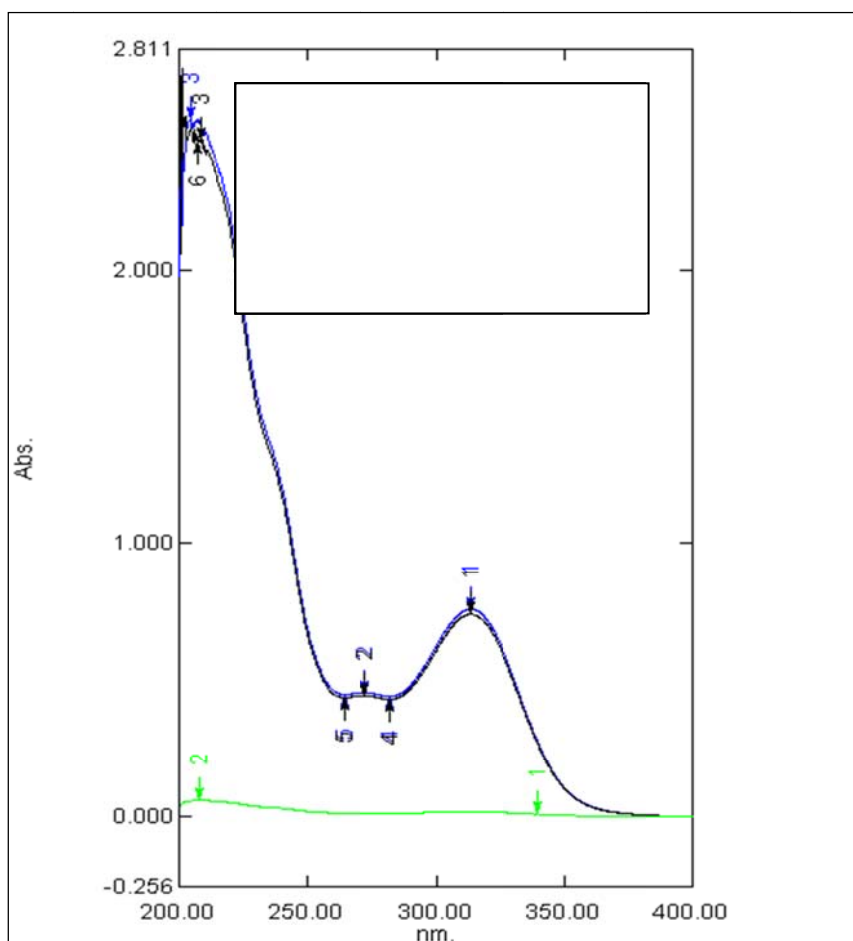


Figure 7.3: Comparison of the UV spectra of the excipients alone, the nevirapine alone and of the nevirapine plus the excipients.

(ii) Dissolution study

As discussed in Chapter 6, dissolution is the most important step towards drug bioavailability. It can determine the success or failure of the drug. The dissolution results of the two formulations for each of the two batches of nevirapine powders are discussed here. The dissolution tests were performed, as described in Chapter 6. The UV spectrophotometer was used to quantify the amount of drug being released from the tablets.

The results of the dissolution studies are summarised in Figure 7.4, whilst the similarity factor analyses outcomes are presented in Table 7.8. For both F1 and F2, the dissolution rates of the tablets, produced from the novel nevirapine powder, were better than those of the tablets manufactured from the nevirapine raw material. The similarity factors further showed that these dissolution profiles were neither equivalent. In both formulations, the tablets containing the fine, novel nevirapine powder, released more than 85% of the nevirapine within 15 minutes, as opposed to the tablets, containing the larger particles of the nevirapine raw material, which only achieved the same dissolution in twice the amount of time. The dissolution profiles further showed that the initial particle sizes of the nevirapine API had influenced the dissolution of the tablets. This was in accordance with the viramune scientific discussion report from the European Medicine Agency (2004), which stated that nevirapine tablet dissolution was found to be correlated with the particle size of nevirapine (European Medicine Agency, 2004).

Comparisons of the two formulations were also done in order to establish the influence of the formulation on the dissolution profiles. The dissolution results showed that the two formulations were similar and may have had little influence on the dissolution profiles obtained.

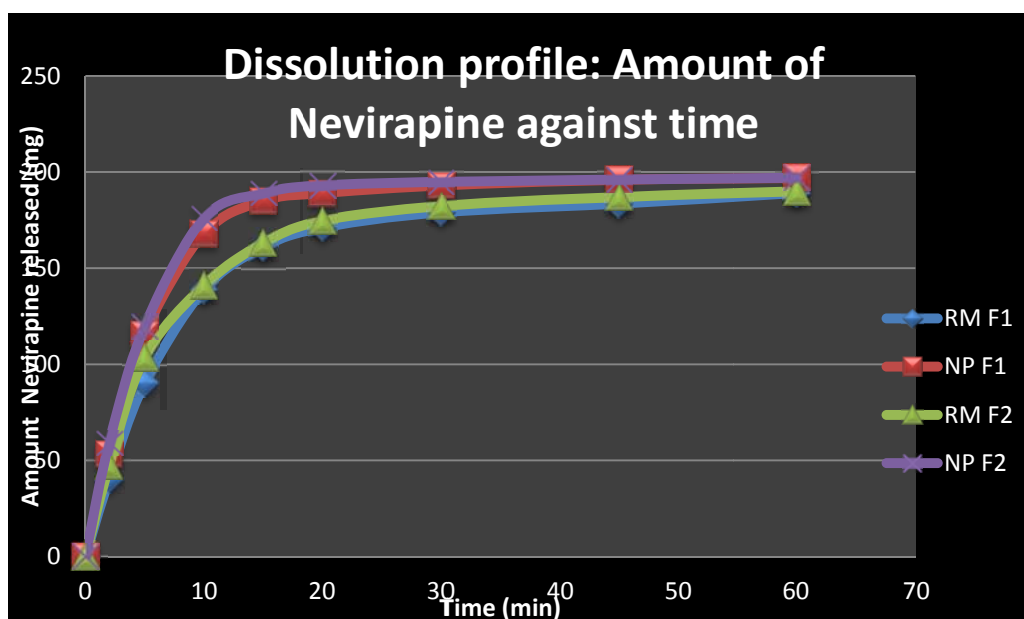


Figure 7.4: Dissolution profiles of the four batches of nevirapine tablets.

Table 7.8: Similarity factors of the four batches of nevirapine tablets

		Similarity factor
1	F1 RM	43 (Not equivalent)
	F1 NP	
2	F2 RM	43 (Not equivalent)
	F2 NP	
3	F1 RM	67 (equivalent)
	F2 RM	
4	F1 NP	77 (equivalent)
	F2 NP	

7.3 Conclusion

Tablets are the most popular dosage forms being manufactured by the pharmaceutical industry and their quality control through tablet analysis is of paramount importance. From the outcomes of the tablet analyses in this study, it could be concluded that the initial particle size of the nevirapine API had an influence on most of the results. A clear correlation between the particle and tablet properties was established. Tablets produced from the novel nevirapine powder were the

strongest and exhibited a better dissolution profile. In addition, the novel nevirapine powder had the smallest particle sizes, and had plate-like shaped particles with irregular edges and cracked particle surfaces. It could thus be assumed that the novel nevirapine powder had more interparticle contact points and larger bonding surfaces, hence the stronger tablets being produced. It could further be assumed that the novel powder also had the largest specific surface areas for contact with the media, hence the better tablet dissolution profiles. The novel nevirapine powder had thus during this study proven preferable in terms of its tablet strength and dissolution. These results were in parallel with several studies that had concluded that tablets, consisting of APIs having small particles, have better physical strength and dissolution properties (Sebhatu & Alderborn, 1999; Alderborn, 2002; Conway, 2008).

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CHAPTER 8

Summary and Conclusion

Nevirapine is a potent, non-nucleoside, reverse transcriptase inhibitor, used in combination therapy for the treatment of HIV infection and AIDS. Nevirapine is also popular for its preference role in the prevention of mother to child transmission of HIV. Nevirapine, like many drug substances, exhibit polymorphism. Until recently, the only known forms of nevirapine were the hemihydrate and anhydrous forms. Now it is known that several nevirapine crystalline forms and solvates exist.

Chapter 1 presented the common properties of pharmaceutical powders and their effects on their subsequent use. Powder is common in pharmaceutical industries and its properties cannot be escaped or ignored. The properties of a powder affect the formulation processes of a dosage form, as well as the after formulation stages, i.e. dissolution and drug bioavailability. This direct influence of the properties of a powder on pharmaceutical dosage forms requires that an intensive study must be conducted to investigate the powder properties of a specific drug substance, prior to formulation. Powder can be characterised according to its particle size and size distribution, shape and surface properties, and its flowability. All of these properties have one or more effect(s) on the different stages of pharmaceutical processes and can be manipulated to suit the requirements.

Chapter 2 dealt with the tablet formulation processes. Tablets are the most common pharmaceutical dosage form available. Nevirapine is also mostly presented in tablet form. Tablets, like any pharmaceutical dosage form, should be of a specific standard. Tablets should be mechanically, chemically and biologically stable, should be uniform in weight and dose content, and most importantly, it should be able to release the drug after oral administration in a reproducible manner. There are two methods of tablet production, namely direct compression and the granulation method. Tablets are produced by a tablet press machine. The actual process of tablet production consists of die filling, tablet formation and tablet ejection. These stages were discussed in Chapter 2.

Tablets are not only the compression of the active ingredient. There are several other ingredients, called excipients, that are included to ensure that pharmaceutically acceptable tablets are produced. The different types of excipients were discussed in Chapter 2.

In Chapter 3, a thorough overview of nevirapine was presented. From this overview, the newly discovered nevirapine form IV occupied the centre of this study. According to earlier reports, nevirapine form IV is highly unstable at room temperature conditions and transforms almost immediately into form I. Upon transformation, nevirapine form I presents as a finely powdered material, instead of the usual agglomerates of raw material. This observation warranted a study of the powder and the tableting properties of the resultant, finely powdered material, in comparison with the commercially available, anhydrous nevirapine raw material.

Chapter 4 dealt with the different techniques used for the characterisation of powders. These techniques were used in this study to characterise the two batches of powder. The following properties were investigated: 1) Particles size and size distribution, 2) Particle shape and surface, 3) Powder flowability using angle of repose, critical orifice diameter and Carr's compressibility index and the Hausner ratio, and 4) Solubility and dissolution rate.

The results from the tests undertaken in Chapter 4 were presented in Chapter 5. Based on those results obtained, the following conclusions were reached. Nevirapine raw material may be suitable for both direct and indirect tablet manufacturing. Novel nevirapine powder posed flowability problems and would only be suitable for use if its flow properties could be improved by a granulation process. However, novel nevirapine powder may be the preferred active ingredient, due to its properties that could aid the dissolution of the final product.

Chapter 6 discussed the tablet formulations and production from the two batches of nevirapine powder. Tablets were produced through a wet granulation method, using the single punch tablet press. The tablets were then subjected to the following tablets tests: 1) Friability, 2) Crushing strength, 3) Disintegration, 4) Dissolution, and 5) Weight variation. The procedures were described in Chapter 6, whereas the results from these tests were presented in Chapter 7. The results showed that,

those tablets that had been produced from the novel nevirapine powder, had several advantages over those, produced from the nevirapine raw material, such as better mechanical strength and dissolution properties.

Small changes in the powder characteristics can have a significant effect on its subsequent processing. The change in the powder properties of nevirapine had proven this statement. There were significant differences in the flowabilities and solubilities of the two nevirapine powders, as well as in their respective tablet properties. Novel nevirapine powder had poor flowability, while offering better solubility. Its poor flowability rendered the production of tablets by direct compression practically impossible. The tablets produced from the novel nevirapine powder showed advantageous properties. Further studies are, however, recommended in order to improve the flowability of the fine, novel, nevirapine powder and to further establish its promising potential to produce effective tablets without prior milling, as is currently being practiced.

A comparison between the tableting properties of nevirapine novel powder and commercially available raw material

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Introduction

Nevirapine is a potent, non-nucleoside reverse transcriptase inhibitor used in combination therapy for treatment of HIV infection and AIDS. Nevirapine is the first FDA approved non-nucleoside reverse transcriptase inhibitor (NNRTI) and was approved in 1996. “Nevirapine does not exhibit isomerism but does exhibit polymorphism and is known to exist in the hemihydrate and anhydrous forms” (European Medicine Agency 2004). Several nevirapine crystalline forms have recently been discovered and others are patented (Reguri, Chakka 2006, Caira, Stieger et al. 2007).

Active pharmaceutical ingredients (APIs), including nevirapine, generally pass through the crystallisation process before being processed into a desired dosage form. This is in order to select the most stable form that will give good formulation and drug product performance. Physico-chemical properties of pharmaceutical concern include polymorphic form, drug stability, dissolution rate, crystal/particle size, morphology, surface properties, bulk density, and flowability among others.

It can not be disputed that many of these properties have a significant effect on the subsequent formulation of the final product. This study stems its interest on the newly discovered nevirapine form IV by Stieger *et al.* (2009). According to this study, nevirapine form IV is highly unstable at room temperature conditions and transforms into form I with ease at room temperature. What is interesting upon transformation is that, instead of forming usual agglomerates of raw material, it disintegrates into a fine powdered material. The aims of this study were to characterise the particle and powder properties of the discovered nevirapine powder and their influence on its tableting in comparison with commercially available nevirapine raw material. In this study, the discovered nevirapine powder shall be referred to as nevirapine novel powder.

Material and methods

The materials used in this study were commercially available anhydrous nevirapine raw material, manufactured by Anhui Biochem United Pharmaceuticals, China. The nevirapine novel powder was prepared in-house, according to a novel method of preparation (as described below). For tableting purpose the materials are indicted in table 1.1. All other reagents used were of analytical grade.

Table 1.1: Composition of the nevirapine formulation

Ingredient	Purpose	% content
Nevirapine	Active ingredient	50
Lactose monohydrate (Flowlac [®] 100 – lot: 04492)	Filler	42
Povidone k30 (Kollidon [®] 30 – lot: 8605852240)	Binder	5
Croscarmellose sodium (Ac-di-sol [®] – lot: T017C)	Disintegrant	2
Magnesium stearate (lot: 01214)	Lubricant	1

Novel method for preparation of nevirapine novel powder

The fine powdered anhydrous nevirapine was prepared as described by Stieger *et al.* (2009). Commercially available anhydrous nevirapine raw material was dissolved in methanol through heating (at about 100°C) based on the following master formula:

<u>Ingredient</u>	<u>Quantity</u>
Anhydrous nevirapine	1 g
Methanol	50 ml

The clear obtained solution was immediately refrigerated to obtain nevirapine form IV. Nevirapine form IV was removed from the mother liquid and then dried in an oven at an average temperature of 30°C to obtain fine powdered anhydrous nevirapine form 1. The fine powdered nevirapine form 1 can also be obtained at ambient conditions. The oven was used to facilitate consistency since under high humidity agglomerates may form instead of the fine powder.

Authentication of nevirapine novel powder polymorphic form

Before tests could be executed, measures were taken to ensure that the nevirapine novel powder was similar to nevirapine raw material in terms of polymorphic form. This procedure ruled out any influence of differences in polymorphism in these studies. This was achieved using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). In this study, a DSC-60 Shimadzu instrument (Shimadzu, Kyoto, Japan) was used to determine melting points and phase transitions at a heating rate of 10°C/min. A PANalytical Empyrean

diffractometer (PANalytical, Almelo, Netherlands) was used to obtain the X-ray diffractograms. Measurement conditions of target, Cu; voltage, 40 kV; current, 30 mA; divergence slit, 2 mm; antiscatter slit, 0.6 mm; detector slit, 0.2 mm and monochromator scanning speed, 2° /min (step size, 0.025°; step time, 1.0 sec.), were used.

Particle and powder properties

Particle shape and surface characterisation

The particle shape and surface characteristics were studied using a FEI Quanta 200 environmental Scanning electron microscope (ESEM) (Philips, Eindhoven, The Netherlands) operating under high vacuum conditions at 10 kv. The samples were mounted on double-sided conductive carbon tabs to ESEM-stubs and dusted with an inert gas. The samples were subsequently sputter-coated with 20 nm gold/palladium (60:40). An Eiko[®] ion coater (model IB-2, Eiko Engineering, Japan) was used in all coating procedures.

Particle size and particle size distribution

The mean particle size and size distribution were measured by laser diffraction using the Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK) fitted with a Hydro 2000SM cassette. Distilled water prepared by Millipore[™] Milli-Q[®] Ultrapure Water Purification system (USA) was used to aid in the dispersion of all samples.

Bulk Density and Tapped Density

Bulk and tapped densities were determined using the methods outlined in the BP. Each sample was passed through a no. 18 sieve prior to the determination. Without compacting, approximately 100 g and 60 g of raw material and fine powdered material respectively were introduced into separate pre-weighed dry 250 ml graduated cylinders and the unsettled initial volumes were recorded. The bulk densities, in g per ml, were calculated according to the following equation:

$$\text{Bulk Density} = \frac{\text{Sample Weight (g)}}{\text{Initial Volume (ml)}}$$

For tap density, the cylinders were then vibrated for 60 minutes on a Fritsch[®] analysette (type 30.502) at amplitude of 10 to obtain tapped volumes. The tap densities were calculated according to the following equation:

$$\text{Tap Density} = \frac{\text{Sample Weight (g)}}{\text{Tapped Volume (ml)}}$$

All densities were determined as the mean of 3 measurements.

Carr's compressibility index

The bulk and tapped densities were used to calculate Carr's compressibility index to provide a measure of the powder flow properties.

$$\text{Compressibility Index} = 100 \times \left(\frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right)$$

where ρ_{tapped} is the tap density (g/ml) and ρ_{bulk} is the bulk density (g/ml). Higher Carr's compressibility index represent greater interparticle interactions and hence poor flowability.

Tableting

Formulation process

Tablets were prepared by traditional wet granulation. Nevirapine powder from each batch was firstly mixed with lactose monohydrate (Flowlac® 100). The powder mixture was then mixed with the granulating fluid (the granulating fluid prepared by dissolving the required amount of binder into pre-boiled distilled water). The water was used while still hot to obtain optimum solution of the binder) to form a wet mass. The resultant wet mass was subsequently forced through a 1000 μm sieve to form granules. The sieved wet granules were then dried using an oven set at 100°C for 24 hours. The obtained dry granules were then gently forced through a 500 μm sieve to produce granules suitable for compression. The granules were then mixed with the remaining ingredients i.e. croscarmellose sodium (Ac-di-sol®) and magnesium stearate. The mixture was then compressed into tablets.

Compression

Tablet production involves the compression of loose powder particles into a compact tablet. Compression of tablets, where applicable, was performed on a Cadmach single stroke tablet press (Ahmedabad, India) equipped with a 10 mm flat-with-bevel-edges punches. The die volume was adjusted to produce tablets of theoretical weight of 400 mg.

Weight variation

The test was carried out in accordance with the British Pharmacopoeia (BP). Twenty (20) tablets were individually weighed using an analytical balance. The tablets were randomly selected and dusted prior to weighing. The average weight was then determined.

Friability

The test was performed in accordance with the British Pharmacopoeia (BP) (British Pharmacopoeia 2009). Twenty (20) tablets from each batch were subjected to a uniform tumbling motion of 25 rpm for 4 minutes using the Roche® friabilitor. The tablets were dusted and weighed on the analytical balance prior to and after executing the test. The percentage weight loss was calculated using the following formula:

$$\%F = 100 \times (W_0 - W_1) / W_0$$

Where:

%F – is percentage weight loss;

W_0 – is total weight of the tablets before the test; and

W_1 – is total weight of the tablets after the test.

Crushing strength

To determine the crushing strength of the tablets, the 15 tablets were individually placed between the platens of the crushing strength tester (Pharma Test®, PTB-311, Switzerland). The test button was pushed and the instrument gave a visual reading of tablet crushing strength which was recorded.

Results and discussion

Authentication of nevirapine novel powder polymorphic form

Both the DSC trace (figure 1.1) and the XRPD (figure 1.2) confirmed the transformation of form IV to form I (anhydrous nevirapine). The transformation to the stable form I occur at ambient temperature or could be placed in an oven for a quicker transformation time.

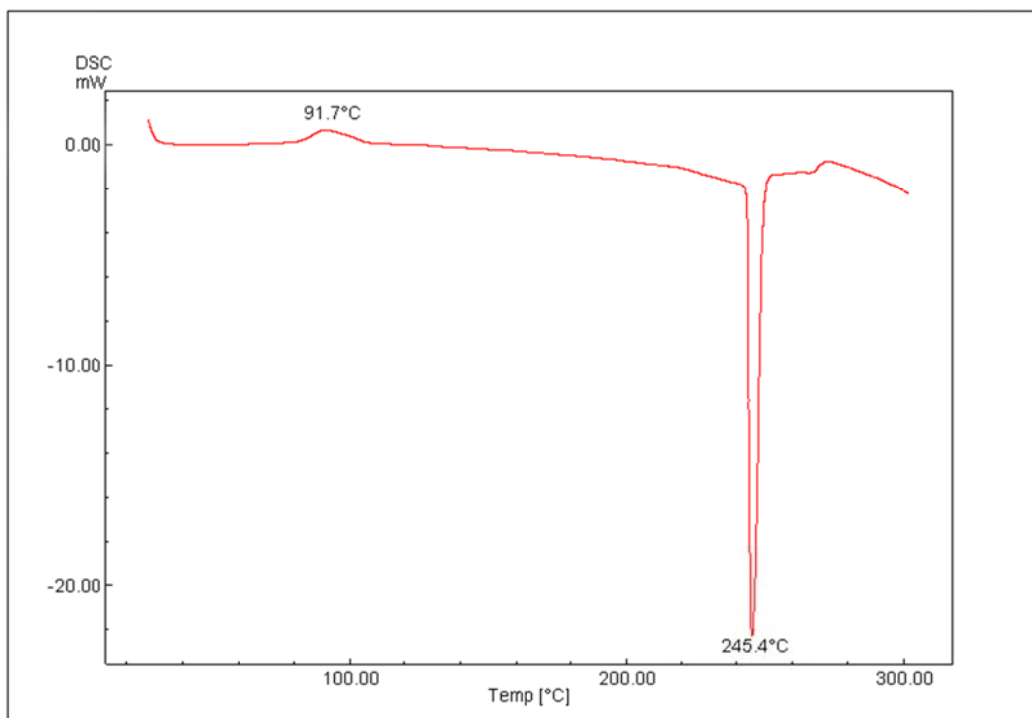


Figure 1.1: DSC trace of metastable form IV showing a phase transformation at 91°C (Stieger, 2009).

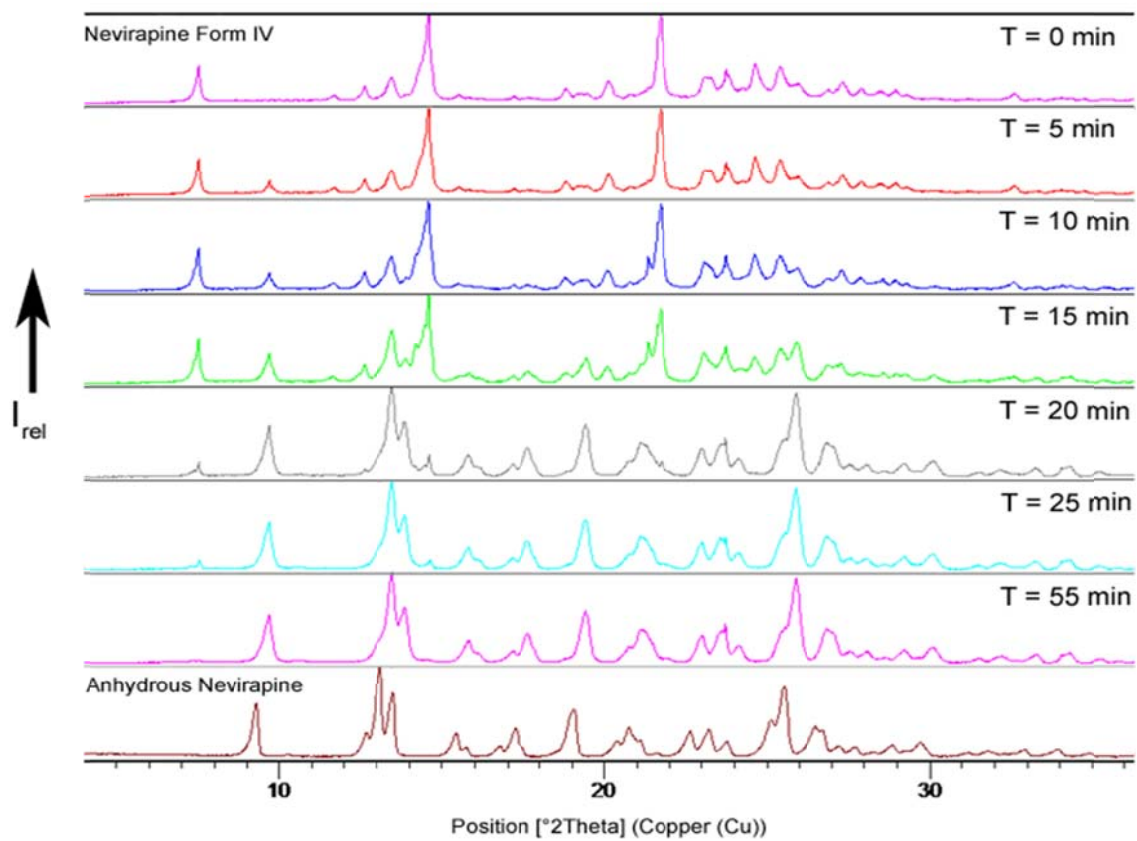


Figure 1.2: XRPD pattern of form IV (top) and transformation to the anhydrous form over time at ambient temperature.

Particle and powder properties

SEM photomicrographs are presented in figures 1.3 and 1.4. These micrographs showed that the two batches of nevirapine powder had distinct particle morphology and size. Commercially available nevirapine raw material (figure 1.3), which has been subjected to milling, consisted of equant-blocky shaped particles. The nevirapine novel powder consisted of relatively plate-like shaped particles with irregular edges. Commercially available nevirapine raw material had a smooth compact particle surface whilst the fine powdered nevirapine prepared by a novel method had cracks on the particle surface. A high magnified photomicrograph of nevirapine powder prepared by this novel method is presented in figure 1.5 to provide a clear view of its surface. The cracks on the surface of the nevirapine novel powder are a distinct characteristic of unmilled particles. During milling, the cracks are taken as an advantage to achieve reduced particle size with less energy consumption. Based on the SEM photomicrographs, it can be further clearly distinguished that commercially available nevirapine raw material had particles of larger size. This was well supported by the results from laser diffraction particle size analysis (table 1.2).

Table 1.2 Particle size distributions of nevirapine raw material and of novel nevirapine powder

Material	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)
Nevirapine raw material	30.740167 ±5.0303449	129.0352 ±12.55036	286.5667 ±16.59585
Novel nevirapine powder	19.347667 ±2.1881401	45.5155 ±3.266414	93.97783 ±4.709396

The results on particle size and particle size distribution are represented in table 5.1. It is evident from the table that the batches of nevirapine differed markedly. Nevirapine novel powder had a mean median particle size (D_{50}) of 45.5155 μm, approximately one third to that of nevirapine raw material (D_{50} – 129.0352 μm). Nevirapine novel powder also exhibited a narrow particle size distribution (figure 5.4). According to the BP classification of powder

by fineness (table 5.2), nevirapine raw material is considered a fine powder whilst nevirapine novel powder is considered a very fine powder.

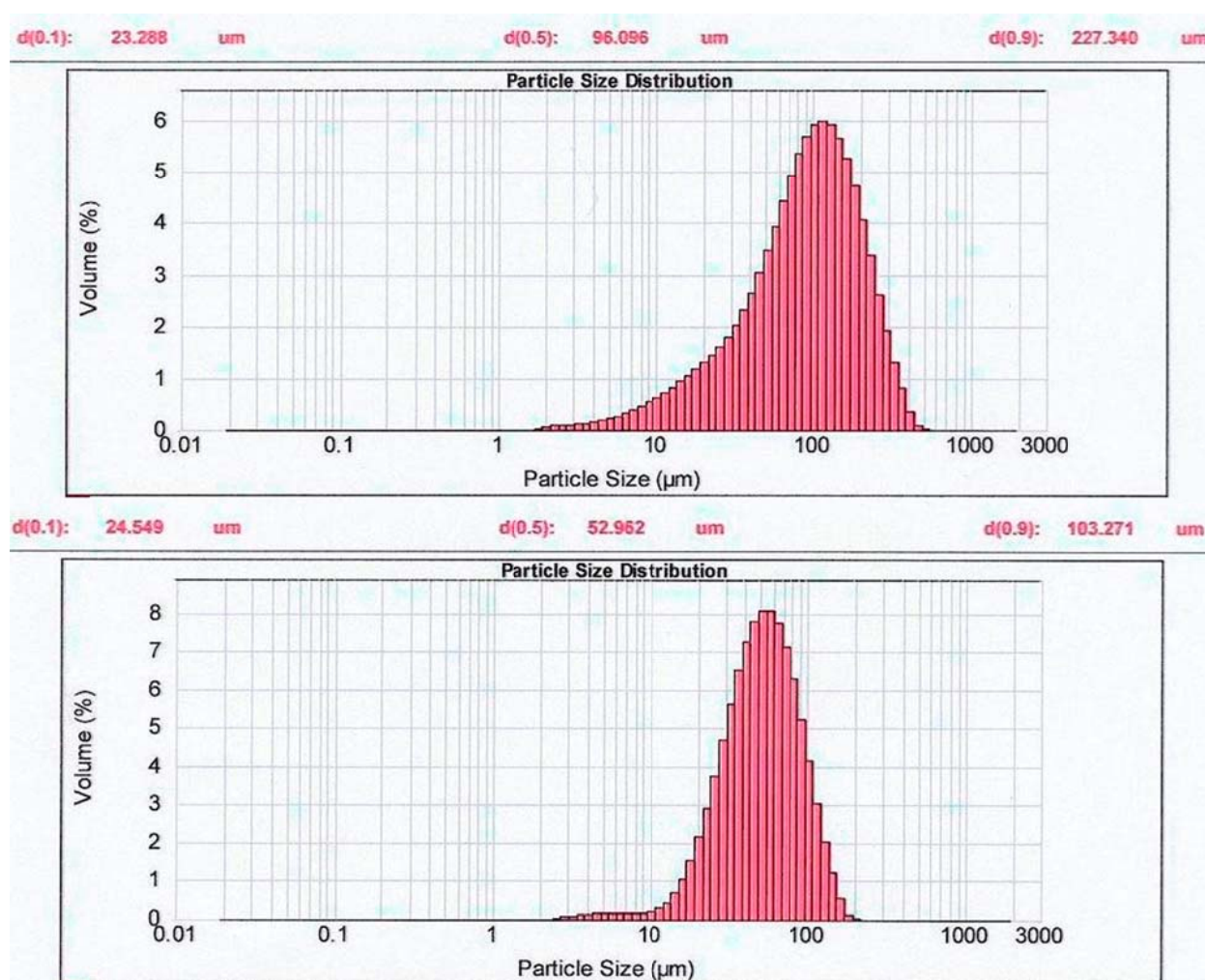


Figure 1.3: Histograms obtained from the particle analysis of nevirapine raw material and nevirapine novel powder respectively.

Table 1.3: Classification of powder according to its measure of fineness (British Pharmacopoeia, 2009)

Classification of powders by fineness	
Descriptive terms	x_{50} (μm)
Coarse	> 355

Moderately fine	180 – 349
Fine	125 – 179
Very fine	< 125

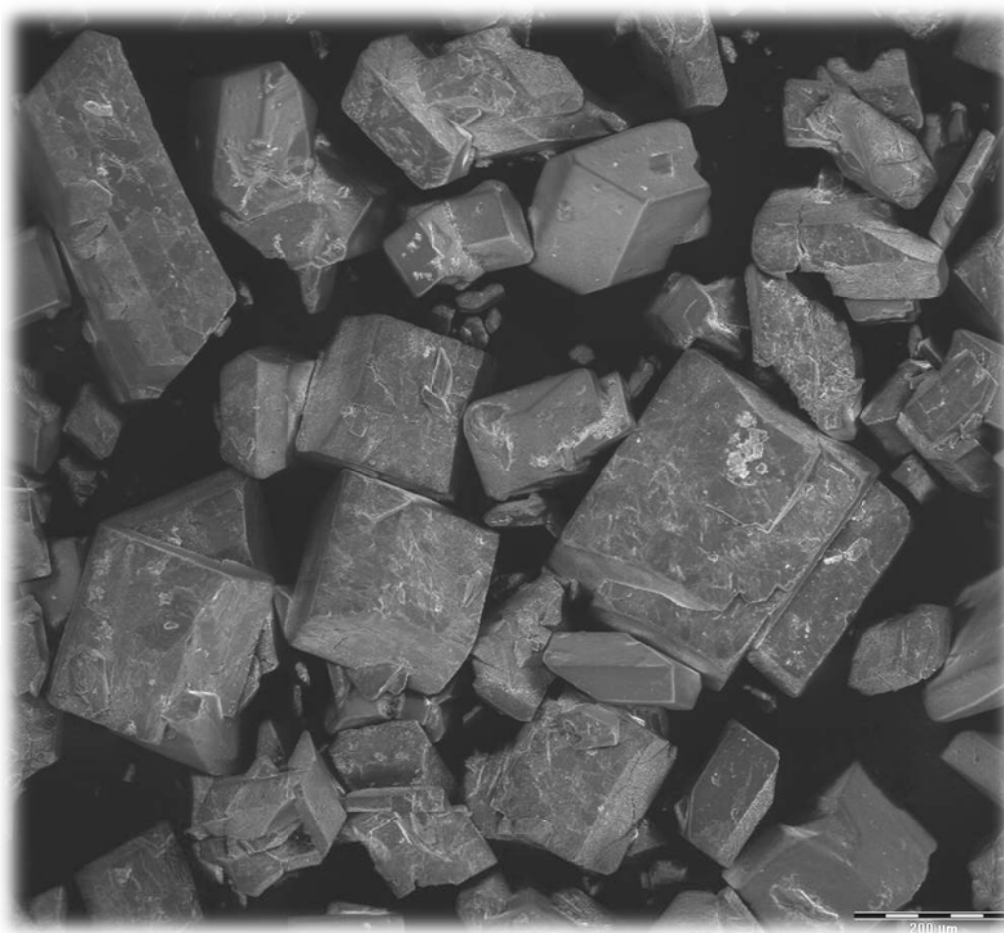


Figure 1.4: SEM Photomicrographs of purchased nevirapine raw material



Figure 1.5: SEM Photomicrographs of nevirapine powder subjected to novel method of size reduction

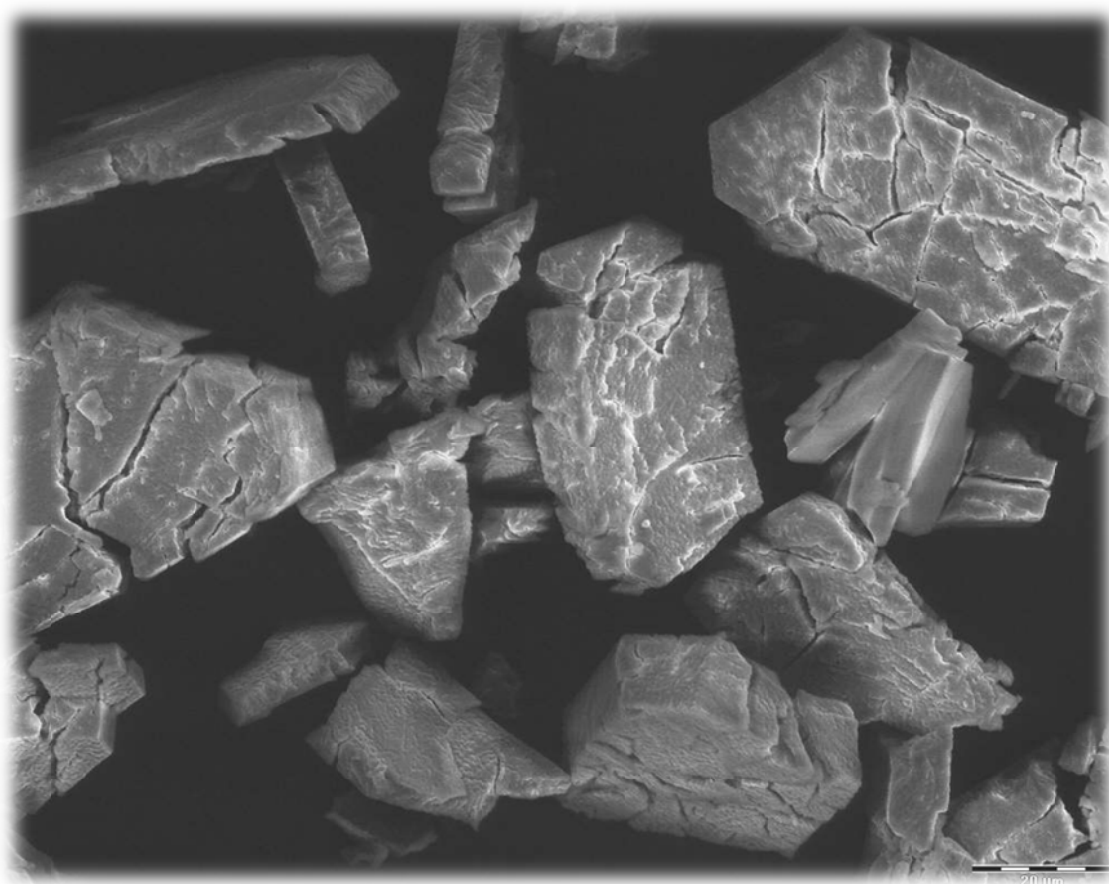


Figure 1.6: SEM Photomicrographs of nevirapine powder subjected to novel method of size reduction under high magnification.

Powder flow characterisation

Compressibility index

The Carr's compressibility index for nevirapine raw material is 3.878563 (table 1.4). According to the BP scale of flowability in table 1.5, this index is indicative of excellent powder flow. As for nevirapine fine powdered material, the obtained value was 21.28803 and it is an indicative of poor powder flow. The results on powder flow characterisation correlated well with the particle size and surface characteristics. The overall results show that nevirapine raw material has superior flow properties to nevirapine novel powder. It is, however, worth noting that the nevirapine fine powdered material differed markedly from the raw material. This can be attributed to the particle properties of nevirapine novel powder and raw material. Nevirapine raw material consisted of large equant-blocky shaped particles with smooth surface and hence it exhibit good powder flow properties as compared to nevirapine novel powder (Hoag, LIM 2008). Nevirapine had small irregular plate-like particles with cracked surface and hence its undesirable flow properties. The irregular shape of fine powdered nevirapine and its associated cracks is thus assumed to promote particle-particle interlocking with the resultant poor powder flow. This may be the reason for the observed cohesive arch during the determination of the critical orifice diameter.

Table 1.4: Flow parameters of the two samples of nevirapine powder

Material	Densities (g/ml)		Compressibility index (CI)
	Bulk	Tapped	
Nevirapine raw material	0.581448 ±0.006761*	0.604932 ±0.009182	3.878563 ±0.373408
Nevirapine fine powder	0.365151 ±0.004651	0.463942 ±0.004164	21.28803 ±1.379494

* The average of three measurements ± the standard deviation.

Table 1.5: BP scale of flowability for Carr's compressibility index

Flow character	Compressibility index (%)
Excellent	≤ 10

Good	11 – 15
Fair	16 – 20
Passable	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very, very poor	>38

Weight variation

The results from weight variation test are summarised in table 1.6. All the tablets comply with the BP specifications, which stated that not more than 2 of the individual tablet weights should deviate from the average weight by more than the percentage deviation shown in table 1.7. The consistence of the tablet weights show that the use of the wet granulation method was an improvement in the flowability of the material, in particular that which contains nevirapine novel powder.

Table 1.6: The weight variation results and the calculated BP acceptable range

Formulation	Weight variation (mg)*	BP acceptable range**
Raw material F1	401.05 ±0.002946	380.9975 – 421.1025
Novel powder F1	407.682 ±0.002715	387.2979 – 428.0661
*As an average of 20 determinants		
**Calculated according to BP acceptable weight variation (British Pharmacopoeia 2009).		

Table 1.7: The BP guideline on tablet weight variation*

Tablet formulation	
Average mass	Percentage Deviation
80 mg or less	10
More than 80 mg and less than 250 mg	7.5
250 mg or more	5
*not more than 2 of the individual masses must deviate from the average mass by more than the percentage deviation shown	

Physical strength: Friability and crushing strength

Results from friability and crushing strength tests for all formulations are summarised in table 1.8. Results from friability test have shown that all tablets produced from nevirapine raw material and the novel powder passed the BP specifications. The BP states that the tablets should not lose more than 1% of their total weight (British Pharmacopoeia 2009). However, there was difference in terms of their % friability. Tablets produced from nevirapine novel powder had lower % friability than those produced from nevirapine raw material. The percentage difference in % friability was at least 14 %.

The results from crushing strength tests coincided with those from friability tests. Tablets produced from nevirapine raw material had a crushing strength of 44.27778 N and tablets produced from nevirapine novel powder had a crushing strength of 71.86667 N (table 1.8).

The results from friability and crushing strength tests have shown that tablets produced from nevirapine novel powder exhibit greater mechanical strength than those produced from nevirapine raw material

Table 1.8: The Friability and crushing strength results

Formulation	Friability (%F)	Crushing strength (N)*
Raw material	0.81	57.83333 $\pm$ 1.917412
Novel powder	0.66	71.86667 $\pm$ 3.62268
*As an average of 15 tables		

Conclusion

Analysis of particle size and surface properties has shown that the two nevirapine powder batches have markedly different properties. The observed differences between the two nevirapine powder batches are of pharmaceutical importance. They may have beneficial and/or deleterious effects during powder processing and dosage formulation. Nevirapine novel powder had small particles which may be important in terms of improving the dissolution of nevirapine (Jinno, Kamada et al. 2006). On the other hand, these small particles were deleterious in terms of its flowability.

From the tablet analysis in this study, it could be concluded that the initial particle size of the nevirapine had an influence in most of the results. A clear correlation between the particle and tablet properties was established. Tablets produced from nevirapine novel powder were in terms of mechanical strength. At the same time, nevirapine novel powder had the smallest particle size, plate-like shaped particles with irregular edges and cracked particle surface. It can thus be assumed that nevirapine novel powder had greater interparticle contact points and large bonding surface hence the stronger tablets produced. These results are in parallel with several studies that tablets from small particles have better

physical strength (Alderborn 2007, Conway 2008, Sebhatu, Alderborn 1999). Further studies on this nevirapine novel powder are recommended to establish a full round advantages it may offer.

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