Cassava starch as modified release excipient in selected gliclazide oral dosage forms

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Our deepest fear is not that we are inadequate. Our deepest fear is that we are powerful beyond measure. It is our light, not our darkness, that most frightens us. We ask ourselves, who am I to be brilliant, gorgeous, talented, fabulous? Actually, who are you not to be? You are a child of God. Your playing small doesn't serve the world. There's nothing enlightened about shrinking so that other people won't feel insecure around you. We are all meant to shine, as children do. We were born to make manifest the glory of God that is within us. It's not just in some of us; it's in everyone. And as we let our own light shine, we unconsciously give other people permission to do the same. As we're liberated from our own fear, our presence automatically liberates others.

Marianne Williamson

~||~

Dedicated to those who've never stopped praying for me, my mentors and loved ones.

FOREWORD

A great journey has many steps and obstacles. To attempt such a journey requires, patience, perseverance, passion and fortitude. Each of these is necessary but they alone cannot sustain any endeavor as this. Where, these personal strengths falter support, care and guidance from loved ones and mentors, sustain you through trying times, times when failure seems to be the inevitable outcome. This in mind, I would like to give my sincerest gratitude to the following:

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Abstract

Cassava starch as modified release excipient in oral dosage forms using gliclazide as model drug

Solid oral dosage forms are still the most leading delivery system employed commercially due to the ease in which it can be handled, administered and even transported. Several varieties of solid oral dosage forms are commercially available which include different types of tablets, capsules, multi-unit particulate systems as well as medicated lozenges. Different designs and manufacturing methods are used for solid oral dosage forms resulting in different release mechanisms. Drug release is an important consideration during dosage form design especially for drugs with short half-lives. These types of drugs require regularly timed dosing intervals. More dose intervals can impede the adherence to therapy, because patients might forget a dose. The lack in adherence adversely affects the treatment protocol necessary for the management of disease. To overcome adversities and to modify drug release, various methods can be employed in order to provide a desirable therapeutic product, including alternative manufacturing methods and the addition of specialised excipients. One of the most promising manufacturing methods to date regarding modified release, whether sustained, controlled or multi-dose release, is the production of pharmaceutical pellets, more commonly known as beads. Several methods can be employed in order to produce beads. For this study it was opted to use a method, which has extensively been researched since the 1950s known as extrusion-spheronisation.

Starches and starch based products have been utilised for many years as multifunctional excipients in the production of solid oral dosage forms. For instance, starches have been used as fillers, binders and disintegrants. The polymer rich matrix of a starch makes it highly versatile in these applications. Furthermore, the low cost involved in manufacturing or sourcing starch and starch based products, also makes it a commercially viable alternative to other market available excipients which might be more expensive. Cassava is one of the world's most predominant sources of starch. It is globally grown and sourced in sub-tropic environments. Being a sustainable product which produces a high yield of starch, this study investigated the applicability of cassava starch as a filler in bead formulations using gliclazide as model drug.

Physical characteristics and flowability of cassava starch were evaluated with various methods, which included thermo-analysis, moisture content, infrared spectrometry, and flow properties. Beads were evaluated in order to determine whether extrusion-spheronisation improved the flow of the starch. The physical characteristics such as friability, swelling and erosion, and disintegration were also evaluated. Dissolution testing and analysis provided profiles which were assessed and compared to a commercially available product, Diamicron®.

It was evident from the study that cassava is not the ideal filler to include in the manufacture of beads, even though a single cassava bead formulation did provide prolonged release of the drug over a 12 h period. Approximately 60% of the drug was pharmaceutically available within the first 30 min of dissolution assessment and the remaining 40% dissolved slowly over the remaining duration of the study. The dissolution profile obtained for this particular formulation correlated with the arbitrary release profile of sustained drug release. It could therefore be concluded that a product could indeed be produced which may be a viable candidate as a commercially substitute for the current commercially available product, in terms of cost-effectiveness and sustainability. From the study it was also evident that Avicel® provided a better prolonged release profile in terms of mean dissolution time. Avicel® formulations proved to render the most similar release profiles to that of the reference product, Diamicron®.

Keywords: Cassava, Starch, Extrusion-spheronisation, modified release, solid oral dosage forms (SODFs), flowability, powder flow. Gliclazide, Avicel®, beads, microcrystalline cellulose (MCC)

Uittreksel

Kassawestysel as ’n vrystellings-modifiserende hulpstof in vaste doseervorms met gliklasied as modelgeneesmiddel

Orale vaste doseervorms is die gewildste geneesmiddelafleweringssisteme wat kommersieel beskikbaar is. Hierdie gewildheid kan toegeskryf word aan die gemak waarmee dit hanteer, toegedien , en selfs vervoer word. Verskeie tipes orale vaste doseervorms is kommersieel beskikbaar insluitend tablette, kapsules, meervoudige partikulêre sisteme en suigtablette. Verskillende ontwerpe en vervaardigingsmetodes word gebruik in die bereiding van vaste doseervorms ten einde verskillende tipes geneesmiddelvrystelling te verkry. Geneesmiddelvrystelling is ’n uiters belangrike oorweging tydens doseervormontwerp, veral vir geneesmiddels met kort halfleeftye. Geneesmiddels met kort halfleeftye benodig gereelde doserings op spesifieke tye. Meervoudige doseerskedules kan tot swak pasiënt-meewerkendheid lei, wat kan lei tot een of meer oorgeslane dosisse. Swak pasiëntmeewerkendheid veroorsaak ’n afname in behandelingseffektiwiteit. Ten einde hierdie struikelblokke te oorkom en geneesmiddelvrystelling te verbeter, word verskeie metodes ingespan, onder andere, alternatiewe vervaardigingsmetodes en die gebruik van spesiale hulpstowwe. ’n Belowende vervaardigingsmetode wat tans baie navorsingsaandag ontvang om verbeterde geneesmiddelvrystelling, hetsy dit verlengde, beheerde of meervoudige dosisvrystelling behels, is die vervaardiging van farmaseutiese korrels, byvoorbeeld krale. Verskeie vervaardigingsmetodes kan gebruik word om krale te vervaardig. In hierdie studie is daar gebruik gemaak van ’n metode wat sedert die 1950s breedvoerig nagevors is, naamlik uitpers-sferonisering.

Stysels en styselgebaseerde produkte word al vir jare as multifunksionele hulpstowwe in die vervaardiging van orale vaste doseervorms gebruik. So byvoorbeeld word stysel of stysel-gebaseerde produkte onder andere as vulstof, bindmiddel en disintegreermiddel aangewend. Die polimeerryke matriks verleen aan stysel die vermoë om as multifunksionele hulpstof gebruik te word. Die lae vervaardigingskoste asook maklike verkryging van stysel en styselgebaseerde produkte maak dit ’n kommersieel aanvaarde alternatief as plaasvervanger vir duurder hulpstowwe. Die Kassaweplant is een van die wêreld se mees algemene bronne van stysel. Dit kom wêreldwyd voor in subtropiese gebiede. Omdat dit ’n volhoubare bron is, wat ’n hoë

stysel-opbrengs lewer, is daar in hierdie studie ondersoek ingestel na die bruikbaarheid van Kassawestysel as vrystellingsmodifiserende hulpstof in die bereiding van krale.

Die fisiese eienskappe en vloeibaarheid van kassawestysel is gekarakteriseer met die gebruik van verskeie metodes, waaronder termiese analise, voginhoudbepaling en infrarooi-spektrometrie. Bereide krale is ook geëvalueer in terme van swelling, verbrokkeling, disintegrasie en dissolusiegedrag.

Die resultate van die studie het getoon dat kassawestysel nie optimale krale gelewer het nie. Ten spyte hiervan het ŉ enkele kassawe-kraalformulering verlengde vrystelling van gliklasied oor ŉ 12 h tydperk getoon. Ongeveer 60% van die geneesmiddel is binne die eerste 30 min. vrygestel, en die oorblywende 40% is in die oorblywende tyd van die studie vrygestel. Die dissolusieprofiel het ooreengestem met die arbitrêre vrystellingsprofiel vir volhoude geneesmiddelvrystelling. Vanuit die data kon gesien word dat die moontlikheid bestaan om ŉ formulering te berei wat oor die potensiaal beskik om huidige kommersieel beskikbare produkte, in terme van koste-effektiwiteit en volhoubaarheid, te vervang. Avicel® (mikrokristallyne sellulose), - tans die standaard vir kraalbereiding — is ook in die studie gebruik om as maatstaf vir kassawestysel te dien. Uit die resultate was dit duidelik dat Avicel® ŉ beter verlengde vrystellingsprofiel verskaf het in terme van die gemiddelde dissolusie tyd. Avicel®-formulerings het ook bewys dat die vrystellingsprofiel van die verwysingsproduk, Diamicron®, nageboots kan word onder spesifieke eksperimentele toestande.

Sleutelwoorde: Kassawestysel, uitpers-sfeervorming, gemodifiseerde vrystelling, vaste orale doseer vorme, dissolusie studies, vloeibaarheid, poeiervloei, gliklasied, Avicel®, krale, mikrokristallyne sellulose.

Chapter 1

AIMS AND OBJECTIVES

1.1 AIM

The aim of this study was to investigate the possible application of cassava starch as an excipient in a modified release solid oral dosage form. In conjunction with this investigation it was also considered prudent to investigate the effects of using a multi-unit pellet (or particulate) system as a modified release solid oral dosage form.

1.2 BACKGROUND

Changes in economies and socio-economic diversity as a result of globalisation and the growth in consumerism have had both advantageous and disadvantageous consequences; e.g. improved transport infrastructure, communication systems, energy generations, increased health risks and increased levels of unemployment (Reddy *et al*., 2006:1-9; Storper 2000: 107-114). This is especially evident on the African continent. An area of concern, however, not only on the sub-Saharan African continent, but also in developed economies such as Europe, Japan and Northern America, is lifestyle dependent health risks. Lifestyle dependent health risks in developed nations are a result of increased consumerism and an ever decreasing labour intensive lifestyle (Badawi *et al.*, 2004:76), whereas sub-Saharan Africa and other global counterparts have increased health risks as a result of limited or no access to sufficient resources, e.g. medical personnel, medical equipment and medication. Consequences of health risks include sexually transmitted infections, low infant mortality rate, low female health care and even the escalation in lifestyle dependent health risks. The latter is brought forth not only by urbanisation but also the impoverishment of economically unstable nations (Addo *et al*., 2007:1013; Meyrowitsch *et al*., 2007:32).

One of the most common lifestyle dependent health concerns is certainly insufficient glycaemic control (Zimmet *et al.,* 2001:782). Hyper- and hypoglycaemia are two pathological manifestations of insulin insufficiencies, brought on either by defects in insulin secretion or desensitised tissue response to insulin and glucose levels. In this study; only hyperglycaemia was addressed.

The most predominant disease characterised by hyperglycaemia is diabetes mellitus type 1 (DMT-1) and 2 (DMT-2). DMT-1 is noted as absolute insulin insufficiency which characteristically manifests in younger individuals, brought on by auto-immune-like degradation of the insulin producing beta-cells located within the pancreas. DMT-2 is of slower onset, manifesting in older individuals, caused predominately by individual lifestyles. DMT-1 is managed by the frequent subcutaneous administration of exogenous insulin, possibly in conjunction with oral medication. In contrast, due to its origin, DMT-2 is mainly managed by lifestyle changes. Followed by therapies which include oral anti-diabetic medication, as first choice regime. If these measures are inefficient at addressing DMT-2 pathophysiology subcutaneous insulin can be employed as add-on therapy (Delamater, 2006:71).

Solid oral dosage forms (SODFs) are preferred, not only in anti-diabetic therapy but also in other treatment protocols. These dosage forms are easier to administer to conscious patients; requires little to no organoleptic consideration; needs little aseptic handling; can easily be stored and transported; and added increased patient compliance with a decreased dosing interval. In contrast to all these advantages, several disadvantages are also present, which include administration difficulties for younger children, comatose and unconscious patients, delayed action before gastro-intestinal absorption, limited dose capacity per dosage, and limited physical size range of the dosage form. For treatment of diseases, such as diabetes that requires regular control and monitoring, it is prudent to design a user friendly dosage form with ideally, no incompatibilities with the patient's physiological, pathological and lifestyle needs. Due to a lack of an idyllic setting, an ideal product is not possible; however, researchers have attempted to design a near perfect product that might fulfill patient related expectations and requirements. These include, but are not limited to the lower dose load, controlled release of the drug, affordability, sustainability and versatility (Bardonnet *et al.,* 2006:2).

Current oral anti-diabetic therapeutic regimens include biguanides, e.g. metformin; sulphonylureas, e.g. gliclazide; and thiazolidinediones, e.g. rosiglitazone. Biguanides are preferred as a first-line regimen in DMT-2, whereas sulphonylureas are the second class of treatment in later stage diabetic patients. Due to patient lifestyles and psychologies, patients rarely pick-up on early symptoms and dismiss pathologies attributed by other factors in their life (Lebovitz, 1999:1339). As a result, a large portion of diabetics might seek medical attention at such a stage that first-line therapy might be insufficient and second-line therapy needs to be initiated to manage symptoms).

Sulfonylureas, effective in the treatment of DMT-2, have been used as anti-hyperglycaemic therapy since the mid-1950s. For many years this class of active compounds has been one of the pillars of oral anti-diabetic therapy. Gliclazide is a second-generation sulfonylurea, which stimulates insulin secretion by closing ATP-sensitive potassium channels in pancreatic beta cells. It is classified as a weak acidic compound that comprises a larger hydrophobic character than first generation sulfonylureas. Gliclazide also shows a lower tendency to induce hypoglycemic episodes in patients. According to Remko (2009:77) gliclazide's hydrophobicity makes its activity more effective over an extended time duration. However, it is well known that insufficient solubility of active compounds may lead to reduced absorption (Dressman *et al.,* 1998:12). Remko (2009:77) stated that although the second generation sulfonylurea derivatives (including gliclazide) wereslightly soluble (water solubility of 138.4 $mg.l^{-1}$ for gliclazide at 25ºC), they did depict a fast absorption rate. Through formulating gliclazide into a controlled release dosage form (once daily dose), it should be possible to extend its activity from a half-life of approximately 11 h. Characteristically this would increase patient compliance due to fewer dose intervals (Bartels *et al*., 2004:9; Remko *et al.* 2009:77; Vanderpoel *et al*., 2004:2073).

Starches, which were used in this study are characterised by bio-polymers that have multiple applications such as fillers, binders and disintegrants in the pharmaceutical and biopharmaceutical fields. Possible reasons for the use of starches are:

- Cost-effectiveness of the starch,
- The fact that they are renewable materials,
- Available in large quantities,
- Non-toxic,
- Biocompatible, and
- Biodegradable.

In the 1980s it was discovered that certain starches retain unique features that suggest their use as an excipient for the manufacturing of controlled release SODFs. Due to their versatile properties, it is possible to obtain quasi-zero-order pharmacokinetic profiles with a very simple and cost-effective manufacturing process. Tablets produced from starches show low sensitivity in their release profiles towards manufacturing conditions such as tableting pressure (Chitedze *et al*., 2012:32; Lemieux *et al*., 2009:172; Lenaerts *et al.,* 1991:43). Furthermore, high amylose cross-linked starch matrix formulations can be manufactured by using conventional tableting techniques. This kind of technology ranks among the most cost-effective means of

manufacturing controlled release dosage forms for orally administered active compounds (Lenaerts *et al.,* 1998:229).

Cassava is produced in Latin America, Southern Africa, China, United Arab Emirates and India. Its standing as a source of starch is rapidly mounting, particularly due to its low price on the world market when compared to starches from other sources. The potential use of cassava starch as binder as well as a matrix for the development of edible films has previously been considered (Chitedze *et al*., 2012:32; Famá *et al.,* 2006:8; Famá *et al.,* 2007:266). However, little has been studied on its ability to act as a controlled release excipient in orally administered formulations (Casas *et al.*, 2010:72).

1.3 OBJECTIVES

In order to achieve the aims of this study, the following will be done:

1) Characterisation of cassava starch with regards to physical properties, powder flow properties, particle size and morphology.
2) Formulation of beads containing cassava starch as excipient in varying concentrations (gliclazide, a weak acidic active ingredient (pKa of 5.6) which is poorly water soluble, will also be included as a model drug).
3) Evaluation of different bead formulations in terms of their physical properties and drug release profiles.
4) Comparison of different bead formulations, in terms of drug release behaviour, to a commercially available equivalent (Diamicron®, a readily available gliclazide solid oral dosage form was selected for this study).

CHAPTER 2

LITERATURE STUDY

2.1 INTRODUCTION

According to the 2013 fact sheet published by the World Health Organisation (WHO), diabetes is prevalent in approximately 347 million individuals worldwide. Furthermore, the WHO also estimates that diabetes will be the 7th leading cause of death by 2030 (WHO, 2013). In the United States alone, an estimated 17.5 million patients were living with diabetes in 2007 at an estimated cost of US$218 billion (Dall *et al*., 2010:297). By the year 2000, the health cost concerning diabetes in sub-Saharan Africa was an estimated US$67.03 billion, both directly and indirectly to patients and economies within this region. In 2010 an estimated 12.1 million patients were living with diabetes and an estimate of 23.9 million will be living with diabetes by 2030 in this region alone (Hall *et al*., 2011:1-2).

Diabetes mellitus is defined as a chronic disease characterised by insufficient glycaemic control, either due to insufficient insulin production, as in the case of DMT-1, or tissue-insensitivity and insufficient response to insulin, as in the case of DMT-2. For the purpose of this study only DMT-2 will be highlighted (Lebovitz, 1999:1339-1340; WHO, 2013).

In contrast to DMT-1, patients with DMT-2 are of an older demographic and have a slower rate of onset. The leading cause for DMT-2 is lifestyle dependent factors e.g., insufficient cardio-vascular exercise, obesity, stress and inappropriate diets. It should also be noted that genetic and environmental factors contribute to the onset of DMT-2 (Lazar, 2005:374; Lebovitz, 1999:1339-1340).

DMT-2 is described as a dysregulation in insulin and glucose control due to cellular decay of pancreatic beta-cells; this being a result of over stimulation of these particular cells. Consequently, these cells are depleted, or completely desensitised to changes in blood glucose levels. In regards to treatment, all depending on the stage of development, early use of oral antidiabetic medications can be used to improve glycaemic control (Fowler, 2007:131).

These drugs include:

- biguanides, e.g., metformin;
- sulphonylureas, e.g., gliclazide, glibenclamide, glipizide;
- meglitinides, e.g., repaglinide, mitiglinide;
- d-phenylalanine derivatives, e.g., nateglinide;
- thiazolidinediones, e.g., pioglitazone, rosiglitazone;
- α-glucosidase inhibitors, e.g., acarbose, miglitol;
- amylin analogues, e.g., pramlintide;
- glucagon-like-polypeptide 1 (GLP-1) analogues, e.g., exenatide, liraglitide; and
- dipeptidyl peptidase-4 inhibitors, e.g., sitagliptin, saxagliptin, vildagliptin.

Each of these oral drugs targets either the improvement of insulin secretion, or the improvement of tissue-sensitivity to insulin. In advanced cases patients might require exogenous insulin administration in conjunction with oral antidiabetic therapy (Katzung, 2009:737; Lebovitz, 1999:1339-1340; WHO, 2013).

The number of patients diagnosed with chronic and lifestyle diseases such as diabetes, has increased drastically since the industrial revolution (Cordain *et al*., 2005:341-344). With the industrial revolution came a more consumer focused economy. The mechanisation of several industries, for example agriculture, has led to a less labour intensive economy. This paradigm shift is dominant in developed economies, e.g. Europe, Japan and North America. Increased consumerism and decreased physical exertion have led to a more obese population (WPRO, 2007:1-27).

Obesity is a condition characterised by a higher than normal body mass index and an increase in plasma lipids. The increase in lipids within tissues influences the metabolic nature of insulin, credited to the mass number of lipids that needs to undergo lipolysis. This places a strain on insulin production by the pancreatic beta-cells (Day & Bailey, 2011:55-57).

Patients in developing nations such as sub-Saharan Africa, South America and some South Asian countries, lack basic health care, education and nutrition. These disparities are present due to socio-economic, geopolitical and industrial factors (Duraiappah, 1998:2167-2176). Education, healthcare and nutrition are respectively perceived as basic human rights. Due to the disparity present in these nations, individuals are deprived of these basic rights (Kawachi *et al.*, 1997:1491-1498; Wagstaff, 2002:97-102). Insufficient nutrition, may lead to insulin

dysregulation. Instead of maintaining a normal metabolism of glucose and lipids, insulin production begins to reduce and metabolise protein in the body as a source of energy. This dysregulation of insulin homeostasis leads to malnutrition associated pancreatic beta-cell degradation (Taksande *et al*., 2008:19).

On the other hand, insufficient healthcare or the lack thereof, leads to delayed or wrong diagnosis. The patient does not receive primary care or education in regards to proper nutrition and healthcare, for example the identification of symptoms associated with diabetes (Motala & Ramaiya, 2010:9-36). Due to the disparities in primary health care, these patients' insufficient diagnosis or delayed diagnosis, palliative care would be considered redundant and costly. Patients, who do receive any type of treatment, are provided treatment at an unsustainable cost. SODFs are considered less expensive than any other dosage form, but even this can amount to unsustainable expenditure on healthcare (Jewesson, 1996:1; Lajoinie *et al*., 2014:1088-1089).

2.1.1 Treatment of type 2-diabetes

The current first line regimen for DMT-2 is oral antidiabetics. This includes biguanides (metformin), whereas sulphonylureas are considered an add-on, or second line therapy in more progressive patients (Lahiri, 2012:73; Mcculloch, 2014:1-2). In this study, formulation strategies, mainly using sulphonylureas, will be the focus.

Sulphonylureas, a second line treatment for early and progressive DMT-2, was first discovered in the 1950s, with tolbutamide, chlorpropamide, acetohexamide and tolazamide being the model drugs. Current treatment available is mainly second generation sulphonylureas, for example gliclazide, glibenclamide and glipizide (Rendell, 2004:1339).

Sulphonylureas' mechanism of action is based on the closure of the adenosine-triphosphate (ATP)-mediated potassium ion channels involved in the secretion of insulin by the beta-cells. Closure of these channels lead to the exocytosis of insulin in response to an increased concentration of blood plasma glucose. These channels are not completely closed which prevents possible sulphonylurea induced inhibition at high plasma concentrations (Panten *et al*., 1996:1; Rendell, 2004:1339).

2.1.1.1 Gliclazide

Gliclazide (figure 2.1) is poorly water soluble and is rapidly absorbed after oral administration. It is an intermediate acting hyperglycaemic drug, has a plasma protein binding of approximately 96% and is predominantly metabolised by the hepatic system, making it readily susceptible to presystemic metabolism. Peak plasma drug concentrations occur within 3 to 4 h after administration and the drug has a half-life of approximately 12 h.

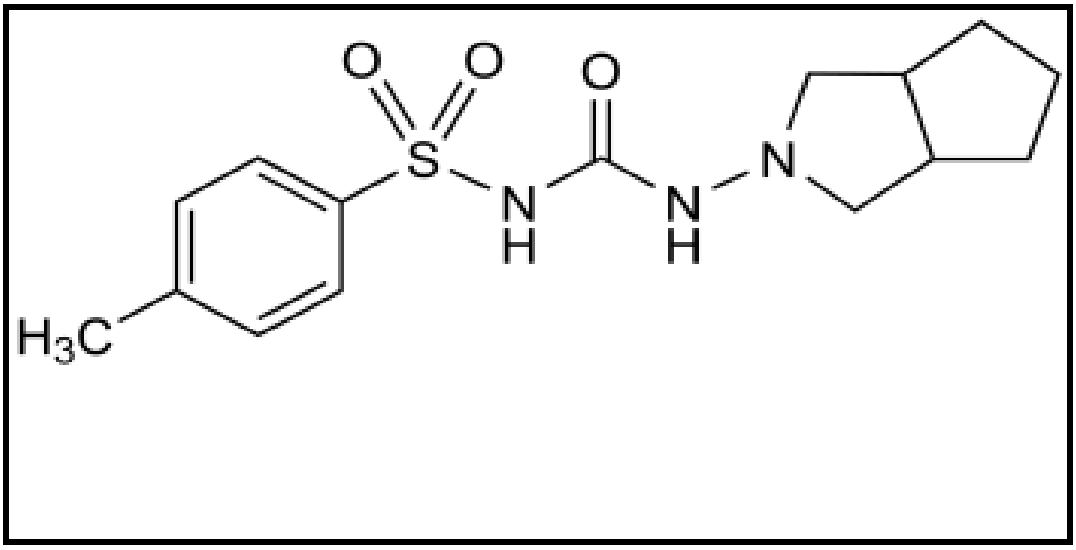


Figure 2.1: Chemical structure of gliclazide

Table 2.1 reflects the physicochemical characteristics of gliclazide. Gliclazide has proven to lead to an increase in insulin secretion in long-term treatment regimens. Due to the efficacious nature of gliclazide in improving insulin secretion, hypoglycaemia is a dominant side-effect and can be worsened by several drugs, for example aspirin, sulphonamides and alcohol. Other adverse effects include cardiac dysregulation, cholestatic jaundice, leucopenia, vomiting, diarrhoea, thrombocytopenia purpura, weight gain, inhibition of alcohol dehydrogenase enzymes; and even cutaneous symptoms, such as photosensitivity (Fowler, 2007:132).

Due to the short half-life of gliclazide, it is predominantly available as a twice daily dose regimen. Multiple dosing intervals increase the complexity of patient compliance. In more complex dosing regimens the possibility of missed doses become more prevalent. With multiple dose intervals a patient requires a larger amount of units. The increase in the amount of units needed, may result in an increase in the cost of therapy per patient (Kardas, 2005:722).

Table 2.1: Physicochemical properties of gliclazide (revised from Drugbank.ca and ChemicalBook.com)

Characteristics	Gliclazide
Chemical Formula	$C_{15}H_{21}N_3O_3S$
Assay	≥ 98%
Form	Powder
Colour	White
Melting Point	± 163 - 169°C
Molecular Weight	323.411 $g.mol^{-1}$
pKa (Basic medium)	1.38
pKa (Acidic medium)	4.07
LogP	2.6
Water solubility	1.9×10^{-01} $g.l^{-1}$
Metabolism	Hepatic, less than 1% is excreted via the urine
Toxicity	LD_{50} = 3000 $mg.kg^{-1}$

By extending the rate of release, it is possible to extend the presence of the drug in the circulation, resulting in less dosing intervals and dose units. Consequently, this leads to a reduction in missed doses and improved adherence to regimes; which ultimately leads to improved therapeutic outcomes (Kardas, 2005:722). Modified release SODFs are a possible approach to counter these disadvantages. The rationale of modified SODFs is based on prolonging the drug present in the blood plasma. By extending drug-plasma levels, it is possible to reduce the number of doses a patient requires and thus, improves patient compliance.

2.2 SOLID ORAL DOSAGE FORMS

Solid oral dosage forms (SODFs) are perceived as the most dominant drug delivery system (Jivraj *et al.*, 2000:58; Perioli *et al.*, 2012:621). Various advantages exist that promote the use of SODFs. These include the following:

- Durability during storage and transport.
- Ease in physical handling.
- Minimal aseptic handling.
- Ease of oral administration (Zhang *et al*., 2003:372; Zhang *et al.*, 2004:371-390).

In contrast to these advantages, several disadvantages can be identified, which include:

- Complexation and agglomeration of the various excipients or substances, and bio-molecules found within the body for example serum albumin.
- Administration difficulties in children, comatose patients, and patients with underlying pathologies for example tumours or constriction of the oesophagus, which in turn makes it difficult for patients to ingest (Sastry *et al.,* 2000:138; Schiele *et al.,* 2013:937).
- Certainly one of the dominant drawbacks of SODFs is the drug susceptibility to various metabolic processes, as in the case of presystemic metabolism (Dresser *et al.,* 2000:42-43; Paine *et al*., 2006:880-881).

To counter the abovementioned disadvantages and improve patient compliance as well as convenience, researchers and manufactures have attempted several methods to modify the release of drugs by altering the mechanism whereby the drug is released. This is accomplished by chemically changing the drug molecule itself or changing the excipients of the product. Mechanism based modifications include erosion-, diffusion-, dissolution- and osmosis controlled release mechanisms (Das *et al.,* 2003:12, Patel *et al.,* 2006:58). However, controlled release mechanisms have their own drawback. In the case of controlled release, the predominant drawback is dose-dumping. Dose-dumping is the premature release of a drug from the controlled-release dosage form. This is contradictory to the base rationale for the development of controlled-release dosage forms (Krajacic *et al*., 2003:70).

2.2.1 FORMULATION OF SOLID ORAL DOSAGE FORMS

The formulation of a SODF is an important process in providing an acceptable and usable pharmaceutical product for patients. Formulation is the process by which different constituents

and processes needed to manufacture a SODF, is determined and optimised. In order to manufacture a SODF for either conventional or modified release of a drug, a number of factors need to be considered. These include the excipients and manufacturing method (Allen *et al*., 2011:2-6).

2.2.1.1 Excipients used in formulations

SODFs, for example tablets, include several excipients in their formulation. Each type of excipient is incorporated to impart various characteristics or properties to the formulation. These excipients include fillers, binders, disintegrants, glidants, anti-adherents, etc. (Alderborn, 2007:449; Allen *et al*., 2011:225). Table 2.2 provides various examples of the different excipient types which can be utilised for the formulation of SODFs.

Table 2.2: Excipient types and examples

Type of excipient	Examples
Fillers	Simple fillers: Microcrystalline cellulose (Avicel®), micro-fine cellulose, lactose, calcium phosphate, sugar, dextrose, etc. Compound Fillers: Avicel® and colloidal sillica, Avicel® and lactose, Lactose and maize starch, Lactose and polyvinylpyrrolidone (Kollidon®), sugars, etc.
Binders	Kollidon® 30, 50, 90, VA-64, etc.
Disintegrants	Ac-Di-Sol®, Primojel®, Explotab®, Kollidon® CL, starches (Sta-RX® 1500), etc.
Glidants	Magnesium stearate, colloidal sillica, etc.

Acting as a carrier agent for the drug and other excipients, fillers account for the majority of the dosage form's weight and volume. This increase in mass and volume allows for a higher degree of control in regards to handling the drug. It should be noted that in some formulations where the amount of drug is large enough, the filler might be redundant (Allen *et al*., 2011:225).

Fillers should fulfil several requirements before they are eligible to be included in a formulation. These requirements include:

- be chemically inert,
- non-hygroscopic,
- have biopharmaceutical acceptable properties,
- have good technical properties,
- possess an acceptable taste, and
- be cost effective (Alderborn, 2007:449, Allen *et al*., 2011:225).

Of all the available fillers, none fulfil all of these requirements simultaneously. Due to the presence of large amounts of filling agent certain properties which include flow rate, compressibility and porosity of the filler, might be of concern (Alderborn, 2007:449, Allen *et al*., 2011:225).

After mixing of the drug with the chosen filler a binder can be added. Adherence of the individual molecules is achieved by the binding agent's inherent mechanism of action. Binders have various mechanisms by which binding occurs, namely:

- Overcoming the electrostatic and intermolecular forces,
- liquid based bonding,
- mechanical interlocking,
- the formation of solid bridges between particles after the evaporation of liquids and
- natural occurring adhesive and cohesive forces (Alderborn, 2007:452; Allen *et al*., 2011:225).

Disintegrants, on the other hand, are added to the powder mix to facilitate drug release from the SODFs after oral administration. Several mechanisms of action are possible for disintegrants. They are:

- swelling of the particles;
- electrostatic repulsive forces between the individual particles;
- restoration of the particle shape after compression, and
- exothermic reactions.

However, there are currently three main mechanisms of importance. The first mechanism is based on tablet rupture caused by swelling of the individual particles of the disintegrant powder, after exposure to moisture. Secondly, disintegration can be facilitated by increasing penetration

of moisture through capillary fissures within the outer layers, eventually resulting in fragmentation of the tablet. The final mechanism by which tablet disintegration can occur is by deformation of the powder particles; particles with a natural elasticity may return to its previous shape (Alderborn, 2007:450-452).

Another excipient that can be included into a formulation is a glidant. Glidants are incorporated in the powder mix to improve flow properties. A glidant's mechanism of action is based on lowering the shearing forces between individual particles or changing the electrostatic interaction between these particles (Faldu & Zalavadiya, 2012:923-924). Sufficient flow is necessary in direct compression of certain SODF manufacturing, e.g. tablets and multi-unit pellet systems. Glidants are recommended, if not required, in direct compression, though it has proven effective and advantageous in wet granulation as well and even mixtures meant for extrusion-spheronisation of pharmaceutical pellets (Alderborn, 2007:452; Allen *et al*., 2011:226).

2.2.2 MANUFACTURING METHODS OF SOLID ORAL DOSAGE FORMS

Different manufacturing methods can be used to form a SODF from the aforementioned constituents. These methods include wet granulation, dry granulation, direct compression and even extrusion-spheronised beads. Each of these methods is used in different ways, all depending on the desired outcome or the characteristics of the excipients and drug.

2.2.2.1 Wet granulation

Wet granulation is considered the most cost effective as well as one of the oldest known SODF manufacturing methods. A homogenous mixture is wetted with a suitable wetting agent (e.g. water). The moist mixture can be milled or granulated by a granulator in order to form granules. Prior to tableting, the granules are sieved to homogenise the granule size and to break agglomerates. The homogenous granules are compressed into a tablet or placed in a capsule. Wet granulation has several advantages; these include the usability of fine powders, flexibility in the amount of wetting agents used, and the mixing of powders which do not adhere to each other. On the other hand, some of the disadvantages include weak cohesion if the wetting agent dries and did not supply sufficient cohesion between powder particles; and possible hydrolysis of the excipients or drug (Summers & Aulton, 2007: 412; Tousey, 2002:8-13).

2.2.2.2 Dry granulation

Dry granulation can be used when excipients are for example moisture sensitive. Again, a homogenous powder mixture is prepared. Two distinct methods can be used to manufacture SODFs from this method:

- Heavy-duty compression of the mixture into a large tablet, and
- Roller compression of the mixture between cylinders.

The resulting product is milled to break it into granules. These granules are sieved to form a homogenous granule size range. Subsequently, the granules are either compressed, or encapsulated. One of the most prominent advantages of dry granulation is the use of this method in manufacturing tablets containing moisture sensitive drugs and/or excipients. In turn, dry granulation is not suitable for fine or physically incompatible powders. Mechanically, this method of manufacturing has a high level of machine noise (Summers & Aulton, 2007:412; Tousey, 2002:8-13).

2.2.2.3 Direct compression

A modern method of SODF manufacturing is direct compression of excipient powders into a single unit. A homogenous mixture of dry powders is introduced into a suitable die via a hopper. Compression of the mixture occurs by applying force to the mixture present in the die. This compression is achieved by an automated press and punch. Compression of this powder causes deformity of the powder particles. In some cases, when the applied force is removed and the tablet exits the die, the individual particles of the powder might return to its original shape due to the elastic nature of some of the excipient particles, possibly resulting in capping or lamination of the solid tablet. These defects decrease the strength and durability of the tablet. Binders can influence the elastic nature of the powder particles and thus prevent capping or lamination; maintaining the integrity of the tablet (Alderborn, 2007: 467-473; Tousey, 2002:8-13).

2.2.2.4 Extrusion-Spheronised pharmaceutical pellets

Extrusion-spheronised pellets (beads) are a modern type of SODFs. Beads are manufactured by extruding a wetted mass of excipients through a perforated screen to form uniform sized extrusion. These extrusions are then spheronised to uniformly sized and shaped beads by the use of a multi-bowl spheroniser. These beads can be delivered individually, collectively or incorporated in a larger unit, e.g. multi-unit pellet tablets or capsules. These individual units are

collectively referred to as multi-unit particulate systems. Multi-unit pellet systems have proven useful and advantageous in modified release SODFs (Gandhi *et al.*, 1999:161).

2.3 IMMEDIATE RELEASE COMPARED TO MODIFIED RELEASE SOLID ORAL DOSAGE FORMS

The basic rationale of any drug release from a SODF is to provide an adequate plasma concentration of the drug. This level falls in a concentration range; ranging from the minimum therapeutic concentration to the minimum toxic concentration and this range is known as the therapeutic index. Any drug concentration below the therapeutic index is sub-therapeutic, whereas any concentration above the index is toxic. Immediate release of a drug is identified by an initial release of drug which peaks after a certain time (relatively short) has passed. After the peak is reached, the concentration level drops. In order to maintain a suitable therapeutic concentration of the drug, the next dose needs to be timed correctly in accordance with the drug half-life. A disadvantage of note is that with immediate release, sub-therapeutic or a toxic level of the drug is possible. To counter this, modified release dosage forms are continuously being developed. The rationale of modified, sustained or controlled release dosage forms is to provide a constant plasma drug concentration over a prolonged time period. This extension of drug present in the blood plasma reduces the number of doses required to provide a therapeutic drug concentration (Allen *et al*., 2011:258). This described rationale for immediate drug release compared to modified drug release is illustrated in figure 2.2.

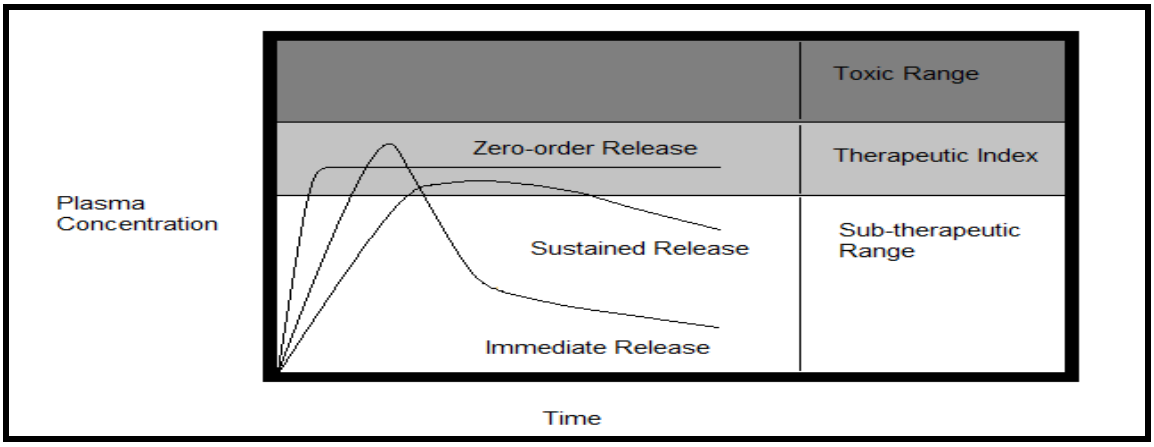


Figure 2.2: Graph comparing immediate and controlled modified drug release

2.3.1 TYPES OF IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS

2.3.1.1 Conventional release solid oral dosage forms

The release of a drug from a conventional release SODF is characterised by the physicochemical properties of the drug and dosage form. Conventional release SODFs are known to release a drug as it transits through the body. These dosage forms are basically administered as a unit-dose, implying for example that one tablet contains a specified dose amount of the active agent. The tablet is easily administered by means of oral intake. Once the tablet enters the gastrointestinal tract, it is exposed to gastrointestinal fluid, enzymes and other biological factors. Transit is necessary for the disintegration and dissolution of the tablet, which releases the drug from the SODF. The fluid present in the body saturates the tablet and saturation allows for the incorporated excipients to fracture the solid tablet into smaller pieces. A decrease in particle size leads to an increase in the surface area exposed to the fluid environment; this increase allows for an increased rate of disintegration. After disintegration of the SODF to a smaller particle size range; the particles will undergo dissolution. Once in solution, the active agent can cross the epithelium into the blood stream, depending on the permeability of the drug. At this stage the drug travels along the circulatory system to the site of action. Both disintegration and dissolution can be described as a rate limiting step in the intended release of a drug. The rate of these different steps can be influenced by the various manufacturing methods, the choice of excipients, or the formulation itself. Other factors can influence these steps as well, such as biological, environmental and physicochemical factors, for example particle size of the excipients and water solubility. Reasons in favour of disintegrating tablets include ease of administration, predetermined dose size, and patient compliance. However, several drawbacks prevent the use of this type of tablet, which include comatose patients, pathologies of the ora-esophogeal tract, and young children or elderly individuals with difficulties in swallowing (Allen *et al*., 2011:225-226; Sahoo, 2007:20-31).

2.3.1.2 Effervescent Tablets

Effervescent tablets are designed to include a higher amount of drug; and most importantly, disintegrate and dissolve within a glass of water. Key ingredients in the design of effervescent tablets are bicarbonates or carbonates, and citric and/or tartaric acid, which in combination form part of the disintegration system. As the effervescent tablet is exposed to water, it starts to permeate the tablet. This in turn causes a reaction between the carbonate and acid which produces carbon dioxide. Release of carbon dioxide disintegrates and dissolves the tablet. The

solution that is formed allows for a rapid onset of action and rapid emptying of the gastrointestinal tract. By dissolving the SODF into a solution, it is possible for patients with underlying pathologies which limit the intake of other SODFs, to ingest the medication. Elderly and young children are also benefitted by using this type of SODF. One of the limitations of this delivery system, however, is the organoleptic properties of the SODF excipients present in solution, particularly the flavour of the solution. Due to the large amount of ingestible liquid, it is recommended that the dosage form contains a flavouring agent (Alderborn, 2002:412; Alderborn, 2007:456; Allen *et al*., 2011:228).

2.3.1.3 Chewable Tablets

Some SODFs are mechanically crushed by means of chewing. This ensures the complete disintegration of the SODF into smaller particles. Though it should be noted that dissolution does not fully occur in the mouth, but still in the gastrointestinal tract, this acts as the disintegration process needed for drug delivery within the gastro-intestinal tract. As a result, this allows for a faster dissolution of the SODF, and thus faster absorption. Due to the prolonged presence within the mouth, flavouring is yet again a concern. If the patients do not prefer the flavour of the tablet after chewing, it will affect patient compliance negatively (Alderborn, 2002:412; Alderborn, 2007:456; Ansel *et al*., 2011:227; Siewert *et al*., 2003:3).

2.3.1.4 Sublingual and Buccal Tablets

Another SODF that releases the drug immediately is sublingual and/or buccal tablets. Sublingual tablets are SODFs which dissolve under the tongue, whereas buccal tablets dissolve on the inside of the cheek or under the lip. The anatomical locations were both sublingual and buccal tablets function can be seen in figure 2.3. These SODFs are designed to dissolve in the mouth and be absorbed through the oral mucosa. Once these SODFs dissolve in the mouth, it should not be swallowed. Again, these dosage forms rely on organoleptic considerations, especially flavouring. A disadvantage of sublingual and/or buccal tablets is the limited dosage size, due to the limited absorption capacity of the oral mucosa (Alderborn, 2002:413; Alderborn, 2007:457; Allen *et al*., 2011:227).

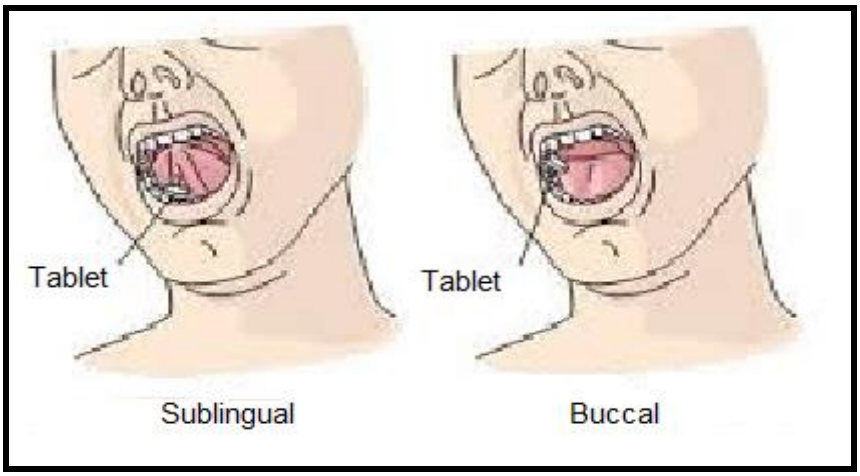


Figure 2.3: Sublingual and buccal route of administration (intranet.tdmu.edu.ua)

2.3.1.5 Multi-layer tablets

The basic concept of conventional multi-layer tablets is based on the repeated compression of multiple layers containing incompatible active ingredients. It is also an acceptable practice to colour the various layers, resulting in a uniquely identifiable product (Alderborn, 2002:412; Alderborn, 2007:456).

2.3.1.6 Lozenges

Lozenges are tablets designed to slowly dissolve in the mouth. They are designed to either have a local or systemic effect. Once lozenges are in the mouth, the saliva supplies the necessary fluid which induces dissolution of the tablet and release of the drug. These tablets can, however, also act as a simple slow release dosage form (Alderborn, 2002:413; Alderborn, 2007:457).

2.3.2 Modified release solid oral dosage forms

The rational by which modified release SODFs function is based on prolonging the presence of the active ingredient in the blood plasma. This extended time of the drug present in the blood plasma improves patient compliance and therapeutic outcomes. This is achieved by lowering the number of doses required for the patient to maintain a therapeutic drug concentration (Siegel & Rathbone, 2012:19-20).

2.3.2.1 Coated tablets

An approach to modified release SODFs is the coating of disintegrating tablets. Various methods of coating were developed for maximum patient convenience, including enteric,

gelatine and film coatings. Each coat is applied using a spaying-dry method. After spraying the tablet with the coating, the product is dried. One of the main reasons for applying a coating is to improve dosage forms resistance in low pH environments. This is advantageous in the case of a drug which is pH sensitive or the location of drug absorption is based in an environment with a high pH (e.g. the intestinal tract) (Alderborn, 2002:412, Alderborn, 2007:456, Ansel *et al*., 2011:227, Das *et al.,* 2003:14).

2.3.2.2 Diffusion-controlled tablets

Diffusion-controlled release SODFs rely on moisture permeating it with subsequent drug release. Diffusion-controlled release dosage forms are divided into two types, namely, matrix and membrane types. In order for this system to function properly, the dosage form needs to remain intact while in transit through the gastrointestinal tract. Upon exposure to moisture the dosage forms starts to release the drug from the matrix or membrane which encompasses the drug. Depending on excipients and manufacturing process used to manufacture this particular SODF, the rate of drug release can be augmented to prolong drug release (Uhrich *et al.*, 1999:3183-3189).

2.3.2.3 Dissolution-controlled tablets

Dissolution-controlled release relies on the dissolution of poorly water soluble salts of the active agent, using a slowly dissolvable carrier or covering of the drug particles with a slowly dissolving coating (Uhrich *et al.*, 1999:3183-3189).

2.3.2.4 Erosion controlled tablets

These tablets are a single unit system consisting of a matrix based structure. The active agent is dispersed throughout the matrix. As the matrix starts to dissolve, the active agent is released. This erosion leads to a loss in tablet weight and a predictable release profile of the active agent (Colombo *et al*., 2000:201-202; Dey *et al*., 2008:1069).

2.3.2.6 Osmosis controlled tablets

Osmosis controlled release is based on a difference in osmotic pressure between the interior and exterior environment of the dosage form. A semi-permeable membrane is permeated by moisture due to this osmotic pressure difference. The active ingredient within the dosage form starts to dissolve and the resulting solution is then pumped out of the dosage form via a single orifice or through a semi-permeable membrane. This transport is a convective transport

process. Several pump mechanisms can be utilised, which include the introduction of a swelling layer that forces the solution out as the layer expands. Another method is that the solution itself exhibits swelling properties. Each of these methods produces pressure, thus forcing the solution through the orifice. Osmosis controlled systems can be manufactured as a single- or multi-dose system (Dey *et al*, 2008:1069; Gupta *et al*, 2010:571-582). Figure 2.4 illustrates an example of an osmotically controlled release tablet.

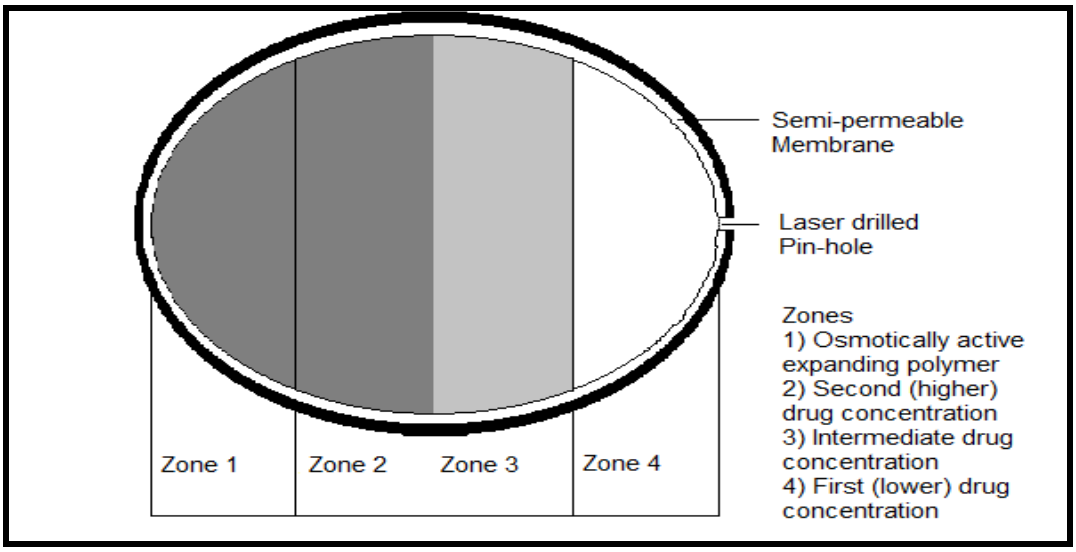


Figure 2.4: Example of an osmotically controlled release tablet

2.3.2.7 Multi-layer tablets

Multi-layer tablets contain layers composed of different drug concentrations per layer; or each layer is compressed to various degrees of density and strength. In the case of varying drug concentration, upon the disintegration and dissolution of each layer, a different amount of the active ingredient is released at various stages during gastrointestinal transit. If the concentration of the drug is constant throughout the layers, the density of each layer influences the rate of disintegration and therefore prolongs the release of the drug from the solid dosage form (Alderborn, 2002:412; Alderborn, 2007:456). These multi-layer tablets are made by compression of an initial amount of powder mix which is introduced into the die. After compression the die is filled again with another layer. As a result of the applied force, the first layer is compressed more densely than with the first compression. This delivers a denser and mechanically stronger first layer. A slight variation on this method is an initial high pressure compression of the first layer and then followed by consequent layers where each layer has a reduced compression force applied to the layer (Abdul & Poddar, 2004:160-161).

2.3.2.8 Multi-particulates

A contemporary approach to modified controlled release dosage forms is the use of multi-particulate components, which is a system constituted out of smaller individual units with identical characteristics and properties. Multi-particulates have many advantages which make them a suitable choice for controlled release, namely:

- improved gastric emptying;
- easily adjustable dosing;
- multi-phase release profiles;
- improved flow properties;
- decreased dust and powder waste;
- decreased tendency for dose dumping to occur;
- reduction in both the dose frequency and dose size;
- uniform transit through the gastrointestinal tract;
- lower tendency to gastrointestinal irritation;
- reduced individual variations;
- possible multi-drug combinations;
- lowered tendency for side-effects;
- cost effectiveness;
- provide a targeted and controlled release and
- a shorter lag time.

This system of a single unit is useful in the case where varying concentrations of a drug need to be present in a single unit, either a tablet of capsule. Individual particles can be designed with different concentrations. Another advantage of multi-particulates is that incompatible drugs can be incorporated into a single unit. The multi-particulates or pellets after manufacturing can now be directly compressed into a single unit-of-use; or the pellets can be incorporated into a capsule as in the case of this study. Several methods of multi-particulate manufacturing exist (Ganhdi *et al*., 1999:160-161; Khan *et al.,* 2014:2137-2140; Vervaet *et al*., 1994:131-132; Young *et al.*, 2002:87-92). These include:

- layering,
- freeze pelletisation,
- cryopelletisation,
- hot-melt extrusion and

- extrusion-spheronisation.

2.3.2.8.1 Layering

Layering or coating is based on deposition of successive layers of an active ingredient. These layers are deposited on a core. This core can be a crystal, an inactive agent or granule (Hirjau *et al*., 2011:210). The following figure (figure 2.5) provides a diagrammatic representation of the layering process.

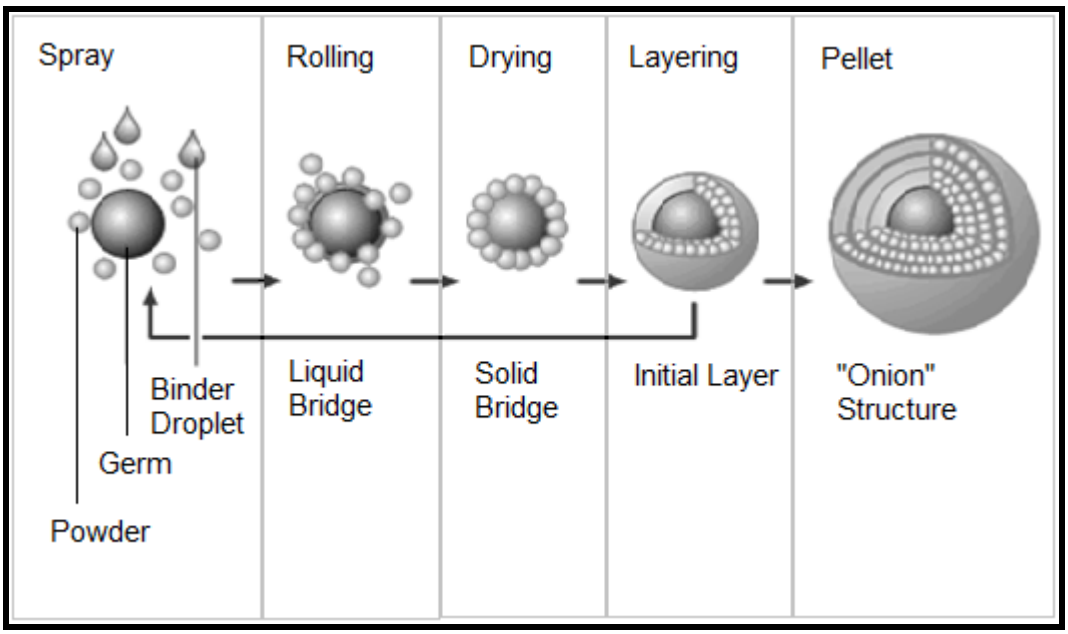


Figure 2.5: Layering process for pharmaceutical beads (revised from slideshare.net)

2.3.2.8.2 Freeze pelletisation

Freeze pelletisation on the other hand is a manufacturing method where spherical matrix pellets containing the drug are produced. A molten droplet containing the drug and excipients is introduced into a temperature regulated column containing an immiscible liquid. .The column consists out of various temperature regions, ranging from -40°C to 100°C. The liquid chosen for the process needs to have a lighter density then the droplet. This difference in density between the liquid and droplet allows for a natural conveyance of the droplet through the liquid. As the droplet “drops” down through the liquid, it moves through the various temperature regions, consequently forming a solid pellet. Layer by layer the pellet continues to form until it enters a low temperature region (0°C to -40°C), at which time the deposited layers start to freeze and solidify. This is an inexpensive and easily reproducible method of manufacturing pellets, depending on the variables (Cheboyina & O’Haver, 2004:98-102; Lavanya *et al.*, 2011:1345).

2.3.2.8.3 Cryopellitisation

Pellets produced via cryopelletisation, is when a droplet of organic or aqueous liquids are conveyed through a perforated plate in the presence of liquid nitrogen and a solid pellet is formed. The shape of the pellets is determined by the distance between the perforated plate and the nitrogen reservoir. Pellet size is determined by the diameter of the perforations present in the plate (Gandhi & Baheti, 2013:1624; Lavanya *et al.*, 2011:1344).

2.3.2.8.4 Hot-melt extrusion

Hot-melt extrusion is a solvent free method, ideal for drugs that are unstable in the presence of moisture. Several processes are used to form pellets by means of hot-melt extrusion and these processes are:

- Plastisation or melting of a drug dispersed throughout a solid medium which acts as a thermal carrier.
- Use of an extruder in order to shape the molten content.
- Spheronisation at high temperatures to form uniform spheres.
- Solidification of spheres into the desired shape (Lavanya *et al.*, 2011:1345; Patel *et al.,* 2010:81-82; Young *et al.*, 2002:87-92).

2.3.2.8.5 Extrusion-spheronisation

Extrusion-spheronisation is a multi-phase method of manufacturing, first developed in the 1950s. First, a homogenous powder mixture is wetted with a suitable wetting agent; for example water. The resulting wet mass is introduced into an extruder. Once introduced into the extruder, the mass enters a chamber via a hopper. The chamber contains multiple cylinders which rotate at pre-set rotations and a perforated screen. As the cylinders rotate the mass is pushed against the screen. Due to the sheering forces and compression of the mass against the perforated screen, it is extruded through the screen. Figure 2.6 provides an approximate idea of how the extruder functions. The size of the extrusions is determined by the diameter of the perforations present in the extrusion screen. Finally, spheronisation of the extruded material in a spheroniser is conducted. The spheroniser consists of a multi-bowl chamber with an attached friction plate. As the extrusion enters the bowl, the rotating friction disk and supplied compressed air create a rotation of the extrusion mass in such a manner that the extrusions break into smaller sizes and produce spherical pellets. The size and shape of the final pellets are determined by the rate at which the spheroniser rotates (Newton *et al*., 1995:101; Vervaet *et al*., 1995:136; Young *et al.*, 2002:87-92). For the purpose of this study and the cost-effective

nature of this method it was opted to use extrusion-spheronisation as the method of choice for the manufacturing of the beads.

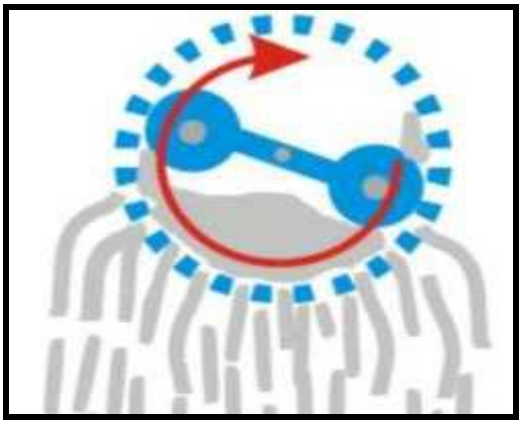


Figure 2.6: Radial extruder (revised from spheronizer.com)

2.4 STARCH AS A VERSATILE EXCIPIENT

Starch has proven versatile and invaluable in dosage form design. Due to the flexible nature of starch and its various applications in the pharmaceutical industry, it is essential to investigate its application in the design of modified release dosage forms (Dumoulin *et al*., 1998:161-162; Ispas-Szabo *et al*., 1999:163-165; Lenaert *et al*., 1998:225). Starch, which is a natural occurring polymer, has a multitude of applications in the pharmaceutical industry; it may be employed as a filling agent, binder, disintegrant or even as a glidant (Bayor *et al.*, 2013:17). It has become a necessity to investigate applications of renewable sources for excipients. Starch is considered a viable candidate in improving the release profile of an active ingredient and resulting therapeutic outcomes (Dumoulin *et al*., 1998:161-162; Ispas-Szabo *et al*., 1999:163-165; Lenaert *et al*., 1998:225).

Two principal polymers, amylopectin and amylose present in starch make for an ideal candidate in the design of controlled release dosage forms. Figure 2.7 shows a structural comparison of the two distinct polymers. These two polymers form a robust polymer-matrix. An important property of starch powders is its tendency to gelatinise when moistened. This proves useful in designing a dissolution- or erosion-controlled release tablet. When the mass is introduced to a moisture rich environment, it begins to expand as it absorbs the moisture. This occurs as the branched polymers expand and moisture permeates the polymer-matrix. The mass becomes gelatinous and forms a pseudo-suspension or matrix. As the starch travels through the gastrointestinal tract, metabolic processes start to dissolve the mass; this dissolution of the

starch allows for release of drug particles from the polymer matrix. An initial dose of the active ingredient is released when the matrix starts to dissolve (Mandal *et al*., 2009:1348). Continuous dissolution of the mass and release allows for sustained release of the drug (Mandal *et al*., 2009:1348). As an abundant source of starch, investigation has been warranted in the possible application of refined cassava starch as modified release filler.

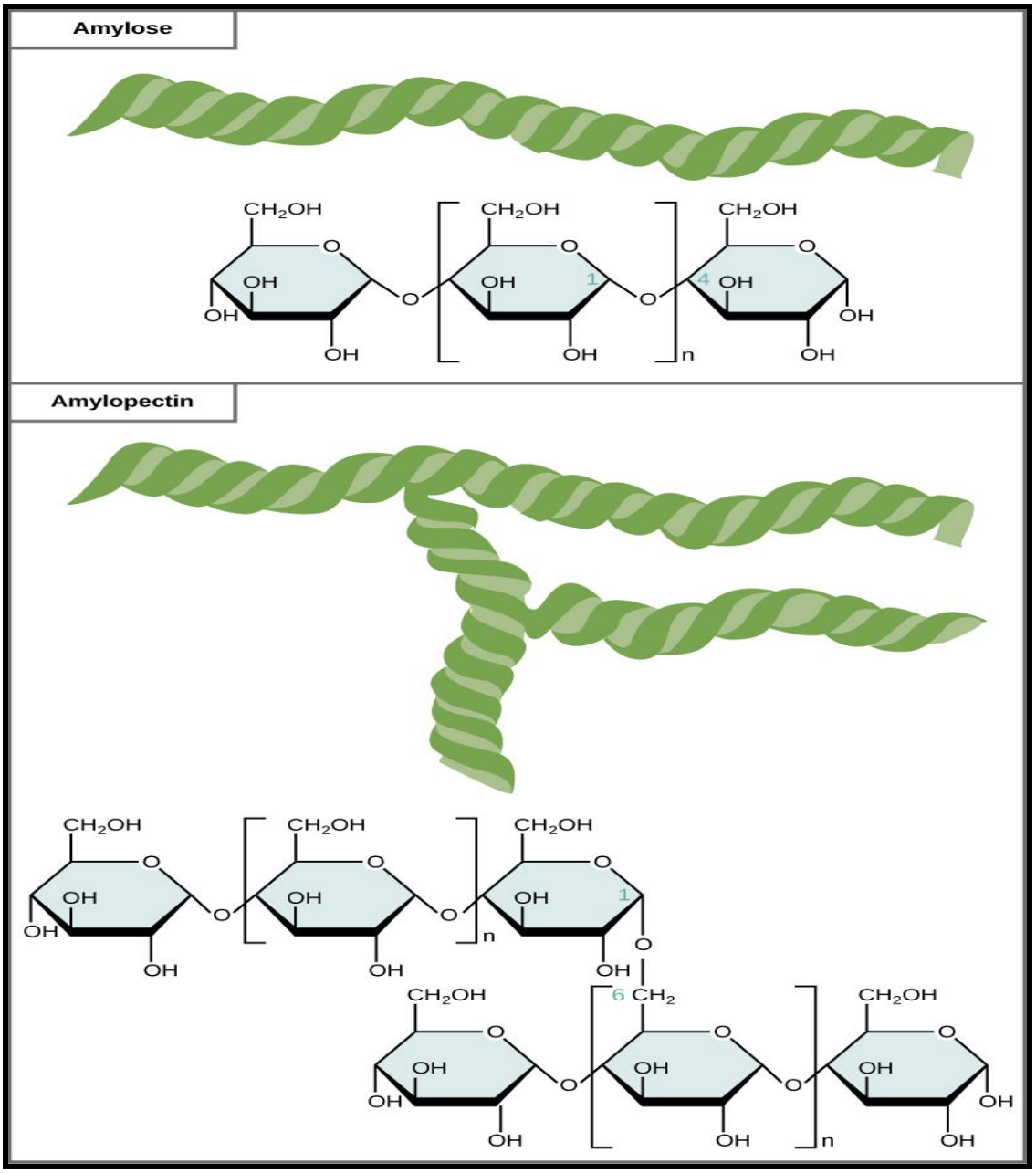


Figure 2.7: Molecular and macroscopic structure of amylose and amylopectin (revised from voer.edu.net)

2.4.1 CASSAVA

The arrival of European explorers in the “new world” has meant the sporadic spread of fauna and flora across the globe. This migration led to many new discoveries within the indigenous or non-indigenous environments (NOAA, 2008). A good example of this is *Manihot eschulenta Crantz* (figure 2.8). *Manihot eschulenta Crantz*, otherwise known as yuca, tapioca or cassava, is a perennial root of the *Euphorbiacea*-family, native to tropical and sub-subtropical climates as seen on the South-American, South-Asian and the sub-Saharan Africa continent. Although native to humid climates, this root is quite adaptable to various environments (FAO, 2013:6-7).

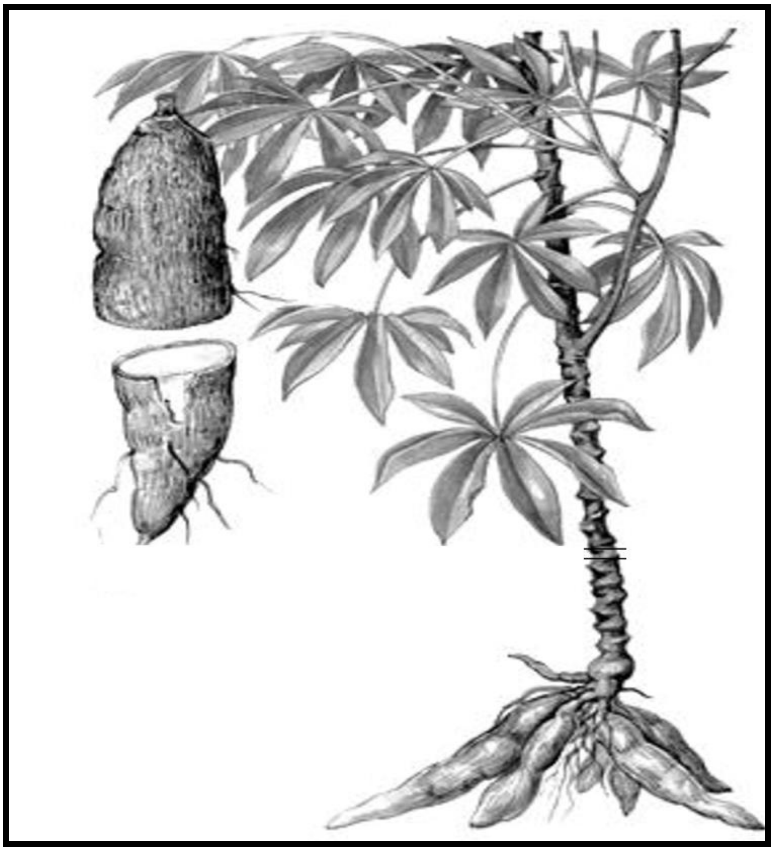


Figure 2.8: Illustration of cassava plant and root (revised form theglyptodon.com)

Cassava is also globally known as one of the main sources for starch with an estimated global production of 290 x 10^6 ton in 2012 (FAO, 2013:6). As a source of energy, cassava proves to be an invaluable staple in the diet of several developing nations. Due to the relative short lifespan of post-harvested roots, the refined starch powder lengthens the lifespan of the starch. The process of refinement ensures a thriving economy, not only for subsistent farmers, but also

for refinement centres and post-refinement trading. Refinement is also crucial in improving the safety profile of cassava starch, due to the presence of cyanide in the cassava root (Fáma *et al*., 2006:8; Fáma, *et al*., 2007:266).

As stated before, cassava starch contains two distinct glucose derived polymers, linear and helical amylose as well as a short chain branch amylopectin, in ratios of 1:3 – 1:4 (Charles *et al*., 2005:2718). Amylose content ranges between 15.0 – 25.0% (Charles *et al*., 2005:2117; De Floor *et al*., 1998:62; Moorthy *et al*., 2002:560-562; Nuwamanya *et al*., 2010:1; Rollande-Sabaté *et al*., 2012:161). The physicochemical compositions of the aforementioned polymers form a robust matrix. This natural matrix influences several important aspects of the starch's physicochemical properties. The level of crystallinity is directly affected by the number of hydrogen bonds. If the crystalline structure shows a high level of rigidity, it would indicate a high number of hydrogen bonds. With a high level of crystallinity, the more robust matrix would show a tendency to lower fluidity and adversely affect physicochemical properties (Huang *et al*., 2007:133). Other properties are highlighted in both tables 2.3 and 2.4.

Tabel 2.3: Content Properties (Revised from Moorthy, 2002:560,561)

Properties	Cassava
% Yield from H_2O-NH_3 extraction medium	21.80 ± 0.540
%Total amylose extracted	0.37 ± 0.010
% Moisture content	10 – 14
% Fibre/Ash Content	0.01 - 0.8
% Lipid content	0.01 - 1.54
% Phosphorus content	0.01 - 0.01
Colour	White
Granule shape	Round, truncated, cylindrical, oval, spherical, compound

Granule size	3 - 43 µm

Table 2.4: Physicochemical properties of cassava variants (Revised from Moorthy, 2002:569)

Variant	Granule size [µm]	Reducing values	Amylose content	Past* temp [°C]	Vis** 2% paste	Swelling volume [ml.g^{-1}]	Sol*** [%]
M-4	5.4 - 35.1	1.8	0.530	60.7	58.0	30.5	22.8
Kalikalan	5.4 - 40.5	1.8	0.550	63.70	58.0	38.8	24.8
H-1687	5.4 - 40.5	1.4	0.540	55.68	58.0	25.5	23.6
H-2304	5.4 - 43.2	1.4	0.525	52.68	55.0	30.5	24.8
H-226	5.4 - 43.2	1.8	0.500	55.66	56.0	33.8	27.8
H-97	5.4 - 43.2	1.2	0.535	58.70	55.0	30.5	17.2
H-165	8.1 - 48.6	1.6	0.505	52.65	54.0	37.8	27.2

*Pasting, **Viscosity, ***Solubility

Cassava starch has a variety of applications in more than one industry. In the textile industry it is used in clothing dye. The pharmaceutical industry utilises it as a versatile excipient, for example fillers. Starch is used in the adhesive, rubber and foam industry. In the paper industry, cassava starch is also utilised to improve the colour and paper quality of paper stocks. Organic sugars and acids can be derived from cassava starch. Fructose syrup and gelatine capsules can also be produced using sugars prepared from cassava starch. Employing bioreactor processes which incorporate *Aspergillus awamori* and *Lactococcus lactalis spp. lactis*, L-lactic acid can be produced. Phytase production is also possible with cassava starch (Fao, 2005; Tonukari, 2004:5-6).

As observed in table 2.4, swelling is an important characteristic of cassava starch. The tendency of the polymers to swell when in contact with moisture is of noteworthy importance in the possible manufacturing of modified SODFs. Being susceptible to digestive processes, the mass is dissolved in the gastrointestinal tract (Beneke *et al*., 2009:2612-2614). Dissolution of the mass releases the drug from the resulting gelatinous mass. Due to the availability and

inexpensive nature of cassava starch, it has been deemed a promising candidate in the pursuit of a cost effective and a renewable excipient in the production of modified release SODFs (Dumoulin *et al*., 1998:361-362; Lenaerts *et al*., 1998:233-234). Though the versatility and its renewability promises cassava starch to be a viable candidate for pharmaceutical product manufacturing, scrutiny regarding the patient safety e.g. allergies and toxicity, would need to be investigated. For the purpose of this study, this line of enquiry was forgone.

2.5 SUMMARY

In this chapter diabetes was briefly discussed, as well as one of the most dominant second line oral antidiabetic drugs, gliclazide. An overview of different factors necessary in the formulation of either immediate or modified release SODFs was also provided. Furthermore, starch as a versatile and matrix-rich excipient in SODFs, specifically cassava starch as an inexpensive and renewable source of starch, was discussed. It is this rationale that warrants the evaluation of cassava starch as a suitable excipient in modified SODFs. In chapter 3, the materials and methodology employed for this study will be discussed.

CHAPTER 3

EXPERIMENTAL METHODS AND MATERIALS

3.1 INTRODUCTION

Any pharmaceutical dosage form, conventional or specialised, is formulated in order for a patient to receive an effective drug dose. Appropriate design and formulation require methodical understanding of the functional factors that affect the physicochemical characteristics of the drug and excipients used, as well as the absorption of the drug. The drug and excipients incorporated into the formulation have to be compatible in order to produce a product that is stable, efficient, striking, easy to administer, and safe. Furthermore, formulation of a solid oral dosage form usually necessitates accurate processing control of the powder mixture to guarantee a homogeneously formed product. Numerous excipients are gravimetrically added to form the bulk powder with which homogeneity is accomplished through optimum mixing. Homogeneity during tablet manufacturing is also accomplished through the correct process used to achieve good flow of the mixture into the tablet die. Extrusion-spheronisation was used in this study to increase the bulk density and increase flowability of the formulations (Aulton & Taylor, 2013:480; Shah & Mlodozeniec, 1977:1377). Thus, in order to evaluate which formulation is most appropriate, it is of utmost importance to evaluate the above-mentioned factors influencing design and formulation.

This chapter deals with the pharmaceutical excipients (materials) used in the various formulations tested. Moreover, it describes the experimental procedures employed to determine the effect of these excipients on the physical properties of the beads formulated as well as on the dissolution profiles of the formulations.

3.2 MATERIALS

The pharmaceutical materials employed in this study, their respective batch numbers as well as where these materials were sourced, are presented in table 3.1. All of the materials were of analytical grade and were used as supplied.

Table 3.1: Pharmaceutical materials employed in the various formulations, batch numbers and suppliers

Materials	Batch nr.	Source
Gliclazide	100111302045	Bal Pharma, Ltd. Bengaluru, India
Cassava starch	169A-27-11-12	Meelunie, BV. Amsterdam, Netherlands
Cassava starch (*Mbundumali-namwera*)	Donated	Malawi
Consolidated Starch	23871	Warren Chem Specialities Cape Town, South Africa
Avicel® pH 200	M939C	FMC International, Wallingstown, Ireland
Kollidon® 30	8608522440	BASF, SE. Ludwigshafen, Germany
Hydroxypromethylcellulose	11040	Shin-Etsu Chemical, Ltd. Tokyo, Japan
Hydrochloric acid	44836	Saarchem, Ltd. Krugersdorp, South Africa
Methanol	L361202	VWR International, Ltd. Poole, England
Ethanol	180914ET	Rochelle Chemicals, Cc. Johannesburg, South Africa

3.3 CHARACTERISATION OF CASSAVA STARCHES

The physical properties of powders have a significant effect on the flowability and tabletability of formulations. The primary physical excipient properties of importance are moisture content, particle size and particle size distribution. Other properties (which are derived from the primary properties) include flowability, compactibility and compatibility. The properties that were evaluated during this study are described in the following sections.

3.3.1 THERMOANALYTICAL CHARACTERISATION

The presence and distribution of moisture depend considerably on the chemical nature of a certain material, its physical properties such as particle size and porosity; and on the ambient relative humidity (RH), which determines the equilibrium moisture content (Garr & Rubinstein, 1992:187-192; Teunou *et al.*, 1999:109-110). Moisture may have noteworthy effects on the density of materials, flowability, binding characteristics, lubrication properties, compression, surface tension, tablet tensile strength and tablet toughness (Teunou *et al*., 1999:109-110; Viljoen *et al.,* 2014:731-741).

Thermoanalytical characterisation of the cassava starch powders was conducted at various time intervals (30; 60; 120; 240; 360 and 480 min) and at various temperatures (25; 30; 40; and 50°C).

3.3.1.1 Differential scanning calorimetric (DSC) analysis

DSC is used to determine physical properties based on thermal transition. Thermal stability of a substance at increasing temperatures and specific time intervals can be evaluated using DSC-analysis (Roy *et al.,* 2002:399-400).

A Shimadzu DSC-60A (Shimadzu Scientific Instruments, Shimadzu, Japan) instrument was used to obtain DSC-spectra of the cassava starch samples. Approximately 2 mg of each sample was weighed into aluminium pans. These pans were sealed with a lid; each lid was crimped in place by using a Du Pont crimper. The lids where pierced to form a small pinhole in order to elevate possible pressure build-up within the pans. A similar sealed, empty pan was used as reference. DSC-spectra were obtained at a heating rate of 10°C.min^{-1} under a nitrogen purge of 30 cm^3.min^{-1}. The individual spectra were determined up to a temperature of 300°C (Lemmer *et al.,* 2012:331; Viljoen *et al*., 2014:732).

3.3.1.2 Thermogravimetric analysis

Thermogravimetric analysis (TGA) is based on the change in weight of a sample at various temperatures (Ko *et al.,* 2014:155).

TGA was conducted on each starch sample at a temperature range of 0 - 300°C. TGA thermograms were recorded with a Shimadzu DTG-60 instrument (Shimadzu, Kyoto, Japan). The weight of each sample was approximately 5 - 8 mg and heating rates of 10°C.min^{-1} under nitrogen gas flow of 35 cm^3.min^{-1} were used. The theoretical weight loss during the

different conditions for each sample was calculated (in percentage) and compared. Equation 3.1 applies to stoichiometric reactions with just partial weight loss such as dehydration.

$$G = \left[\frac{\Delta_m \times M}{n \times M_{Gas} \times m_0} \right] \times 100\% \qquad [3.1]$$

Where the percentage content (G) is calculated from the weight loss (Δ_m) and the initial sample weight (m_0). M is the molar mass of the sample tested; M_{Gas} is the molar mass of the gas liberated and n is the number of molecules liberated per starting molecule (Lemmer *et al*., 2012:331; Viljoen *et al.*, 2014:732).

3.3.1.3 Karl-Fischer titration

Moisture content for each sample was determined with a Mettler DL 18 Karl-Fischer titrator (Mettler Toledo International LLC, USA). The Karl-Fischer solution was calibrated against a predetermined mass of water. An accurately weighed (250 mg) cassava starch sample was added to ethanol which was neutralised with the Karl-Fischer solution beforehand in a titration beaker. The mixture was magnetically stirred and titrated with the Karl-Fischer solution. Experiments were conducted in duplicate and the percentage water (w/w) calculated as follow:

$$\%\,Moisture = \left[(M - B) \left(\frac{C}{1000 \times W} \right) \times 50 \right] \times 100 \qquad [3.2]$$

Where M is the Karl-Fischer titrant volume (ml); B is the volume (ml) of Karl-Fischer titrant for the blank; C is the calibration amount (mg $H_2O.ml^{-1}$ Karl-Fischer titrant) and W is the sample weight in grams (Aucamp *et al*., 2013:20; Viljoen *et al*., 2014:732).

3.3.2 Infrared (IR) analysis

Vibrational characteristics, e.g. stretching and bending of different molecular bindings can be examined and identified with the use of infrared (IR) spectrometry. Compounds can even be identified using these IR-spectra due to individual compounds having distinctive IR-spectra (Chistian, 2004:469-472; de Kock, 2005:60).

IR-spectra of the cassava starches were recorded on a Nicolet Nexus 470 FT IR ESP spectrometer (Thermo Fischer Scientific, Waltham, Massachusetts, USA) over a range of 4000 - 400 cm^{-1} using the potassium bromide (KBr) referencing technique. Small samples of approximately 2 mg were collected at different temperatures and time intervals; and individually

mixed with 200 mg KBr (Merck, Darmstadt, Germany) prior to analyses. This analysis was repeated (with identical parameters, excluding the KBr reference) with a Bruker® Alpha Platinum FT-IR Spectrometer (Bruker®, Billerica, Massachusetts, USA) in order to provide spectra with a higher resolution (Aucamp *et al*., 2013:20; Lemmer *et al*., 2012:331).

3.4 SOLID ORAL DOSAGE FORMS

SODFs are presently the most preferred dosage form globally. The preference for SODFs is accredited to the many advantages, for example: improved patient compliance due to ease of administration, ease of transport, long shelf life and cost effective manufacturing (Alderborn, 2007:455-456; Hirani *et al.,* 2009:162; York, 2013:7-8). As described in chapter 2, SODFs consist of various excipients and the active pharmaceutical ingredient (drug). Each of these ingredients is included in a formula for the manufacturing of a specific SODF. These ingredients comprise, but are not limited to; fillers, binders, glidants and disintegrants, and most importantly the drug. The drug and the different excipients as well as varying amounts of each of these constituents need to be incorporated into a basic formula in order to be able to manufacture a SODF.

3.4.1 PREPARATION OF BEADS

Pharmaceutical pellets (beads) are a modern method of SODF manufacturing and have proven useful in the application for modified release dosage forms as well as the improvement of drug release and physicochemical characteristics for example flow or physicochemical compatibility between different drugs (Gandhi *et al*., 1999:160-162, Vervaet *et al*., 1994:131). The table (table 3.2) below represents the factors and levels required to design the necessary experimental formulations.

Table 3.2: Variables and different levels of each variable as employed in this study.

Factor	Levels		
	0	**1**	**2**
Drug (Gliclazide)	5% (w/w)	10% (w/w)	15% (w/w)
Filler	Avicel® PH 101	Cassava starch	Not applicable
Binder: Kollidon® 30	0% (w/w)	3% (w/w)	5% (w/w)

Polymer: HPMC	0% (w/w)	5% (w/w)	10% (w/w)

Powder mixtures were prepared. The composition of these mixtures were determined using a partial factorial design. The composition of these mixtures were noted in table 4.2. The filler, drug and binder for each formulation were weighed (mixture weighing 100 g) and transferred to a glass bottle. Each of these bottles was covered with Parafilm® before closure with a screw cap. The powders were mixed using a Turbula®-mixer (Model T2C, W.A., Switzerland) at 69 rpm for 10 min. After mixing, each powder mixture was wetted using a 70:30 deionised water and ethanol mixture. The wetted mass was mixed using a mortar and pestle. After each 5 ml volume of the wetting agent added, the mixture was blended with a blender (Model FP731 Multi-Pro, Kenwood®, South Africa) for approximately 2 min. This was repeated till the correct consistency was acquired. Upon completion of the addition of the wetting agent, the wetted mass was passed through an extruder (Caleva® Extruder 20, Sturnminster Newton, England), with the roller speed set at 32 rpm. A 1 mm diameter perforated screen was employed during the extrusion. The resulting extrudate was spheronised in a multi-bowl spheroniser at 3000 rpm for 10 min (Caleva®, Sturnminster Newton, England) (Chinyemba, 2012:21; Mallepeddi *et al.,* 2010:54). After spheronisation, beads were formed and the beads were dried at 40°C for 24 hr. Bead samples were sieved to provide a mono-dispersed size range.

3.4.1 MORPHOLOGY OF POWDER PARTICLES AND BEAD FORMULATIONS

Morphology is defined as: “the study of the forms of things, in particular” (Oxford dictionary) and with the investigation of powder, bead and tablet morphology, various macroscopic phenomena can be observed (de Kock, 2005:62). Differences between powder formulations, especially in terms of flowability, packing formation and compression can be explained through differences in their morphology. It is therefore important to investigate particle shape and size in order to be able to predict for example, powder flow and packing arrangement (Hancock *et al.,* 2004:980; Lavoie *et al.,* 2002:892; Velasco *et al.,* 1995:2385).

3.4.1.1 Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to identify the particle shape and surface structure of the different starches used and bead samples that were prepared in this study.

SEM analysis provides information on microscopic level to better understand the macroscopic behaviour of a powder or bead formulation (de Kock, 2005:62).

Each starch and bead sample was fixed to an aluminium stub using double-sided conductive carbon tape to a sampling tray and dusted with an inert gas. Samples were subsequently sputter-coated with a mixture of gold:palladium (80:20) to form a layer of approximately 28 nm on the surface of the samples. In order to investigate the internal morphology of the different bead samples, one or more beads of each sample were cut in half with a scalpel under a stereomicroscope and the internal structure of these beads were coated with the gold:palladium coating (Marais *et al.,* 2013:6742; Sungthongieen *et al.,* 2004:149). An Eiko® ion coater (model IB-2, Eiko Engineering, Tokyo, Japan) was used in all coating procedures and operated under a vacuum higher than 0.06 Torr. A FEI Quanta® 250 Environmental Scanning Electron Microscope with a Field Emission Gun (FEI©, Eindhoven, Netherlands) was used to study the samples and displayed on a commercial computer (Frizon *et al*., 2013:534; Marais *et al*., 2013:6742).

3.4.1.2 Particle size analysis

Particle size analysis offers essential information reflecting the mean particle size and particle size distribution within a powder or bead formulation. Understanding these physical properties of powders and beads enables the formulation scientist to explain observed behavioural differences between powders, especially in terms of powder flowability (Horn, 2008:38).

Particle size analysis of the cassava starch samples was conducted with a Malvern® Mastersizer® 2000 instrument fitted with a Hydro 2000SM small volume dispersion unit (Malvern® Instruments, Malvern, UK). The Hydro 2000SM dispersion unit was employed during the particle size analysis of the raw material samples. For particle size determination of the bead formulations, the analysis was performed with a 2000MU dispersion unit fitted to the Mastersizer® instrument. As dispersion medium for all samples (powder and bead samples), absolute ethanol was used at a stirring rate of 1500 rpm. The small volume dispersion unit (Hydro 2000SM) was filled with 100 ml absolute ethanol for the powder samples, whereas the (Hydro 2000MU) dispersion unit for the bead formulations was filled with 500 ml absolute ethanol. A background measurement was taken for all samples to compensate for electrical interference as well as possible interference from the dispersion medium. Upon completion of the background measurement, a sample of the appropriate material was added to the dispersion unit. Samples of the beads were dispersed in 6 ml absolute ethanol prior to addition

to the small volume dispersion unit. A sufficient quantity of the sample was added to obtain an obscuration of between 10 and 20%. After a suitable obscuration was obtained, the particle size of each of the samples was measured. Each measurement consisted of 12000 sweeps. The particle size and distribution of each sample were measured in triplicate and calculated with Malvern® Software (Malvern® Instruments, Malvern, UK).

3.5 FLOW PROPERTIES

Flow performance is often best described by quantification of the flow process. Several methods have been defined, either directly, using dynamic or kinetic methods, or indirectly, normally by measurements conducted on static powder beds (Staniforth, 2002:601). This section describes the different methods utilised to determine the flow properties of the various starch samples and bead formulations. These include the critical orifice diameter, flow rate, angle of repose, powder density and compressibility.

3.5.1 CRITICAL ORIFICE DIAMETER

Critical orifice diameter (COD) is defined as the smallest orifice through which a powder will flow freely without the application of any external aid or interference. The apparatus, developed by Buys and co-workers (2005:40-42) was used to determine the COD of the powders (figure 3.1). A set of copper rings (between 5 and 10 mm thick) with a centrally located orifice was used to determine the critical orifice diameter. By placing the copper rings in increasing size on top of one another, a tapered cone was formed. Each ring has a different size opening and the orifice of each disc was machined to a set angle. The largest disc opening was 32 mm and the smallest was 1.5 mm. A stainless steel hopper was fitted to the top of the funnel to create a holding chamber for the powder. This set was placed on top of a three legged stand to a height of 95 mm.

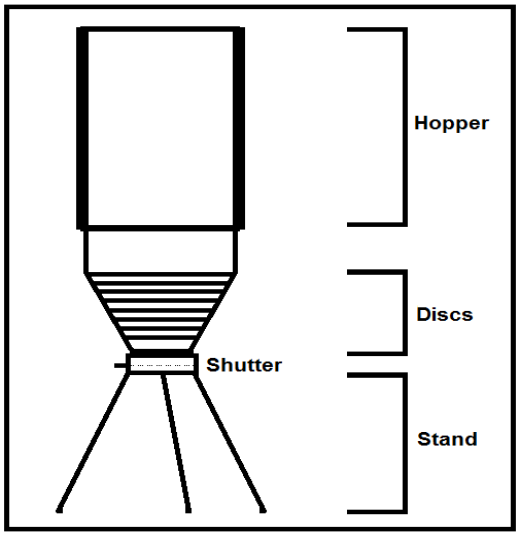


Figure 3.1: Apparatus used for the critical orifice diameter determination

A powder or bead formulation mass of 100 g was gently poured into the holding cylinder, while the opening on the bottom ring was kept shut. Opening the bottom orifice resulted in the discharge of the powder or bead formulation (if possible) from the holding chamber. Interchanging the stacked rings allowed for changing the bottom orifice diameter, whilst keeping the slope of the funnel constant until the smallest diameter was found through which each powder could flow freely. This specific diameter was noted as the COD. Each study for both original and dried powder, as well as for each bead formulation, was done in triplicate and the average COD, standard deviation (SD) and percentage relative standard deviations (%RSD) were calculated (Buys, 2005:40-42; Lambrechts, 2008:40).

3.5.2 FLOW RATE

The most direct method of assessing powder flow properties is the hopper flow rate. This method describes the amount of powder that could be discharged through a funnel in a specific time unit; normally per second (de Kock, 2005:64).

In order to determine the flow rate of the powders (original and dried samples) and bead formulations, a stainless steel hopper with a diameter of 30 mm was used. A hopper, fitted with a closed shutter at the bottom and which was raised 100 mm above the work surface, was filled with a predetermined amount of powder or beads (approximately 100 g).

Subsequently, the shutter was opened and the time required to complete the discharge of the powder mass was recorded (Lavoie *et al*., 2002:887-893). By dividing the powder weight with

the time recorded, a flow rate for the specific sample was calculated (using either equation 3.3 or 3.4). The procedure was performed in triplicate using different samples (100 g each) and the average flow rate ($g.sec^{-1}$), SD and %RSD were calculated (Sonnekus, 2008:23).

$$\mathbf{F} = \frac{\mathbf{M}}{\mathbf{T}} \qquad \textbf{[3.3]}$$

$$\mathbf{F} = \frac{\mathbf{V}}{\mathbf{T}} \qquad \textbf{[3.4]}$$

Where F represents the flow rate in $g.sec^{-1}$; t represents time (sec). Mass (in g) is represented as M and volume (in ml) as V.

3.5.4 ANGLE OF REPOSE

Angle of repose (AoR) is defined as a dynamic and static angle at which a powder comes to rest when discharged from a container (Geldart, *et al*., 2006:104). Interactions between cohesive and free-flowing powders can influence the flowability of powders. A higher angle indicates a greater cohesive powder, whereas a lower angle is suggestive of a less cohesive powder (Staniforth *et al*., 2007:170; BP, 2015: XVII N). The following table (table 3.3) provides the quality of flow respective to possible angles at which a powder may come to rest.

Table 3.3: Flow quality of powders for various angles of repose (revised from Wells *et al*., 2007:356)

Flow quality	Angle of repose (degrees)
Excellent	< 20
Good	20 - 30
Acceptable	30 - 34
Very poor	> 40

After the complete discharge of the powder and bead formulations from the hopper, the height and diameter of the resulting heap were measured and recorded (Martin *et al*., 1993:447; Staniforth, 2002:207; Wong, 2002:2636). Figure 3.2 below represents these factors and their respective dimensions in regard to the resting heap. Each experiment was done in triplicate. Using the obtained data, the angle of repose was calculated using the following equation:

$$\mathbf{Tan\theta = \frac{h}{r}} \qquad \textbf{[3.5]}$$

Where h represents the height (mm) of the powder cone and r (mm) is the radius of the base cone.

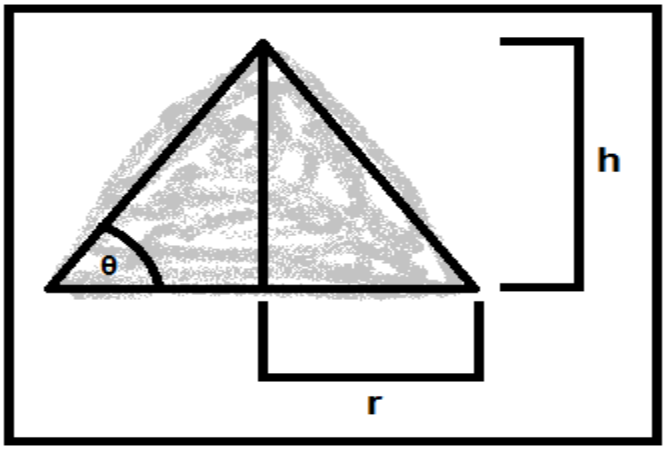


Figure 3.2: Angle of repose of a resting powder heap (bed)

3.5.4 POWDER DENSITY

Another characteristic of powders that influence powder flow which merits consideration, is the density of a powder or formulation. The density of matter, including powders and beads, is described as the mass of that matter divided by the volume that amount of matter may displace. The flow of powder is affected by the density of a powder. Another property directly influenced by the density of powders, is the compressibility of a powder. More densely powders tend to have a weaker flowability, whereas a less dense powder tends to flow more freely (Jallo *et al*., 2012:213; Traina *et al*., 2013:843).

The bulk and tapped densities of the powders and bead formulations were determined by pouring 100 g of cassava starch or bead formulation into a graduated measuring cylinder. The initial occupied volume was measured and the filled cylinder was placed on an Erweka® Tapped Density Tester SVM 12/221 (Heusenstamm, Germany), which was set at an amplitude of 5 A. Each sample was vibrated until a constant volume was obtained (BP, 2015:XVII A). Powder densities were calculated by the following equations:

$$\mathbf{\rho_b = \frac{m}{V_b}} \qquad \textbf{[3.6]}$$

$$\rho_p = \frac{m}{V_p} \quad [3.7]$$

$$\rho_t = \frac{m}{V_t} \quad [3.8]$$

Bulk density (ρ_b) was calculated as the ratio of the mass (m) to the initial (bulk) volume (V_b). Similarly, the tapped density (ρ_t) was calculated as the ratio of mass to the final (tapped volume, V_t) volume of the sample.

3.5.5 COMPRESSIBILITY

Carr's index (percentage compressibility) and the Hausner ratio were respectively calculated from the calculated powder and bead formulation densities. This provided a better understanding of the compressibility of the starch powders and bead formulations (BP, 201:XVII N, Jallo *et al*., 2012:216; Traina *et al*., 2013:843). Table 3.4 reflects the flow quality corresponding to different values of Carr's index and Hausner's ratio. Equation 3.9 and 3.10, were employed to determine the compressibility.

$$\text{Carr's Index (CI)} = \frac{\rho_t - \rho_b}{\rho_t} \quad [3.9]$$

$$\text{Hausner Ratio} = \frac{\rho_t}{\rho_b} \quad [3.10]$$

Table 3.4: Flow quality as indicated by Carr's index and the Hausner ratio (revised from Aulton & Wells, 2002:134)

Flow Quality	Carr's Index (%)	Hausner Ratio
Excellent (free flowing)	5 - 15	1.05 - 1.18
Good	15 - 18	1.18 - 1.22
Fair	18 - 21	1.22 - 1.27
Acceptable	23 - 28	1.27 - 1.39
Poor	28 - 35	1.39 - 1.54
Very poor	35 - 38	1.54 - 1.61

Extremely poor (cohesive)	> 40	> 1.61

3.6 EVALUATION OF THE BEAD FORMULATIONS

3.6.1 FRIABILITY

Durability is another consideration of importance for all SODFs. Mechanical and physical resilience are required during transport and handling. In order to determine the durability of SODFs, the friability was determined. This can be simulated by a tumbling motion of a SODF in a friabilator (Allen *et al*., 2011:233).

Friability was measured using an Erweka® Friabilator (Type TAR 220, Heusenstamm, Germany). As described by the BP (2015), a bead sample of approximately 3 g from each formulation, which was dusted and weighed beforehand, was loaded into the friabilator; 10 glass beads were added to this sample. The initial weight was recorded as W_0. The apparatus was run for a total of 100 revolutions; at 25 rpm for 4 min, followed by the removal of the sample. These samples were dusted and weighed again (W_1) (BP, 2015:XVII G), and the percentage friability was calculated for each formulation using equation 3.11. Each sample was evaluated in triplicate.

$$\%\,\text{Friability} = \frac{W_0 - W_1}{W_0} x100 \qquad [3.11]$$

3.6.2 SWELLING AND MASS LOSS

Swelling was evaluated per published method (Singh *et al.*, 2009:1123). A bead sample of approximately 250 mg was evaluated for each formulation where the initial weight (W_0) was recorded beforehand. Each sample was placed in a basket and introduced into a USP type II dissolution apparatus at 37 ± 0.5°C. The dissolution medium used was 675 ml of a 0.1 M hydrochloric acid (HCl) solution for the first 2 h. Subsequently 225 ml of a 0.2 M phosphate buffer was added and the pH adjusted to 6.8. Samples were drawn at predetermined time intervals of 30, 60, 90, 120, 180, 360, 480, 600 and 720 min, blotted with filter paper and weighed. The measurement of the swollen weight (W_1) was noted. In order to determine the loss (erosion) of the matrix, the swollen samples were dried in a regulated oven at 40 ± 05°C for 12 h and weighed afterwards to record the mass after erosion (W_2). Percentage swelling as well as percentage erosion was calculated with the following equations:

$$\%\,\text{Swelling} = \frac{W_1}{W_0} x100 \qquad [3.12]$$

$$\%\,\text{Erosion} = \frac{W_1 x W_2}{W_0} \qquad [3.13]$$

3.6.3 DISINTEGRATION

Disintegration of SODFs is recognised by the loss of its initial size as a result of the initial unit breaking into smaller pieces. As described in chapter 2, the SODF is fragmented into smaller particles; this in turn increases the surface area of the unit, thereby increasing the rate of dissolution. Disintegration is a constant process (Ashford, 2007:300).

Empty capsules (size 0) were weighed. Each capsule was subsequently filled with beads and weighed again. Six capsules containing spheronised beads were evaluated for disintegration. This was evaluated using a disintegration tester (Erweka® Type ZT 323, Heusenstamm, Germany). Distilled water was used as the disintegration medium and maintained at 37 ± 0.5°C with a thermostat. The encapsulated beads were placed in baskets attached to the disintegration tester, these baskets were dropped into the medium and then raised out of the medium and this process was repeated until the capsules dissolved. The time it took for each capsule to disintegrate was recorded (BP, 2015: XVII A).

3.6.4 ULTRAVIOLET-SPECTROPHOTOMETRIC ANALYSIS

Analytical chemistry is the field which encompasses the many methods relevant to chemical analysis and quantification. Various methods can be employed in order to determine the chemical composition or chemical presence of unknown substances, these include: spectrometric, titrimetric and chromatographic methods (Krull *et al*., 2014:1-7). In the pharmaceutical industry it is vital to determine the quality, composition and quantities of the drug and other excipients present in dosage forms. One of the most widely used methods is ultraviolet-spectrophotometry (UV-spectrophotometry). The science of UV-spectrophotometry is based on the analysis of the energy transition that occurs when a compound is irradiated with ultraviolet light. UV-spectrophotometry is a cost-effective analytical method which can be utilised in order to determine the presence of a compound in solution, if a reference for comparison for that specific compound is available. This rational can be used to determine the concentration of a drug in solution, which in turn can be used to determine the dissolution

behaviour of a drug from a dosage form (Kassab *et al.*, 2010:968-971, Krull *et al*., 2014:10; Wilson *et al*., 2005:591-599).

3.6.4.1 Standard curve

A 25 mg gliclazide sample was vortexed in 10 ml methanol. The solution was added to 75 ml methanol and placed in an ultrasonic bath (Labotec© EcoBath® model 103, Labotec©, Midrand, South Africa) for 20 min. A standard solution of 250 ml was made by adding a 0.1 M HCl-solution to the methanol mixture, which in turn was ultrasonicated for 20 min. The solution was filtered with a 0.45 µm nylon membrane pre-filter attached to a syringe in order to remove contaminants. The resulting filtrate wasultrasonicated for another 20 min. A concentration range of 2 - 40 $\mu g.ml^{-1}$ was prepared. These concentrations were acquired by adding 5 ml of the stock solution to a 250 ml volumetric flask; 10 ml to a 100 ml flaks; 20 ml to a 100 ml flask; 15 ml to a 50 ml flask and 20 ml to a 50 ml flask. Each sample was made up to volume with deionised water. A spectral analysis at 229 nm was conducted using an Analytikjena® UV-spectrophotometer (Speccord® 200 Plus, Jena, Germany). The absorbance values obtained from these analyses where used to determine if a linear relationship exists between the various concentrations within the range. In order to determine the precision of this method, inter- and intraday validations were conducted (Kassab *et al.,* 2010:986-971, Jamadar *et al.,* 2011:339).

3.6.4.1.1 Interday precision

Using the method described in 3.6.4.1 an analysis for linear regression was conducted in triplicate on the same day to determine the precision of the range used, with a resulting %RSD of less than 5% (Chinyemba, 2012: 27-29; Marais, 2013:98-101).

3.6.4.1.2 Intraday precision

For intraday variance the method described above was repeated on three consequent days. %RSD must be less than 5% (Chinyemba, 2012: 27-29; Marais, 2013:98-101).

3.6.5 Dissolution Behaviour

The dissolution behaviour of pharmaceutical dosage forms is important with regards to determining the release profile of the drug from the dosage form. By comparing the dissolution behaviour and release of a commercial SODF (Diamicron®) to that of an experimental SODF, it is possible to determine the viability of the experimental SODF as a candidate for modified release SODFs.

3.6.5.1 Assay

In order to determine the drug loading capacity of the beads, a 100 mg bead sample from each formulation was crushed using a mortar and pestle. It was dispersed in 100 ml ethanol, stirred for 12 h and sonicated in a Labotec EcoBath® (Model 103, Labotec©, South Africa) for 30 min. The subsequent suspension was filtered through a 0.45 µm membrane filter. A 3 ml sample was pipetted into a 100 ml volumetric flask to obtain the correct dilution. This dilution was analysed at a wavelength of 229 nm using a spectrophotometer (Speccord 200 Plus, Analytikjena®, Germany) (Chinyemba, 2012:45).

3.6.5.2 Dissolution studies

Dissolution studies were conducted using a USP paddle method in a six station dissolution apparatus (Distek® 2500 dissolution apparatus, USA). For the first two hours 675 ml of 0.1 M HCl was used as the dissolution medium. Thereafter the pH was adjusted to pH 6.8 by adding 225 ml phosphate buffer (pH 6.8). The stirring rate was set at 50 rpm and the temperature maintained at 37 ± 0.5°C. Samples of approximately 5 ml were withdrawn using an auto sampler (Distek® evolution 4300, USA) at predetermined time intervals of 0, 2.5, 5, 7.5, 15, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720 and 1440 min. A sample was withdrawn at the 24 h interval; the stirring rate was adjusted to 250 rpm for a further 15 min and the last sample was collected (BP, 2015:XII B; Singh *et al*., 2009:1123; USP, 2008:268-269). Samples of 3 ml withdrawn at the various time intervals were diluted to a volume of 10 ml. The withdrawn volume from the vessels, were replaced. This replacement medium was collected from a vessel containing blank medium which was calibrated at each pH level and kept at the same temperature as the experimental vessels. All withdrawn samples were analysed with a ultra-violet (UV) spectrophotometer at 229 nm (BP, 2015: XII B; Singh *et al*., 2009:1123; USP, 2008:268-269).

3.7 STATISTICAL ANALYSIS

To compare the dissolution profiles, three statistical parameters were calculated. These were the mean dissolution time (MDT), the dissimilarity factor (f_1) and the similarity factor (f_2). MDT is the statistical moment of the cumulative dissolution process and is the mean time taken for the drug to dissolve under *in vitro* conditions (Reppas & Nicolaides, 2000:231-232). MDT was calculated with the following equation:

$$\mathbf{MDT} = \frac{\sum_{i=1}^{n} \mathbf{t_{mid}} \Delta \mathbf{x_d}}{\sum_{i=1}^{n} \Delta \mathbf{x_d}} \quad \textbf{[3.14]}$$

Where, MDT is the mean dissolution time in minutes, i the sample number, n the total number of sampling times, t_{mid} the midpoint between i and i-1 and Δx_d the additional mass dissolved between i and i-1 (Chinyemba, 2012:29; Marais, 2013:54-56)

Moore and Flanner (1996:64-74) used the similarity factor (f_2) to compare dissolution profiles. This factor compared the difference between the percentage drug dissolved per unit time for a test and reference formulation. The value of the similarity factor is 100 when two dissolution profiles are identical and approaches 0 as the dissimilarity increases. According to the Food and Drug Administration (FDA), two dissolution profiles can be considered similar when f_2 values between 50 and 100 were obtained (Costa *et al.,* 2001:129). The following equations can be used to calculate the dissimilarity factor (f_1) and the similarity factor (f_2)

$$\mathbf{f_1} = \left\{ \frac{\sum_{t=1}^{n} |\mathbf{R_t} - \mathbf{T_t}|}{\sum_{t=1}^{n} \mathbf{R_t}} \right\} \times \mathbf{100\%} \quad \textbf{[3.15]}$$

$$\mathbf{f_2} = \mathbf{50 log} \left\{ \left[\mathbf{1} + \frac{\mathbf{1}}{\mathbf{n}} \sum_{t=1}^{2} (\mathbf{R_t} + \mathbf{T_t})^2 \right]^{-0.5} \right\} \times \mathbf{100} \quad \textbf{[3.16]}$$

Where, f_1 is the difference factor and f_2, the similarity factor. R_t represents the assay time at time t, T_t the test assay at the same time, n the number of pull points and w_t the optional weight factor.

3.8 SUMMARY

To determine the viability of this study, the previously described experimental methods were utilised. It was the hope that through these methods a suitable formulation for modified release could be produced in order to provide a modified release dosage form. The experimental methodology was employed in such a manner to optimise a formulation containing suitable excipients and concentrations of all the relevant ingredients, including the drug. The viability of cassava starch as an excipient in modified release dosage forms was also determined using

these methods. In chapter 4 the results of these experimental methods will be given and discussed in order to provide a clearly defined picture.

Chapter 4

EXPERIMENTAL RESULTS

4.1 INTRODUCTION

The determination of flow properties provides valuable information on powder mixtures intended for the manufacturing of SODFs. Arguably, the most important properties that influence powder flow are the size and morphology of powder particles. A range of parameters or properties can be investigated to determine whether a powder exhibits acceptable flow. These parameters or properties include compressibility, flow rate, angle of repose and critical orifice diameter, to name a few. Another factor which could affect the quality of powder flow is the moisture content of the powder. Moisture present in the powder can significantly diminish a powder's flow quality (Emery *et al.*, 2009:409).

Physical characteristics of SODFs influence a product's commercial suitability. These characteristics include: friability, disintegration time and dissolution profile of a specific SODF. Friability provides an indication of the robustness of the product during transport and handling. Disintegration describes the process by which an SODF is broken down into smaller pieces and as a consequence increase the surface area available for drug dissolution. Disintegration time, therefore, is the time taken by the SODF to break up into smaller particles as specified by the official pharmacopoeias (BP, 2015:XII A1). Dissolution profiles are used to determine the rate and extent of drug release from a dosage form. Furthermore, dissolution data is useful in determining the similarity or difference between respective formulations. Dissolution data may also be employed to determine whether the release of a drug from a particular dosage form is conventional or modified (Lourenço *et al.,* 2013:367-368).

The different formulation variables and their levels were investigated by means of a fractional factorial design (as discussed in Chapter 3). In order to provide a simplified method of reference to the different formulations, it was decided to provide an identifier, as seen in table 4.1. The identifier consists of a sequence of letters and numbers, representing excipients and levels, for example, M.G5.5.5; where M/C is the filler; G5 is the drug and its concentration (% w/w); the second 5 is the concentration (% w/w) of the binder and the final number (5) represents the concentration (% w/w) of HPMC in the formulation.

Table 4.1 Identifiers for each successful formulation and the composition of each formulation

Identifier	Filler		Gliclazide concentration (% w/w)	Kollidon® 30 concentration (% w/w)	HPMC concentration (% w/w)
	Type	Concentration (%)			
M.G5.3.5*	Avicel®	87	5	3	5
M.G5.5.10	Avicel®	80	5	5	10
M.G10.5.5	Avicel®	80	10	5	5
M.G10.0.10	Avicel®	80	10	0	10
M.G15.0.5	Avicel®	80	15	0	5
M.G15.3.10	Avicel®	72	15	3	10
C.G5.5.5	Cassava	85	5	5	5

*M/C = Filler (M = Avicel® or C = Cassava), G5 = concentration (% w/w) of gliclazide, second number (3) = concentration (% w/w) of Kollidon® 30, last number (5) = concentration (% w/w) of HPMC

4.2 PHYSICAL CHARACTERISTICS OF CASSAVA STARCH

Selected physicochemical properties of the cassava starches were evaluated accordingly to the methodology as put forth in chapter 3, in order to decide which type of starch w could be used as received or whether further processing was necessary. These properties tested included relative humidity (RH) and moisture content. Infrared (IR)-spectrometry was employed to determine if the two samples of starch were identical or represented different crystal forms of the starch.

4.2.1 MOISTURE CONTENT AND THERMAL ANALYSIS

The average moisture content as determined by means of Karl-Fischer titrations of the purchased and donated cassava starch is presented in figure 4.1. At time 0 min, the moisture content for each sample was 15.82 ± 0.339% and 11.84 ± 0.156%, respectively.

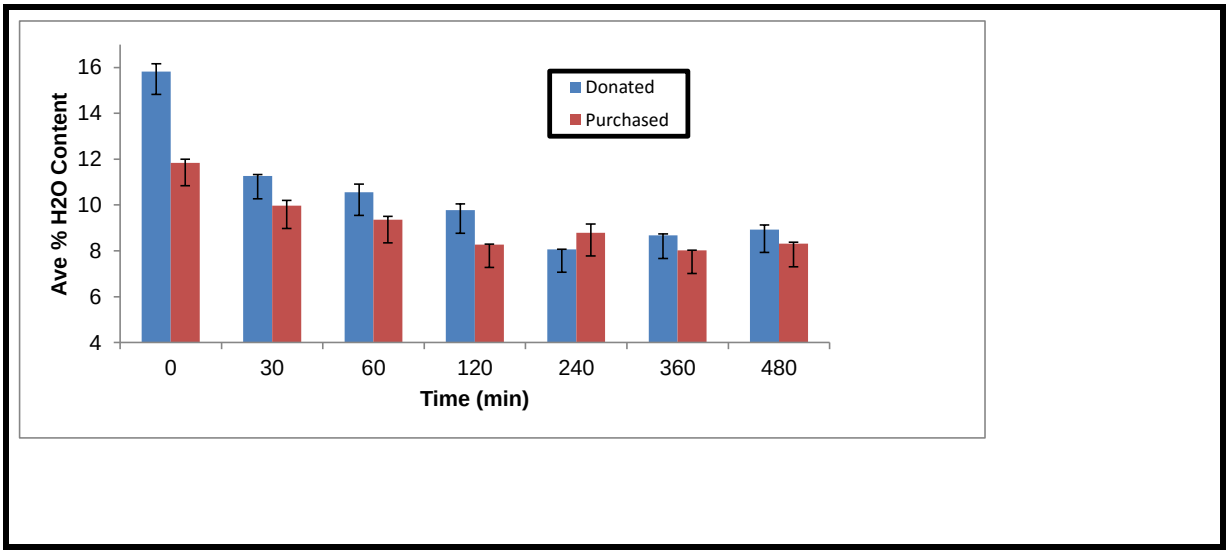


Figure 4.1: Average moisture content of the donated and purchased Cassava starch, at 40°C for various drying times

Powders that contain high levels (> 10%) of moisture have been associated with poor flowability as well as poor powder characteristics (Crouter & Briens, 2014:70-73; Emery *et al.* 2009:414; Nokhodchi, 2005:50). In order to determine whether the moisture was due to hygroscopicity or a constituent of the polymer matrix, differential thermal (DT) and thermogravemetric (TG) analyses were conducted. The thermograms are depicted in figures 4.2 and 4.3.

From these thermograms it was evident that weight loss, due to moisture evaporation, occurred from the initial onset of heating, therefore indicating that the moisture present in the starch samples was not part of the polymer matrix itself, but was present in the powder due to hygroscopicity. Consequently, the temperature and time interval at which the moisture content would be acceptable (6 – 10%) to provide conditions at which the flowability of the powder would be acceptable, was determined (Crouter & Briens, 2014:70-73; Emery *et al.* 2009:414; Nokhodchi, 2005:50).

After drying the starch samples at 25°C, 30°C and 40°C, over a time period of eight hours, the moisture content was re-evaluated. It was determined that for the samples to show acceptable flow, it should be dried at 40°C for 4h in order to achieve a moisture content of 6 – 10%. The average moisture content of the samples dried at 40°C for 4h was measured at 8.07 ± 0.007% and 8.79 ± 0.389%, respectively (Viljoen *et al.,* 2014:730-742).

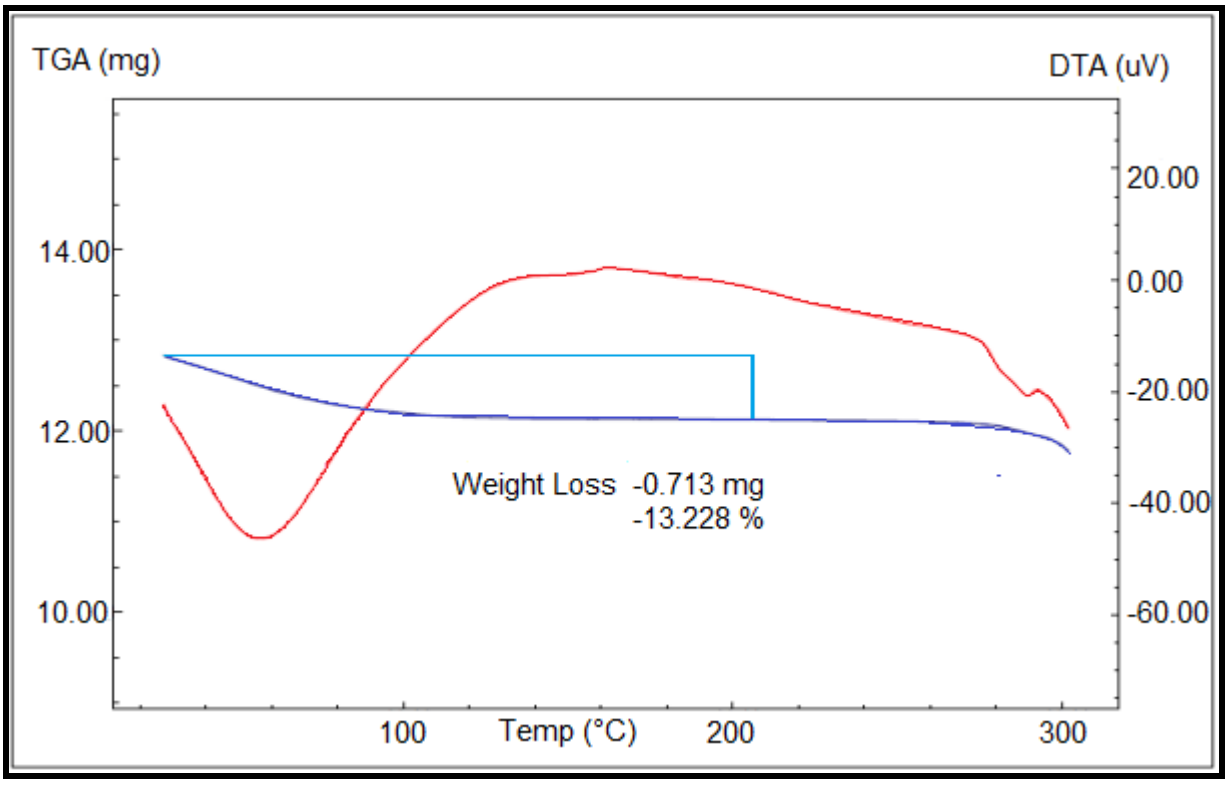


Figure 4.2: Thermogram of donated Cassava starch

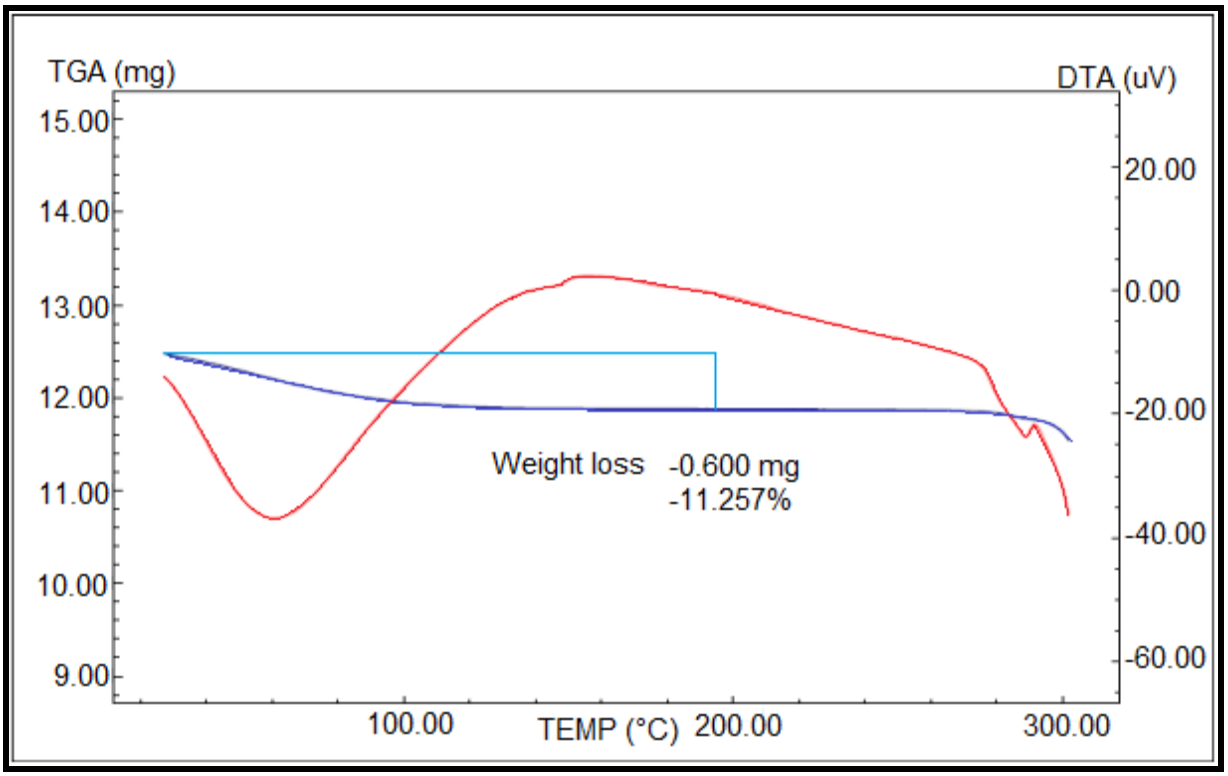


Figure 4.3: Thermogram of purchased Cassava starch

4.2.2 INFRARED-SPECTROSCOPY

Figures 4.4 and 4.5 reflect the IR-spectra for both the donated and the purchased starch.

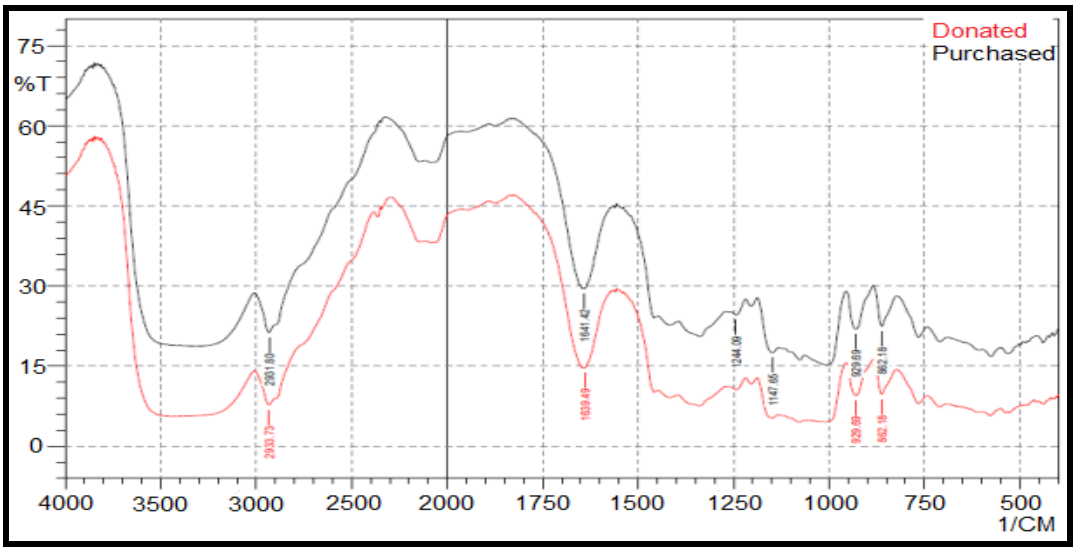


Figure 4.4: Overlay of IR-spectra for the donated (red) and purchased starch (black)

According to the IR-spectrum region of 1500 – 350 cm^{-1}, the two samples of cassava starch proved to be similar. This area serves as a fingerprint to determine, identify and compare substances. Both samples contained a high amount of OH-groups and strong N-triple bonds. In order to confirm the composition of the starch samples, it was opted to improve the resolution of the IR-spectra. The resolution of the spectra was improved with the use of a Fourier transform IR-spectrometry (FTIR). This improved resolution can be seen in figure 4.5.

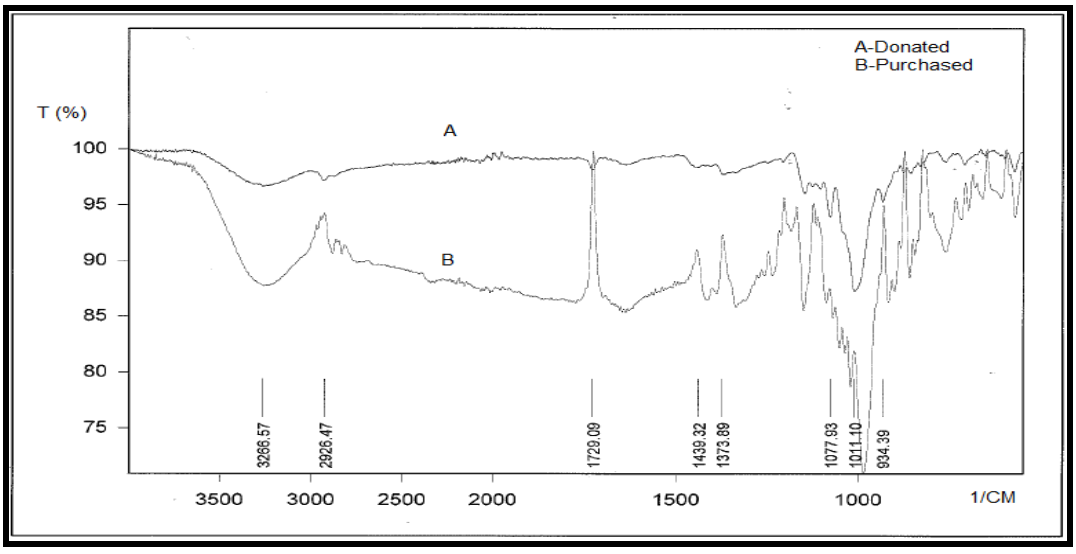


Figure 4.5: IR-spectra from FTIR-analysis of the donated and purchased Cassava starch

FTIR provided a higher resolution and identification of the finger print region, 1500 – 350 cm^{-1}, which indicated that the two starch samples were indeed related. However, the improved resolution did indicate differences between the two samples. This proved that both samples were of two unique starches (Vicentini *et al.*, 2007:756-758). The finger print region of the IR-spectra (obtained using FTIR-analysis) correlated with the IR-spectra given by Huang *et al.* (2007:133).

4.3 PRELIMINARY EXPERIMENTS AND BEAD MANUFACTURING

A 100 mg sample of purchased cassava starch was wetted with distilled water to determine if a wet mass suitable for extrusion could be formed. The purchased starch was selected due to its lower moisture content and possibly higher flowability. This mass needed to have a firm consistency in order to be introduced into the extruder to obtain an acceptable extrudate. These extrusions would be used in the manufacturing of beads. The first attempt proved difficult in producing a mass of acceptable consistency for extrusion. A wet mass was produced with a high concentration of water. This mass seeped through the perforations of the extrusion screen. A mass of this consistency proved inefficient for the production of beads. Consequently, it was decided to use a different wetting agent. An ethanol-water mixture was selected for wetting the mass. With the addition of this wetting agent to another 100 g sample, a firmer wetted mass was produced. This improvement in the consistency of the wetted mass correlates with the data acquired by Millili and Schwartz*.,* (1990:1411) who found that an ethanol:water mixture provided a firmer consistency for extrusion-spheronisation. At 32 rpm, the radial extruder produced extrusions of adequate consistency for spheronisation. After repeated adjustments with regards to the rotation speed of the spheroniser as well as the duration of spheronisation, spherical beads with irregular surface characteristics were obtained (Dhandapani *et al.*, 2012:10-16; Joshi *et al.*, 2011:113). Kumar *et al.* (2012:1) stated that ideally beads should have a spherical shape and a size range of approximately 600 – 1000 µm.

To improve bead quality with regards to size and shape, Kollidon® VA64 was added as binder. The inclusion of Kollidon® VA64 was based on its use in matrix and tablet formulations (Bhaskaran & Lakshmi, 2010:2431; Bühler, 2008:199-241). However, the mass that was produced depicted a more viscous consistency which made extrusion difficult. It was decided to investigate the the substitution of Kollidon® VA 64 with Kollidon , as an alternative binder. Kollidon® 30 provided a mass with a less viscous nature; and consequently the extrusion-

spheronisation of the beads was successful. Beads produced from Kollidon® 30-containing mixtures depicted a more spherical shape. The production of spherical beads prompted the addition of gliclazide. A fractional factorial design (Table 3.2) was employed to investigate the effects of excipients and concentrations on bead formulation.

Microcrystalline cellulose (Avicel®)was selected as alternative filler to cassava starch. Avicel® is an industry standard for both direct compression and bead production (Dukic-Ott *et al.*, 2009:38-39; Vervaet *et al.*, 2008:39). Smooth and spherical beads were successfully produced with Avicel® containing formulations. After this production it was opted to improve the bead spherocity by adding HPMC. HPMC was also selected for its application in matrix based SODFs. However, Avicel® formulations containing no HPMC tended to produce irregularly shaped and non-spherical beads, whereas all formulations containing HPMC rendered spherical beads. HPMC has been described by Gandhi *et al.* (1999:166-168) as a recommended aid with regard to bead manufacturing and bead quality. This could be attributed to the water solubility and consequent gelling of HPMC, which is a low molecular weight polymer (Dukic-Ott *et al*., 2009:42-43; Gandhi *et al.,* 1999:166-168). Cassava starch on the other hand, produced one viable formulation that consisted of spherical beads. These beads therefore had a desirable shape, size and mechanical strength. The success of the formulation, C.G5.5.5, could be attributed to the respective concentrations of each excipient and the drug (Gandhi *et al.*, 1999:163-165; Khan *et al.*, 2001, 350-354; Vervaet *et al.*, 1995:136-143).

The aforementioned process in conjunction with the factorial design was used to determine which mixtures would provide acceptable beads for the remainder of this study. These formulations with acceptable quality is identifiable in table 4.1.

Table 4.2 provides the selected formulations and an indication of whether a successful formulation could be manufactured from the selected combination of excipients.

Table 4.2: Selected formulations and respective excipients and concentration

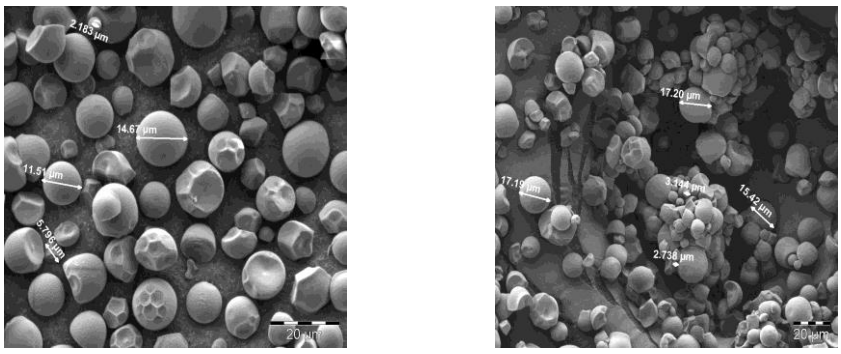
Identifier	Type of filler	Filler concentration	Drug concentration	Kollidon concentration	HPMC concentration	Experimental status*
M.G5.00	Avicel	95	5	0	0	Unsuccessful
C.G5.30	Cassava	92	5	3	0	Unsuccessful
M.G5.3.5	Avicel	87	5	3	5	Successful
C.G5.5.5	Cassava	85	5	5	5	Successful
M.G5.5.10	Avicel	80	5	5	10	Successful
C.G5.0.10	Cassava	85	5	0	10	Unsuccessful
M.G10.3.0	Avicel	87	10	3	0	Unsuccessful
C.G10.3.0	Cassava	86	10	3	0	Unsuccessful
M.G10.5.5	Avicel	80	10	5	5	Successful
C.G10.0.5	Cassava	85	10	0	5	Unsuccessful
M.G10.0.10	Avicel	80	10	0	10	Successful
C.G10.3.10	Cassava	77	10	3	10	Unsuccessful
M.G15.5.0	Avicel	80	15	5	0	Unsuccessful

C.G15.0.0	Cassava	75	15	0	0	Unsuccessful
M.15.0.5	Avicel	80	15	0	5	Successful
C.G15.3.5	Cassava	77	15	3	5	Unsuccessful
M.G15.3.10	Avicel	72	15	3	10	Successful
C.G15.5.10	Cassava	70	15	5	10	Unsuccessful

4.4 MORPHOLOGY AND SIZE

4.4.1 MORPHOLOGY

The morphology of the cassava starch powder particles was visualised by means of SEM, as described in section 3.4.1.1 of this study. Both purchased and donated powders exhibited spherical particles with occasional surface irregularities due to indentations (figure 4.6). From these images it could be seen that both starch samples were in the same size range. It was furthermore clear that the majority of the particles for both starches were less than 50 µm. As poor flowability is usually observed for powders with an average particle size smaller than 100 µm, it would be expected that both starches will probably exhibit poor powder flow. Additionally, agglomeration behaviour was observed in the micrograph depicting the particles of the donated starch. Agglomeration behaviour is usually evident for small particles, indicating cohesive behaviour which affects powder flow negatively (Kim *et al.* 2005:182-186; Landillon *et al.*, 2008:178-179, Lavanya *et al.*, 2011:1338-1339; Staniforth & Aulton, 2007:169).



A **B**

Figure 4.6: Scanning electron microscopy micrographs of (**A**) purchased and (**B**) donated starch

In figure 4.7 SEM-micrographs from the individual bead formulations are shown. For each formulation, the bead shape, surface and internal structure are demonstrated, as indicated by the letters A, B and C, respectively. Each micrograph in each (A, B and C) was conducted on the same scales of magnification respective to that set. Set A had a scale of 1:500 µm, B a scale of 1:20 µm and C a scale of 1:10 µm.

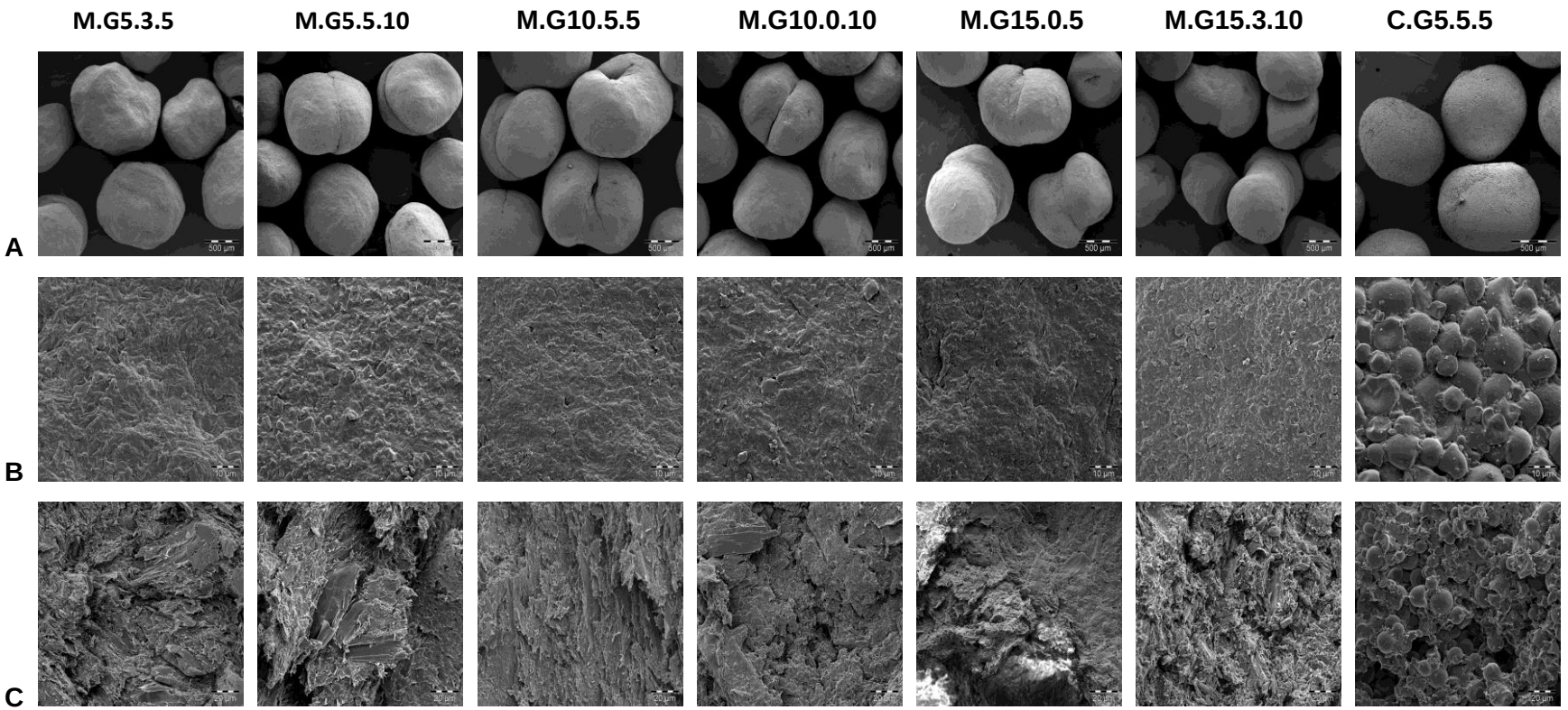


Figure 4.7: SEM - micrographs of the different bead formulations (each set of three micrographs represents the following: **A** - full view of the beads, **B** - the exterior surface morphology and **C** - the internal structure)

It was evident from figure 4.7 that a fairly spherical morphology was exhibited by the majority of the formulations. The formulations, M.G5.3.5 and C.G5.5.5, each depicted a more spherical shape whereas the remaining formulations portrayed either a bean (M.G10.5.5) or dumbbell (M.G15.3.10) shapes that were indicative of insufficient spheronisation (Koester & Thommes, 2010: 1549-1550; Vervaert *et al.*, 1995:136-141). These findings are in agreement with Chopra *et al.* (2013:139), who stated irregularities in shape could occur with Avicel®-containing formulations. The exterior surface morphology of each Avicel® formulation (figure 4.7 A) was smooth and could be suggestive of good flowability (Kim *et al.* 2005:182-186; Lavanya *et al.*, 2011:1338-1339).

Avicel® formulation C.G5.5.5 depicted a general smooth surface, however, with closer inspection of the exterior morphology (figure 4.7 B); a rough surface could be observed. This formulation was the only formulation that contained cassava starch and considering the micrograph of the cassava starch, the rough surface might have been attributed to the cassava particles. The individual beads were grouped together with the assistance of a web-like matrix.

This matrix was formed due to the addition of the binder, HPMC. Both HPMC and Kollidon® tend to form polymer matrices which influence the binding of excipients, as well as drug release (Budiasih *et al.,* 2014:54; Ingle *et al.*, 2013:13; Mustafa *et al.,* 2014:309-311).

In contrast to the cassava-containing formulation (C.G5.5.5), the individual particles of the Avicel® filler could not be identified (figure 4.7 B) in the Avicel® bead formulations. The internal structure of the Avicel®-containing beads (figure 4.7 C) tended to be more densely packed together, whereas, C.G5.5.5 clearly showed cavities within the beads. These voids or cavities could encourage moisture to penetrate the interior core of the beads, which possibly influenced the dissolution rate of the drug (Yang *et al.,* 2014:187-196).

4.4.2 SIZE DISTRIBUTION OF POWDER PARTICLES

Figure 4.8 represents the size-distribution of the individual powder particles and beads.

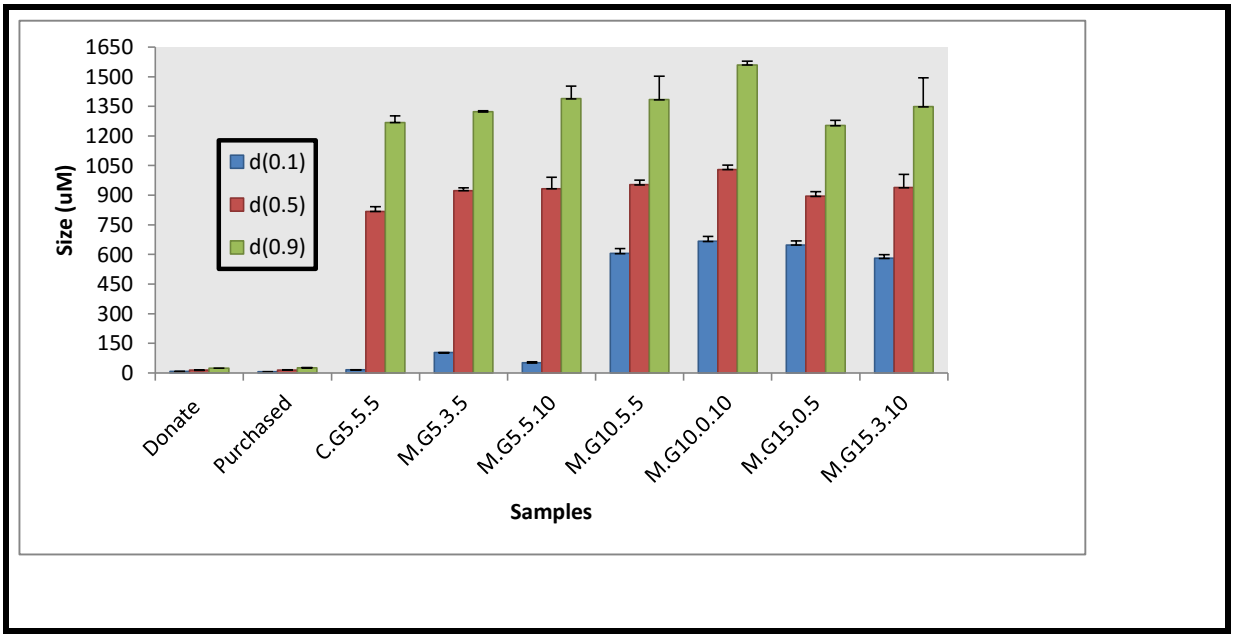


Figure 4.8: Size distribution histogram of both starches and bead formulations. Where d(0.1) = 10% of particles smaller than, d(0.5) = 50% particles smaller than, and d(0.9) = 90% of particles smaller than

Upon comparison of the particle size of both starch powders it could be postulated that the starch powders are likely to exhibit poor powder flow. Lui *et al* (2008:109) stated that if the mean particle size of material is smaller than 100 µm, the cohesive forces between the particles would be higher. This could negatively affect the flow of the powders (Hart, 2015:2; Liu *et al.,* 2008:109; Staniforth & Aulton, 2007:170). From the size distribution of the bead formulations it can be seen that they depicted an average median size range (d(0.5)) of 800 – 1000 µm, as illustrated in figure 4.8. From the particle size data it is expected that all the bead formulations should exhibit good or acceptable flow as the d(0.9) values for all the bead formulations were > 1000 µm. This indicated that 90% of the beads in the measured samples were larger than 1000 µm. Additionally, from figure 4.8 a clear size difference can be seen between the cassava starch powder particles and the C.G5.5.5 beads. This difference in size could presumably improve the flowability of the product (Hart, 2015:2; Lui *et al.*, 2008:109; Vervaet *et al.*, 1994:131-132). Size variation of the beads could be attributed to variation that is seen in all pharmaceutical manufacturing processes. These processes include the amount of

wetting agent added and the duration of time after extrusion, before introduction into the spheroniser (Mallipeddi *et al.*, 2010:56-62; 2014:362-366).

4.5 FLOW PROPERTIES

Several parameters were used to describe the flow behaviour of the cassava powders and the bead formulations. These parameters and the values obtained are reported in table 4.3.

Both starches presented a critical orifice diameter (COD) value of 16 mm, whereas all the bead formulations depicted a COD value of 6 – 7 mm. A high COD value indicates poor powder flow and a smaller COD value is an indication of improved flow. The improved flow was a consequence of the enlarged size of the beads as described in section 4.4. No marked differences were observed pertaining to the COD values for the individual bead formulations.

Neither flow rate nor angle of repose could be determined for both starches. These results indicated weak powder flow which corroborated the postulation in section 4.4, i.e. that the small size of the starch powder particles is expected to be detrimental to powder flow. The moisture content (15.82 and 11.84%) of the donated starch and purchased starch may also aggerasvate the poor flow behaviour. Although a marked improvement (in comparison to the starch powders) in the flow rate was observed for all bead formulations, differences could be seen concerning the different bead formulations. These differences can be attributed to the shape of each formulation's individual beads as depicted in figure 4.6 and 4.7. As the shape of the different bead formulations is not perfectly spherical, contact between the beads might increase providing more friction and thus impeding flow (Javadzadeh *et al.,* 2015: 86-97; Korhonen *et al.,* 2000:1141; Zhang *et al.,* 2003:6-7; Zhang *et al.,* 2004:371-390).

Table 4.3: Flow properties of both starches and bead formulations

	Critical orifice diameter (mm)	Flow Rate ($g.s^{-1}$)	Average angle of repose (°)	Density ($g.cm^{-3}$)		Compressibility	
				Bulk	Tapped	Carr's Index (%)	Hausner Ratio
Donated	16 ± 0.0	No flow	No flow	0.6 ± 0.01	0.8 ± 0.02	0.3 ± 0.01	1.4±0.02
Purchased	16 ± 0.0	No flow	No flow	0.5 ± 0.02	0.8 ± 0.03	0.3 ± 0.01	1.5±0.02
M.G5.3.5	6 ± 0.6	4.8 ± 0.23	26.6 ± 0.22	0.8 ± 0.05	0.9 ± 0.01	0.1 ± 0.06	1.2±0.09
M.G5.5.10	6 ± 0.0	4.7 ± 0.13	28.3 ± 2.59	0.8 ± 0.01	0.9 ± 0.00	0.1 ± 0.02	1.1±0.02
M.G10.5.5	6 ± 0.0	4.6 ± 0.12	25.7 ± 1.45	0.8 ±0.01	0.9 ± 0.01	0.1 ± 0.01	1.1±0.01
M.G10.0.10	7 ± 0.6	5.2 ± 0.15	28.3 ± 1.23	0.8 ± 0.01	0.9 ± 0.00	0.1 ± 0.01	1.1±0.01
M.G15.0.5	6 ± 0.0	3.8 ± 0.08	29.8 ± 2.24	0.8 ± 0.00	0.9 ± 0.00	0.0 ± 0.01	1.0±0.01
M.G15.3.10	6 ± 0.0	3.6 ± 0.0	30.1 ± 0.22	0.8 ± 0.01	0.9 ± 0.00	0.1 ± 0.11	1.1±0.01
C.G5.5.5	6 ± 0.0	4.9 ± 0.14	26.3 ± 0.55	0.8 ± 0.01	0.9 ± 0.00	0.1 ± 0.00	1.1±0.01

Despite the differences in flow rate, all bead formulations exhibited an approximate flow rate of 3.64 – 5.17 $g.sec^{-1}$, indicating good flowability. Both starches and all the bead formulations exhibited Carr's indices and Hausner ratios of < 1 and 1.07 – 1.18, respectively, which is indicative of excellent (free) flow.

The bulk density of 0.60 $g.cm^{-3}$ and 0.55 $g.cm^{-3}$ for the donated and purchased starches, respectfully, were less than that of the beads, which ranged from 0.79 - 0.83 $g.cm^{-3}$. Tapped densities of both starches and beads ranged from 0.81 – 0.91 $g.cm^{-3}$. These results indicated that the powders packed more densely after tapping, which could be ascribed to the smaller particles, leaving less void spaces after being rearranged. The beads on the other hand, did not rearrange as compact as the powder due to the rigidity of the beads and their inability to fill the void spaces in-between. Considering the data for the different flow parameters, it is evident that all the parameters on powder flow for the different bead formulations indicated good to excellent flow behaviour. This is to be expected as beads are known to exhibit acceptable to excellent flow due to their size and more spherical nature. It is therefore clear that the formulation of beads resulted in a pronounced improvement in the flow properties in comparison to the flowability of the starch powders.

From the data it could be concluded that cassava starch does not have an acceptable flow quality, which excludes it as an excipient for direct compression without modification or the inclusion of a glidant. However, the cassava bead formulation exhibited the necessary flowability and therefore potential to be introduced into a tablet press for compression into a multi-unit pellet system. The data also corroborates the influence of size on flow quality, by increasing the size of the particles, with the help of bead manufacturing, the flow quality improved dramatically.

4.6 EVALUATION OF BEAD FORMULATIONS

Each bead formulation was subjected to various experiments in order to determine the viability of the individual formulations for manufacturing as a SODF. In this study one of the objectives was to attempt the compression of the beads into a single unit product. The compression of these beads into a single tablet is known as a multi-unit pellet system(Reddy *et al*., 2012:42-54). This method of SODF manufacturing is based on the concept of providing a modified release dosage form or a fixed dose combination. Each of these has their respective rationale in support of multi-unit pellet system manufacturing. Different types of multi-unit pellet system could be manufactured including direct compressed multi-unit pellet system and encapsulated

particulates. One of the most researched types, are manufactured with direct compression of particulates into a single tablet (Reddy *et al.*, 2012:42-54). The rationale behind a multi-unit pellet system compressed from beads was in part to produce a convenient product for drug delivery. Samples of the bead formulations were introduced into a Korsch® XP1 tablet press. The tablets produced from these beads proved difficult to produce. As each produced batch ejected from the die they either crumbled as they left the die or as they were moved . This could be attributed to insufficient mechanical strength of the compressed tablets. The insufficient mechanical strength may be attributed to the hardness of the individual beads being too high for the necessary deformation in order to compress into a single tablet, or insufficient cohesion between the individual beads. Therefore, it was decided to encapsulate intact beads in size 0 gelatine capsules to render a SODF.

4.6.1 FRIABILITY

Friability of the individual bead formulations provided information regarding the resistance of the beads to breaking or splitting during handling and transport (Chapter 3). Table 4.4 presents the average percentage friability results obtained for the different bead formulations.

Table 4.4: Percentage friability of bead formulations

Bead formulations	Average % friability
M.G5.3.5	1.6 ± 3.22
M.G5.5.10	0.1 ± 0.27
M.G10.5.5	0
M.G10.0.10	0.7 ± 0.20
M.G15.0.5	0
M.G15.3.10	0
C.G.5.5.5	2.0 ± 0.88

Friability values could only be successfully determined for four formulations as the other formulations depicted extremely brittle beads. The analysis indicated that C.G5.5.5 provided a poor friability (2.0 ± 0.88); and M.G5.5.10 and M.G10.0.10 passed the 1% acceptance value specified by the British Pharmacopoeia (BP, 2015: XVII G).

4.6.2 SWELLING AND MASS LOSS

During the swelling and mass loss study the results relating to the cassava starch beads were not obtainable due to the disintegration of the beads. With the removal of the basket containing the cassava beads, the residue of these beads seeped out of the basket, which consequently made the determination of the weight impossible. This could be ascribed to the pH susceptible nature of cassava starch. Cassava rapidly dissolves in a low pH or acidic medium. Figure 4.9 reflects the cumulative increase/decrease in mass (mg) measured for the Avicel® bead samples per time interval (min).

A drastic increase in mass was observed during the first 30 min for all of the Avicel® bead formulations, whereafter no substantial increase or decrease in mass for the following 90 min could be observed. During the first 120 min, the beads were exposed to an acidic medium whereafter the medium was changed to a more alkaline medium (pH 6.8). In the alkaline medium (180 – 720 min) clear differences could be observed between the different Avicel® formulations.

Low gliclazide content allowed for a higher degree of swelling and this could be attributed to the ease at which the moisture permeated the beads due to the fact that less hydrophobic drug was present that would be able to form a barrier against water penetration into the beads. The formulations containing a higher concentration of gliclazide (10 or 15% w/w) depicted decreased swelling. The higher drug content might have decreased the rate as well as quantity of liquid that penetrated the beads due to its natural hydrophobic character (chapter 2). Moreover, formulations comprising higher concentrations of HPMC in combination with a lower concentration Kollidon® 30 portrayed a marked increase in the percentage swelling. This increased swelling could be attributed to the polymer rich HPMC. HPMC is highly hydrophilic and thus attracts moisture into the beads resulting in swelling/expansion of the matrix. The swelling of the polymer could cause pores present in the beads to open and allow more moisture into the beads (Akhgari *et al.*, 2007:51-58; Ghori *et al.*, 2014:1-17;Scholtz *et al.,* 2014:486-501; Viridén *et al.*, 20010:60-67; Viridén *et al.,* 2011:470-479).

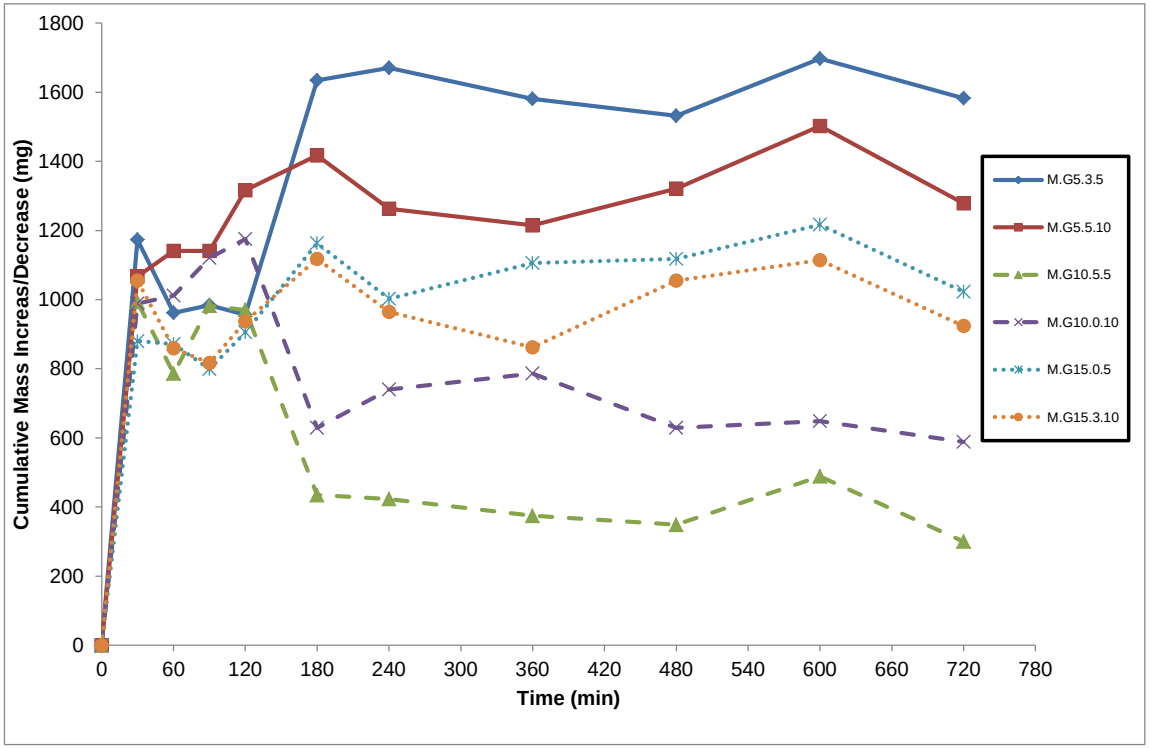


Figure 4.9: Cumulative mass increase or decrease of Avicel® beads as a function of time (min) after exposure to calibrated pH environments.

According to Goyal *et al.* (2009:95-96) swelling of HPMCcontaining formulations are pH dependent. This was also evident within this study as the amount of swelling in the alkaline medium increased noticeably relative to the amount of swelling in the acidic medium. The lower the concentration of Kollidon®, the lower the amount of swelling and also the mass loss. After the swelling experiment, the beads were dried for 12 h until no noticeable weight loss was observed. Annexure C displays the results obtained after drying of the beads and from these results it was evident that the loss on mass of the different Avicel® bead formulations all averaged approximately 170 mg after drying, thus portraying an approximate loss in mass of 30% (Akhgari *et al.*, 2007:51-58; Ghori *et al.*, 2014:1-17; Viridén *et al.*, 2011:470-479).

4.6.3 DISINTEGRATION

All capsules, irrespective of formulation disintegrated in less than 5 min, which complies with specifications of the British Pharmacopoeia (2015: XVII S). Upon disintegration of the capsule shells, the beads were dispersed throughout the disintegration medium.

4.6.4 DISSOLUTION BEHAVIOUR AND STATISTICAL ANALYSES

Several variables needed to be optimised in order to evaluate the bead formulations. This included the amount of beads required to compare dissolution profiles with the control product, i.e. Diamicron®, and standardisation of the analytical method that was employed.

4.6.4.1 Standard curve

A stock solution was prepared according to the method described section 3.6.4. The solution consisted of 25 mg gliclazide dissolved in a 2:3 methanol:HCl - solution. This stock solution was used to prepare a standard solution to construct a standard curve which was utilised for the first 2 h of the dissolution study. Another stock solution was prepared with a 2:3 methanol and phosphate solution with a pH of 6.8. This solution was used to prepare a standard solution in order to construct a standard curve that was used for the remainder of the dissolution study (2 hr to 12 hr).

4.6.4.2 Linearity

The following figure (figure 4.10) provided a graph depicting a linear relation between the absorbance and concentration of gliclazide in a methanol:HCl solution.

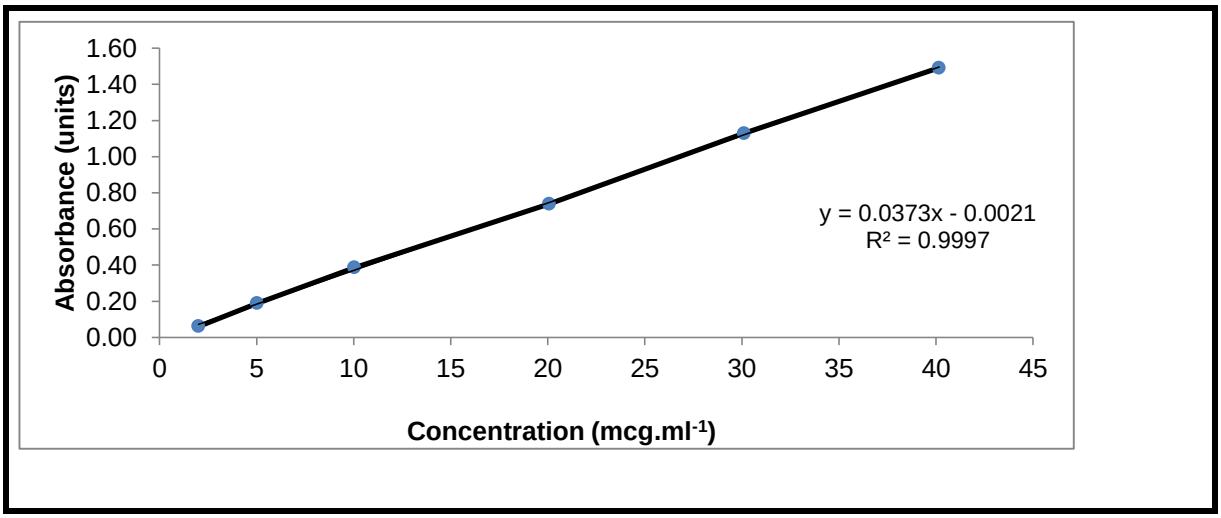


Figure 4.10: Standard curve for gliclazide dissolved in 2:3 methanol:HCl solution

Standard solutions were prepared according to the method described in section 3.6.5. Linearity was observed in a concentration range of 2 – 40 µg.ml^{-1}, with a R^2 - value of ≥ 0.999 for both the acidic and alkaline media. At concentrations higher than 40 µg.ml^{-1} deviation from Beer's law was observed. This phenomenon was also noted by Ibragimova and Ikramov (2015:73-74) with another sulphonylurea, glieipiride. Glimepiride and gliclazide are both examples of the same drug classification, namely second generation sulphonylureas, which are chemically and pharmacologically related (Kalra & Gupta, 2015: 101-104, Kalra *et al*., 2015:314-315).

4.6.4.2.1 Intra- and interday precision

Intra- and interday precision fell within acceptable limits as a %RSD value of ≤ 5% was obtained for both intra- and interday precision (Chinyemba, 2012: 27-29; Marais, 2013:98-101).

4.6.4.3 Dissolution

Dissolution studies were conducted on samples from each formulation containing 30 mg gliclazide. The sample weight was determined based on assay results obtained as per described method (section 3.6.5.1). The selection of the 30 mg drug dose per bead sample was based on the drug dose of the control (Diamicron® tablets; 30 mg gliclazide per tablet). The dissolution profiles of the different bead formulations as well as the control are presented in figure 4.11.

From the dissolution profiles it is observed that the profiles of two formulations appear differently from the other profiles, namely, formulation C.G5.5.5 and M.G15.3.10. From figure 4.11, it is evident that C.G5.5.5 exhibited a burst release of drug within 15 min of the study.

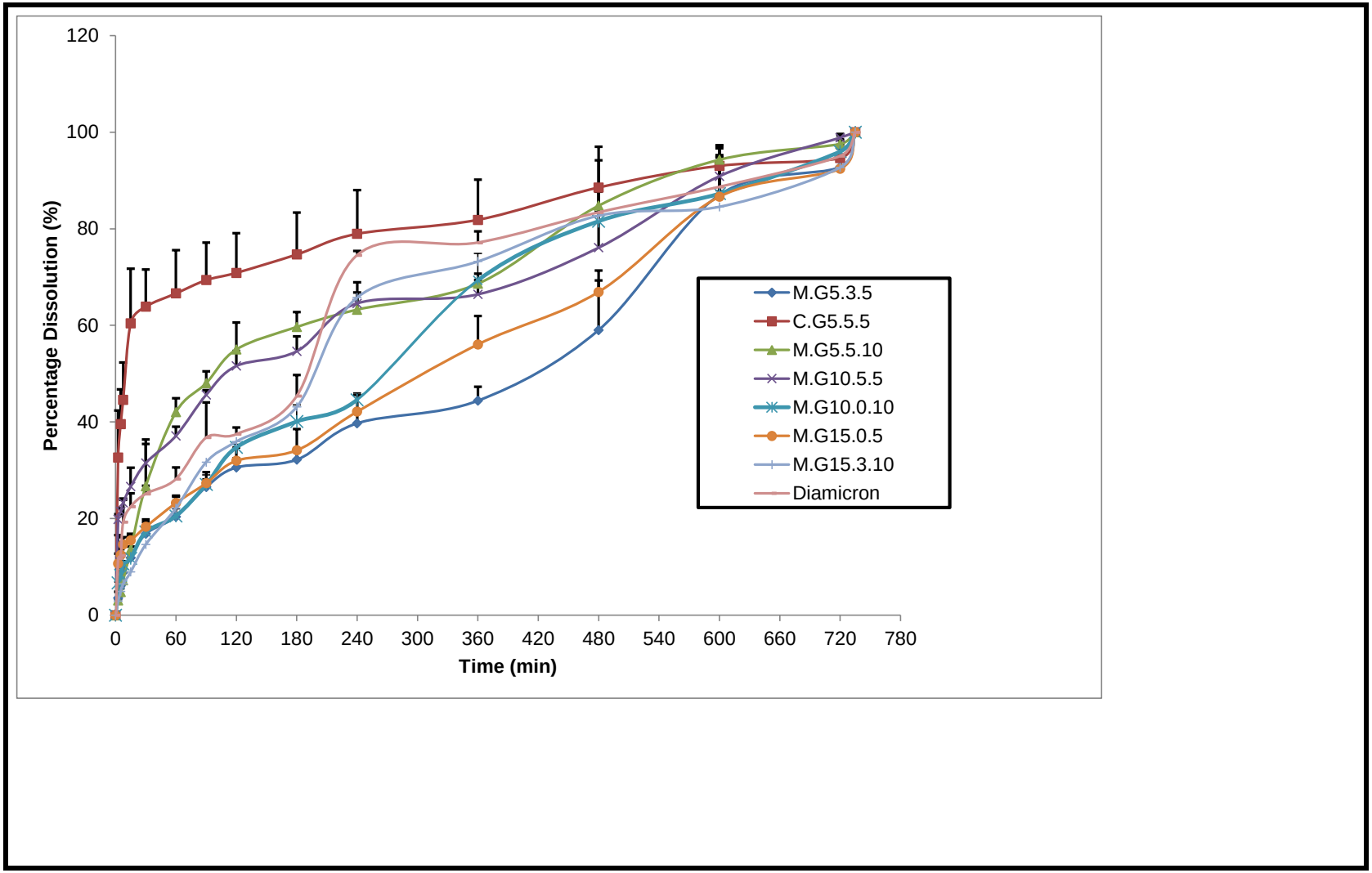


Figure 4.11: Percentage of the drug dissolved as a function of time (min) within pH calibrated medium form simulating either a acidic or alkaline gastric environments

This release is indicative of a fast release of the drug. Burst release can be advantageous in certain applications e.g., drugs which require an immediate release and continuous release for predetermined time interval, though in certain dosage form designs which require a slow initial release, a burst release could be disadvantageous (Huang & Brazel, 2001:121-135). The burst release may be attributed to the existence of cavities within the bead structure as was evident from the SEM micrographs. It was postulated that the existence of these cavities might be beneficial for liquid penetration into the bead structure and thereby benefited the dissolution rate of the drug. This can contribute to the burst release seen within the first few minutes of the dissolution study from this formulation. However, the remaining drug content (± 40 - 50%) was released over the remaining period of the study. The corresponding release profile seen here correlates with figure 2.2.

Although this formulation did not mimic the release profile of the control precisely, it is still evident that extended release was observed over a period of approximately 6 h. Formulation M.G15.3.10 exhibited a dissolution profile similar to the control, Diamicron®, under the test conditions which indicated that it was possible to prepare a multiple pellet system that rendered modified release of gliclazide.

Table 4.5: Mean dissolution time and similarity factor values for each bead formulation and Diamicron®

Formulation	Mean Dissolution Time (min)	Similarity Factor (f_2)
M.G5.3.5	307.1 ± 27.17	37.3 ± 3.55
M.G5.5.10	201.7 ± 5.34	45.8 ± 3.11
M.G10.5.5	226.9 ± 9.21	49.9 ± 3.76
M.G10.0.10	268.3 ± 3.53	45.8 ± 27.00
M.G15.0.5	281.1 ± 9.79	42.8 ± 2.63
M.G15.3.10	215.6 ± 6.42	50.6 ± 4.45
C.G5.5.5	120.0 ± 54.45	27.9 ± 5.07
Diamicron®	211.7 ± 13.59	

In table 4.4, the average MDT-values and similarity factor values of the different formulations are given. This statistical analysis from the dissolution profile (figure 4.11 and table 4.4) provided a more empirical analysis regarding the similarity between dissolution profiles of the respective bead formulations and the control. It also provided data concerning the mean dissolution time.

From table 4.4 it could be seen that, several of the formulations containing Avicel© had MDT values notably longer (20 - 45%) than Diamicron®. A longer MDT indicates a slower rate of release and a low MDT is indicative of a faster release. From the MDT values it could be seen that M.G5.3.5 depicted a MDT 45.50% higher than Diamicron®. The cassava formulation (C.G5.5.5) illustrated a dissolution profile, with an MDT of 43.60% less than that of the control. This low MDT (119.99 ± 54.451) could be attributed to the rapid dissolution of the beads within the first 15 min of the study. Formulation M.G15.3.10 exhibited a MDT-value similar to that of Diamicron®. This correlates with the profile seen in figure 4.11; and the f_2-value of M.G15.3.10 exceeded 50%, thus rendering M.G15.3.10 similar to the control. Although extended release for formulation C.G5.5 can be observed from figure 4.11 it exhibited the fastest MDT value (119.99 ± 54.541 min) and lowest similarity factor value (27.86 ± 5.071); and therefore it can be concluded that the cassava-containing formula did exhibited a dissolution profile that differed markedly from the profile observed for the control. Based on the dissolution parameters and dissolution profiles depicted in figure 4.11, all formulations exhibited extended release although to different degrees in comparison to the control, Diamicron® tablets. This highlights the versatility of a multiple unit pellet system in modifying drug release.

HPMC has been described as an aid for modified drug release (Moodley *et al.*, 2011:18-43; Okunlola, 2015:1). This attribute could be ascribed to the high swellability and hydrophilic nature of HPMC's polymer matrix and consequent dissolution of the expanded matrix during dissolution (Jiyauddin *et al.*, 2014: Moodley *et al.*, 2012:18-43; Oliveira *et al.*, 2013:2; Scholtz *et al.*¸ 2014:486-501; Siepmann & Peppas, 2012:163-173; Uhrich *et al.*, 1999:3181-3198). These various characteristics of HPMC contributed to prolonged MDT-values of the Avicel® formulations.

4.7 SUMMARY

Moisture content as determined by Karl-Fischer titration indicated the starches were highly susceptible to humidity. Conversely, powders with lower moisture content proved

advantageous in regards to flow. IR-spectroscopy indicated the relationship betweenthe two starches and FTIR-analysis confirmed the difference between the two starch samples.

The bead formulations were evaluated with regards to surface morphology and internal structure by means of SEM. SEM-micrographs, revealed that although not perfectly spherical, beads were successfully prepared. The bead formulation containing cassava exhibited a rough surface that could be accredited to the morphology of the cassava particles itself. Bead formulations containing Avicel® demonstrated a more tightly packed internal structure. Size analysis indicated that the majority of bead samples were larger than 1000 µm. Furthermore, the starch powders exhibited poor powder flow properties, whereas all of the bead formulations exhibited good powder flow properties. This was confirmed by all the powder flow parameters that were determined.

With regards to swelling and erosion studies, the cassava-containing beads formulation disintegrated quickly and swelling could therefore not be determined. However, Avicel® swelling for all the Avicel®-containing formulations was evident. Moreover, it appeared that the inclusion of HPMC resulted in an increased degree of bead swelling; however, its inclusion also resulted in an increase in bead erosion.

Parameters and data obtained from the dissolution studies provided evidence which promotes the application of cassava starch as an excipient in the production of modified release SODFs. Depending on the excipients and manufacturing parameters used in production, the dissolution behaviour can be similar to that of a commercial product or even be significantly greater.

Chapter 5 will conclude the study with a general summary and conclusion as well as possible avenues for further study.

Chapter 5

General Summary and future Prospects

5.1 SUMMARY & FUTURE PROSPECTS

The aim of this study as stated in Chapter 1, was to investigate the possible application of cassava starch as a modified release excipient; and whether a modified SODF could be manufactured. Chapter 2 provided a literature overview regarding SODF manufacturing, different types of SODFs and excipients used to manufacture SODFs. It continued with the description of starch as a versatile excipient and the selected starch source, cassava. Cassava, one of the dominant sources of starch, is widely spread throughout sub-tropic environments and easily cultivated. Being a biodegradable and renewable source of starch, cassava is promising in many industries, e.g. clothing, paper, pharmaceutical, *etc.*. It is rich in amylopectin and amylose, the two dominant biopolymers found within cassava. These polymers are cross-linked forming a natural occurring matrix. Polymer-matrices have proven advantageous in the development of various dosage forms, especially in modified release SODFs. For the above mentioned reasons, the use of Cassava as a renewable source of starch can be advocated with merit. Chapter 3 dealt with the experimental methods that were employed to determine the physical characteristics, size, morphology and flow properties of the starch and extrusion-spheronised beads.

From the results, it was evident that cassava starch was a hygroscopic starch, with weak flow properties. This poor flowability would adversely affect the ability of the cassava starch to be used in terms of direct compression. The moisture content of the powders was determined as 15.82 ± 0.339% and 11.84 ± 0.156% respectively for the donated and purchased starch. IR-spectra were obtained to provide a fingerprint in order to compare the two starches. Thermo-graphs were constructed for both starches and this indicated whether the moisture was present as part of the chemical structure of the powder or whether it was present due to hygroscopicity. From the thermo-graphs it could be seen that the moisture was present due to hygroscopicity and not part of the chemical structure. This indicated the possibility of altering the powder flow by simply heating the powder in a regulated oven.

By manufacturing beads from cassava the flow was drastically improved. The manufacturing of cassava beads were difficult due to the presence of the hydrophobic drug, gliclazide, which was

selected as a model drug due to its importance as a second line treatment in Diabetes Mellitus Type-2. Several successful bead formulations were manufactured with Avicel® as filler. The production of Avicel® provided a product to which a bead manufactured frm cassava can be compared. It was also evident from the study, that HPMC played a vital role in the manufacture of quality beads. HPMC containing beads depicted a higher quality in terms of spherocity, which corroborates findings by Dukic-Ott *et al*. (2009:42-43) and Ghandi *et al.,* (1999:166-168). HPMC furthermore contributed to the modification of drug release (Moodley *et al.*, 2012:21-36; Oliveira *et al.*, 2013:2). Multi-unit particulate system tablets could not be manufactured with cassava beads due to the inability of the tablet to hold its shape. These tablets crumbled into deformed beads. It was opted to encapsulate different intact bead samples in hard gelatine capsules.

SEM-micrographs provided visual data relating to the shape of the powder particles, as well as the whole beads, their internal structure and external morphology. These micrographs indicated that the powder particles were spherical and exhibited surface irregularities. Size-distribution analyses on the cassava powder particles and bead formulations were conducted. The D(0.9) value for the starch particles were < 100 µm and all bead samples were < 1000 µm. Flow properties of the powders and beads were characterised using various parameters (e.g. critical orifice diameter, angle of repose, compressibility, etc.). Collectively, these parameters indicated that the starches exhibited poor flow and that the beads portrayed acceptable flow. Friability analyses illustrated that that the cassava bead formulations might not have acceptable physical stability to withstand transport or handling.

Dissolution studies were conducted over a 12 h period. Samples were taken at predetermined, time intervals and analysed with a UV-spectrometer for gliclazide content. Dissolution profiles were characterised by means of the mean dissolution time (MDT) and similarity factor (f_2). Cassava starch beads provided modified drug release, where 60% of the total drug content was pharmaceutically available within the first 15 min of the study. The remaining 40% dissolved slowly over the remaining duration of the study. These beads depicted a MDT markedlyf less than that of Diamicron®, at approximately 120.00 ± 13.59 min compared to a MDT value of 211.70 ± 13.59 min for the Diamicron® tablets. The release profile of the Cassava beads were not similar to the control (Diamicron®) as evidenced by a similarity factor value of 27.86 ± 5.07%. Avicel® containing formulations exhibited MDT values ranging from 201.68 ± 5.34 to 307.05 ± 27.17 min. HPMC did not appear to affect drug release as no clear tendency could be identified related to HPMC content.

5.2 FUTURE PROSPECTS

This study employed cassava starch, a sustainable, renewable and cost-effective, source of starch as an excipient in modified release SODFs. Test formulations contained a binder, HPMC and the poor water soluble drug, gliclazide. Extrusion-spheronisation was the chosen method of bead manufacturing for the production of a modified release SODF. From the results of this study, the following prospects for future studies are identified:

1) The effects of a water soluble drug can be investigated, instead of a poorly water soluble drug, to evaluate the possible manufacturing of beads with cassava starch.
2) Multi-unit particulate system MUPS tablets containing cassava starch should be re-manufactured, by altering the method of bead drying. Instead of using a regulated oven, the beads could be lyophilised. This might provide a less rigid bead, capable of deforming during compression and improving cohesion, which in turn could provide a more stable and resilient MUPS tablet.
3) Another consideration in the manufacture of MUPS tablets from beads in this study, is the mixing of a binder or filler to provide cohesion between the individual beads, before compression.
4) Investigation of cassava starch in combination with other fillers, e.g. Avicel®, Microcelac®, etc., in order to explore cassava starch as a release modifying excipient in bead formulations and to evaluate the effect of these additions on bead manufacture.
5) An enteric coating can be applied to the cassava starch beads to prevent fast/immediate dissolution of the cassava starch in the acidic environment of the stomach, which in turn can influence the release profile of bead formulations containing this starch.

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I hereby confirm and declare that this study is my own and where suitable reference and acknowledgement is given to external parties and sources

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ANNEXURE A

THERMOANALYSIS, MOISTURE CONTENT AND SIZE-DISTRIBUTION

MOISTURE CONTENT

Table A.I: Karl-Fischer titration values for moisture content of the donated Cassava starch

Donated Starch						
Time (min)	**Moisture (%H_2O)**					**%Weight Loss**
	Run 1	**Run 2**	**Average**	**SD**	**%RSD**	
Reference Sample						
0	15.58	16.06	15.82	0.339	0.24	10.80
Moisture Content at 25°C						
30	14.15	14.11	14.13	0.028	0.02	10.21
60	12.89	12.88	12.89	0.007	0.01	5.75
120	11.94	12.1	12.02	0.113	0.08	5.63
240	11.61	11.65	11.63	0.028	0.02	9.167
360	11.37	11.71	11.54	0.240	0.17	8.84
480	11.49	11.98	11.74	0.346	0.25	9.46
Moisture Content at 30°C						
30	12.89	13.04	12.97	0.106	0.08	6.67
60	11.85	11.75	11.8	0.071	0.05	6.79
120	10.82	10.88	10.85	0.042	0.03	7.83
240	10.77	10.49	10.63	0.198	0.14	9.35
360	9.79	10.45	10.12	0.467	0.33	8.26
480	10.56	11.78	11.17	0.863	0.61	8.12
Moisture Content at 40°C						

30	11.31	11.23	11.27	0.057	0.04	9.67
60	10.81	10.29	10.55	0.368	0.26	9.40
120	9.57	9.97	9.77	0.283	0.20	8.86
240	8.06	8.07	8.07	0.007	0.01	9.06
360	8.72	8.62	8.67	0.070	0.05	5.01
480	8.78	9.07	8.93	0.205	0.15	4.39
Moisture Content at 50°C						
30	9.62	9.65	9.65	0.042	0.03	5.81
60	8.81	8.76	8.79	0.035	0.03	8.79
120	6.76	6.50	6.63	0.184	0.13	1.60
240	6.33	6.21	6.27	0.084	0.06	7.07
360	6.52	6.38	6.45	0.099	0.07	4.52
480	6.66	6.81	6.74	0.106	0.08	2.18

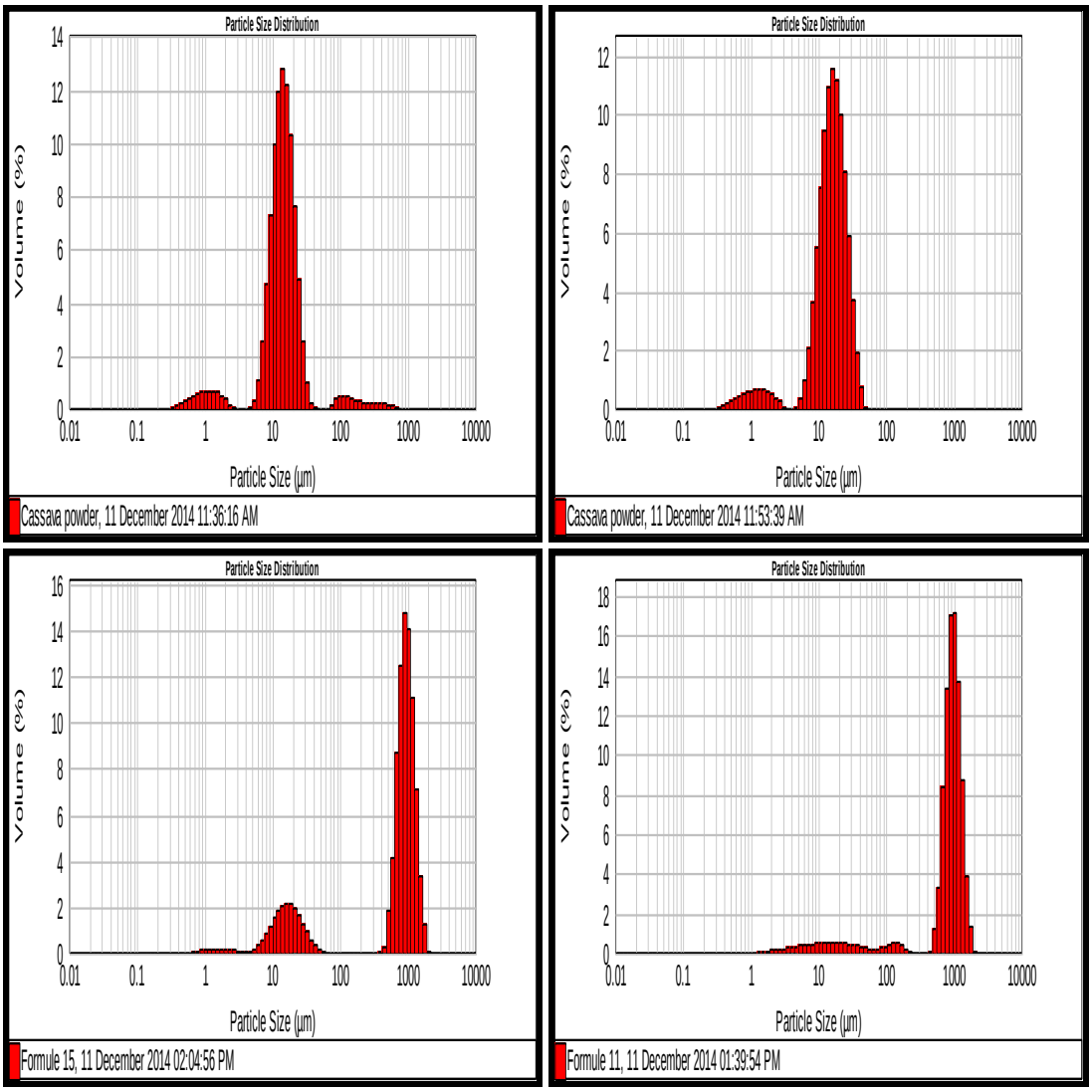
Table A.II: Karl-Fischer titration values for moisture content of the purchased Cassava starch

Purchased Starch						
Time (min)	**Moisture (%H_2O)**					**%Weight Loss**
	Run 1	**Run 2**	**Average**	**SD**	**%RSD**	
Reference Sample						
0	11.95	11.73	11.84	0.156	0.11	7.89
Moisture Content at 25°C						
30	12.28	11.81	12.05	0.332	0.24	4.47
60	12.61	12.51	12.56	0.071	0.05	10.19

120	12.1	12.37	12.24	0.191	0.14	7.44
240	12.59	12.42	12.51	0.120	0.09	7.87
360	12.39	11.62	12.01	0.544	0.39	10.64
480	11.64	11.82	11.73	0.127	0.09	6.61
Moisture Content at 30°C						
30	11.63	11.75	11.69	0.085	0.06	10.10
60	11.58	11.39	11.49	0.134	0.10	9.94
120	11.2	10.63	10.92	0.403	0.29	8.79
240	10.14	9.97	10.06	0.120	0.09	3.43
360	10.19	10.18	10.19	0.007	0.01	8.79
480	10.69	10.74	10.72	0.035	0.03	3.88
Moisture Content at 40°C						
30	10.13	9.82	9.98	0.219	0.11	4.49
60	9.46	9.25	9.36	0.148	0.07	3.91
120	8.26	8.29	8.28	0.021	0.01	8.47
240	9.06	8.51	8.79	0.389	0.19	10.06
360	8.02	8.01	8.02	0.007	0.00	3.86
480	8.36	8.26	8.31	0.070	0.04	8.86
Moisture Content at 50°C						
30	8.91	8.87	8.89	0.028	0.02	4.97
60	7.72	7.71	7.72	0.007	0.01	8.19
120	7.21	7.04	7.13	0.120	0.09	3.65
240	6.29	6.81	6.55	0.368	0.26	2.92

360	6.06	6.68	6.37	0.438	0.31	7.15
480	6.84	7.13	6.99	0.205	0.15	4.25

MALVERN MASTERSIZER® SIZE DISTRIBUTION



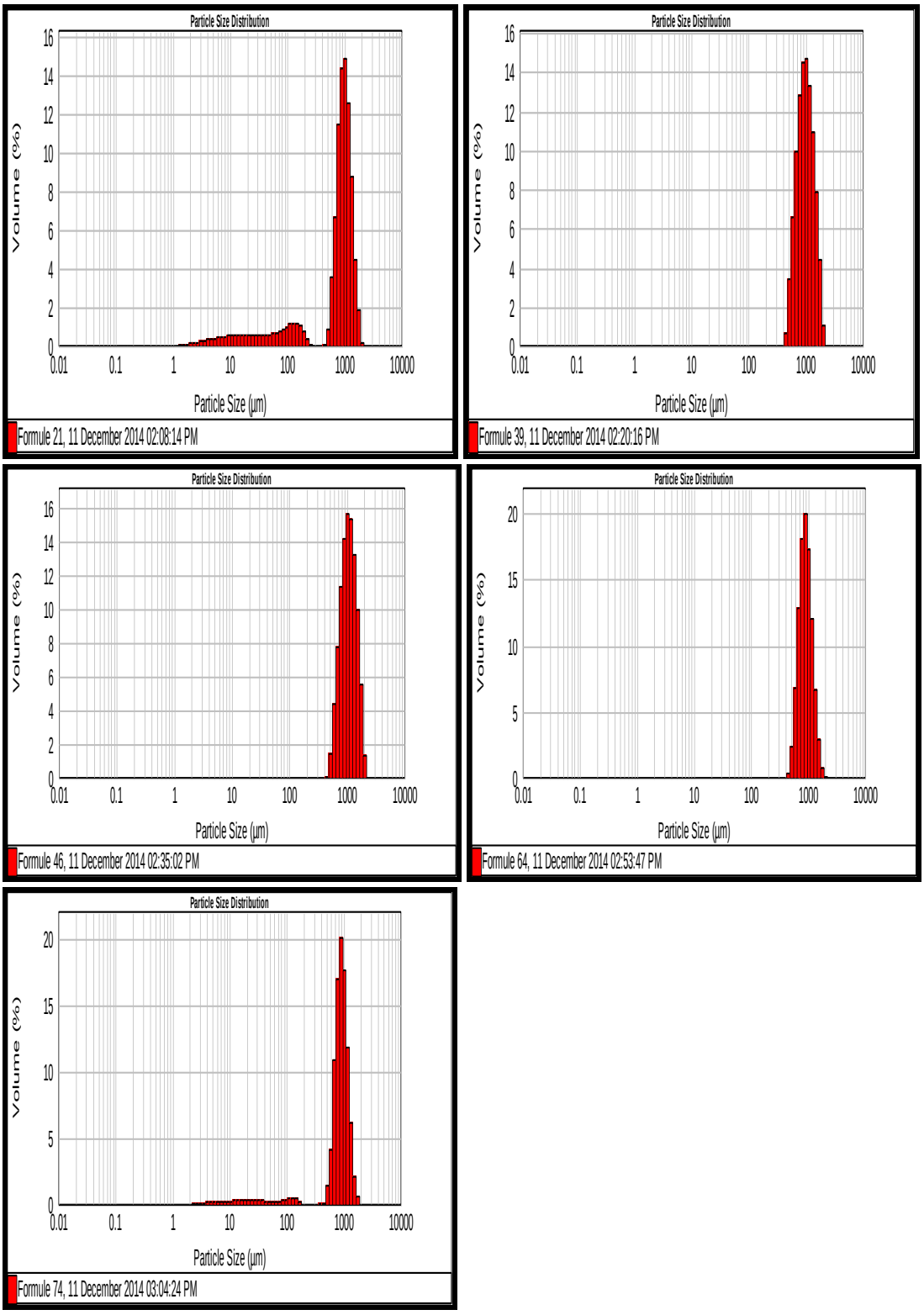


Figure A.I: Example graphs of size distribution graphs for starch powders and bead formulations

Table A.III: Size distribution values starch powders and bead formulations

Donated starch				Purchased starch				C.G5.5.5 (Formula 15)			
Run	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**
1	7.57	14.09	24.97	**1**	7.52	15.68	27.56	**1**	11.92	809.98	1282.51
2	7.51	13.99	24.48	**2**	7.40	15.36	26.76	**2**	15.06	844.49	1292.73
3	7.53	14.02	24.56	**3**	7.27	15.10	26.19	**3**	22.25	800.28	1229.79
AVE	7.54	14.03	24.67	**AVE**	7.39	15.38	26.83	**AVE**	16.41	818.25	1268.35
SD	0.032	0.053	0.263	**SD**	0.125	0.293	0.688	**SD**	5.293	23.240	33.776
%RSD	0.43	0.38	1.07	**%RSD**	1.69	1.91	2.56	**%RSD**	32.26	2.84	2.66
M.G5.3.5 (Formula 11)				**M.G5.5.10 (Formula 21)**				**M.G10.5.5 (Formula 39)**			
Run	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**
1	130.48	915.14	1324.80	**1**	42.20	891.28	1353.65	**1**	625.00	974.89	1520.93
2	99.55	915.95	1326.34	**2**	33.04	909.48	1351.75	**2**	608.12	930.42	1303.36
3	80.79	939.39	1316.49	**3**	80.58	998.27	1461.19	**3**	583.63	955.66	1327.95
AVE	103.61	923.49	1322.54	**AVE**	51.94	933.01	1388.86	**AVE**	605.58	953.66	1384.08
SD	25.091	13.776	5.301	**SD**	25.223	57.246	62.647	**SD**	20.803	22.303	119.153
%RSD	24.22	1.49	0.40	**%RSD**	48.56	6.14	4.51	**%RSD**	3.44	2.34	8.61

M.G10.0.10 (Formula 46)				M.G15.0.5 (Formula 64)				M.G15.3.10 (Formula 74)			
Run	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**	**Run**	**d(0.1)**	**d(0.5)**	**d(0.9)**
1	685.42	1052.65	1579.03	**1**	635.24	875.93	1221.62	**1**	557.14	881.13	1236.32
2	665.75	1028.05	1559.55	**2**	635.91	888.56	1266.07	**2**	512.80	921.78	1295.57
3	649.22	1009.31	1540.53	**3**	673.76	920.55	1269.95	**3**	672.52	1013.07	1513.84
AVE	666.80	1030.00	1559.70	**AVE**	648.30	895.01	1252.55	**AVE**	580.82	938.66	1348.58
SD	18.123	21.7367	19.249	**SD**	22.048	22.998	26.857	**SD**	82.454	67.569	146.157
%RSD	2.72	2.11	1.23	**%RSD**	3.40	2.57	2.14	**%RSD**	14.20	7.20	10.84

ANNEXURE B

FLOW AND PHYSICAL PROPERTIES

FLOW PROPERTIES

Table B.I: Time and flow rate for Cassava starch powders and beads

Samples	Mass (g)	Time (s)					Flow Rate ($g.s^{-1}$)				
		1	2	3	Ave	SD	1	2	3	Ave	SD
Donated	100.14	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow
Purchased	101.07	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow
M.G5.3.5	99.59	22.00	20.00	21.00	21.00	1.000	4.53	4.98	4.74	4.75	0.226
M.G5.5.10	100.84	22.00	21.00	21.00	21.33	0.577	4.58	4.80	4.80	4.73	0.126
M.G10.5.5	99.72	22.00	21.00	22.00	21.67	0.577	4.53	4.75	4.53	4.60	0.125
M.G10.0.10	99.97	19.00	19.00	20.00	19.33	0.577	5.26	5.26	5.00	5.17	0.152
M.G15.0.5	100.02	26.00	26.00	27.00	26.33	0.577	3.85	3.85	3.70	3.80	0.082
M.G15.3.10	100.73	28.00	28.00	27.00	27.67	0.577	3.60	3.60	3.73	3.64	0.077
C.G5.5.5	100.10	20.00	20.00	21.00	20.33	0.577	5.01	5.01	4.77	4.93	0.138

Table B.II: Parameters relating to angle of repose, angle of repose and critical orifice diameter

Samples	Mass (g)	h (mm)					r (mm)				
		1	2	3	Ave	SD	1	2	3	Ave	SD
Donated	100.14	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow
Purchased	101.07	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow	No Flow
M.G5.3.5	99.59	3.00	3.10	2.90	3.00	0.100	5.95	6.15	5.85	5.98	0.153
M.G5.5.10	100.84	3.00	3.00	3.10	3.03	0.058	5.00	6.21	5.80	5.67	0.615
M.G10.5.5	99.72	3.10	2.70	2.90	2.90	0.200	6.05	6.00	6.00	6.02	0.029
M.G10.0.10	99.97	3.20	3.30	3.30	3.27	0.058	6.20	6.25	5.80	6.08	0.247
M.G15.0.5	100.02	3.10	3.50	3.30	3.30	0.200	5.95	5.60	5.75	5.77	0.176
M.G15.3.10	100.73	3.40	3.40	3.50	3.43	0.058	5.80	5.90	6.05	5.92	0.126
C.G5.5.5	100.10	2.90	3.00	3.00	2.97	0.058	6.00	5.50	6.20	6.02	0.361
Samples	**Mass (g)**	**AoR (°)**					**COD (mm)**				
		1	2	3	Ave	SD	1	2	3	Ave	SD
Donated	100.14	No Flow	No Flow	No Flow	No Flow	No Flow	16.00	16.00	16.00	16.00	0.000
Purchased	101.07	No Flow	No Flow	No Flow	No Flow	No Flow	16.00	16.00	16.00	16.00	0.000
M.G5.3.5	99.59	26.76	26.75	26.37	26.63	0.223	5.00	6.00	6.00	5.67	0.577
M.G5.5.10	100.84	30.96	25.78	28.12	28.29	2.594	6.00	6.00	6.00	6.00	0.000
M.G10.5.5	99.72	27.13	24.23	25.80	25.72	1.453	6.00	6.00	6.00	6.00	0.000

M.G10.0.10	99.97	27.30	27.83	29.64	28.26	1.226	6.00	7.00	7.00	6.67	0.577
M.G15.0.5	100.02	27.52	32.01	29.85	29.79	2.243	6.00	6.00	6.00	6.00	0.000
M.G15.3.10	100.73	30.38	29.95	30.05	30.13	0.223	6.00	6.00	6.00	6.00	0.000
C.G5.5.5	100.10	25.61	26.57	26.57	26.25	0.551	6.00	6.00	6.00	6.00	0.000

Densities & compressibility

Table B.III Volumes, densities and compressibility data for both starches and bead formulations

Bulk											
Samples	**Mass (g)**	**Volume (cm^3)**					**Density ($g.cm^{-3}$)**				
		1	**2**	**3**	**Ave**	**SD**	**1**	**2**	**3**	**Ave**	**SD**
Donated	100.14	168.00	166.00	164.00	166.00	2.000	0.60	0.60	0.61	0.60	0.007
Purchased	101.07	192.00	182.00	180.00	184.67	6.429	0.53	0.56	0.56	0.55	0.019
M.G5.3.5	99.59	138.00	124.00	122.00	128.00	8.718	0.72	0.80	0.82	0.78	0.051
M.G5.5.10	100.84	120.00	122.00	122.00	121.33	1.155	0.84	0.83	0.83	0.83	0.008
M.G10.5.5	99.72	126.00	126.00	124.00	125.33	1.155	0.79	0.79	0.80	0.80	0.007
M.G10.0.10	99.97	124.00	122.00	125.00	123.67	1.528	0.81	0.82	0.80	0.81	0.010
M.G15.0.5	100.02	120.00	121.00	121.00	120.67	0.577	0.83	0.83	0.83	0.83	0.004
M.G15.3.10	100.73	128.00	127.00	125.00	126.67	1.528	0.79	0.79	0.81	0.80	0.010
C.G5.5.5	100.10	121.00	122.00	123.00	122.00	1.000	0.83	0.82	0.81	0.82	0.007
Tapped											
Samples	**Mass (g)**	**Volume (cm^3)**					**Density ($g.cm^{-3}$)**				
		1	**2**	**3**	**Ave**	**SD**	**1**	**2**	**3**	**Ave**	**SD**
Donated	100.14	124.00	122.00	118.00	121.33	3.055	0.81	0.82	0.85	0.83	0.021
Purchased	101.07	130.00	124.00	120.00	124.67	5.033	0.78	0.82	0.84	0.81	0.033
M.G5.3.5	99.59	110.00	110.00	112.00	110.67	1.155	0.91	0.91	0.89	0.90	0.009
M.G5.5.10	100.84	116.00	114.00	114.00	114.67	1.155	0.87	0.88	0.88	0.88	0.009

M.G10.5.5	99.72	114.00	114.00	114.00	114.00	0.000	0.87	0.87	0.87	0.87	0.000
M.G10.0.10	99.97	111.00	110.00	111.00	110.67	0.577	0.90	0.91	0.90	0.90	0.005
M.G15.0.5	100.02	115.00	115.00	116.00	115.33	0.577	0.87	0.87	0.86	0.87	0.004
M.G15.3.10	100.73	116.00	116.00	116.00	116.00	0.000	0.87	0.87	0.87	0.87	0.000
C.G5.5.5	100.10	114.00	114.00	115.00	114.33	0.577	0.88	0.88	0.87	0.88	0.004

Packed

Samples	**Mass (g)**	**Volume (cm^3)**					**Packed Density ($g.cm^{-3}$)**				
		1	**2**	**3**	**Ave**	**SD**	**1**	**2**	**3**	**Ave**	**SD**
Donated	100.14	44.00	44.00	46.00	44.67	1.155	2.28	2.28	2.18	2.24	0.057
Purchased	101.07	62.00	58.00	60.00	60.00	2.000	1.63	1.74	1.68	1.69	0.056
M.G5.3.5	99.59	28.00	14.00	10.00	17.33	9.452	3.56	7.11	9.96	6.88	3.208
M.G5.5.10	100.84	4.00	8.00	8.00	6.67	2.309	25.21	12.61	12.61	16.81	7.278
M.G10.5.5	99.72	12.00	12.00	10.00	11.33	1.155	8.31	8.31	9.97	8.86	0.960
M.G10.0.10	99.97	13.00	12.00	14.00	13.00	1.000	7.69	8.33	7.14	7.72	0.596
M.G15.0.5	100.02	5.00	6.00	5.00	5.33	0.577	20.00	16.67	20.00	18.89	1.925
M.G15.3.10	100.73	12.00	11.00	9.00	10.67	1.528	8.39	9.16	11.19	9.58	1.446
C.G5.5.5	100.10	7.00	8.00	8.00	7.67	0.577	14.30	12.51	12.51	13.11	1.032

Compressibility

Samples	**Mass (g)**	**Carr's index**					**Hausner Ration**				
		1	**2**	**3**	**Ave**	**SD**	**1**	**2**	**3**	**Ave**	**SD**
Donated	100.14	0.26	0.27	0.28	0.27	0.010	1.35	1.36	1.39	1.37	0.019
Purchased	101.07	0.32	0.32	0.33	0.32	0.008	1.48	1.47	1.50	1.48	0.017
M.G5.3.5	99.59	0.20	0.11	0.08	0.13	0.063	1.25	1.13	1.09	1.16	0.087
M.G5.5.10	100.84	0.06	0.07	0.07	0.06	0.004	1.06	1.07	1.07	1.07	0.005
M.G10.5.5	99.72	0.03	0.07	0.07	0.05	0.019	1.03	1.07	1.07	1.06	0.021
M.G10.0.10	99.97	0.10	0.10	0.08	0.09	0.008	1.11	1.11	1.09	1.10	0.010
M.G15.0.5	100.02	0.10	0.10	0.11	0.11	0.007	1.12	1.11	1.13	1.12	0.009
M.G15.3.10	100.73	0.04	0.05	0.04	0.04	0.005	1.04	1.05	1.04	1.05	0.005
C.G5.5.5	100.10	0.09	0.09	0.07	0.08	0.011	1.10	1.09	1.08	1.09	0.013

SWELLING AND EROSION

Table B.IV: Swelling and erosion data for Avicel® bead formulations

Time (min)	Parameter	M.G5.3.5				
		Run 1	Run 2	Run 3	Average	SD
Initial mass		251.50	249.00	249.50	250.00	0.500
30	Mass	1429.76	1424.00	1416.76	1423.51	4.045
	%Swelling	102.71	102.69	102.68	102.69	0.009
	%Erosion	177.37	175.20	173.94	175.50	0.829
60	Mass	1230.20	1205.50	1198.80	1211.50	6.353
	%Swelling	102.25	102.19	102.18	102.20	0.015
	%Erosion	176.58	174.34	173.09	174.67	0.834
90	Mass	1269.80	1218.80	1214.30	1234.30	10.492
	%Swelling	102.34	102.22	102.21	102.26	0.024
	%Erosion	176.74	174.39	173.15	174.76	0.844
120	Mass	1259.60	1181.40	1178.70	1206.57	15.369
	%Swelling	102.31	102.14	102.13	102.19	0.035
	%Erosion	176.70	174.25	173.01	174.65	0.854
180	Mass	1923.80	1873.10	1857.90	1884.93	13.552
	%Swelling	103.84	103.72	103.69	103.75	0.031
	%Erosion	179.33	176.96	175.66	177.32	0.874
240	Mass	1929.70	1920.90	1910.30	1920.30	5.954
	%Swelling	103.85	103.83	103.81	103.83	0.014
	%Erosion	179.36	177.15	175.86	177.45	0.846
360	Mass	1832.40	1839.80	1819.30	1830.50	10.265
	%Swelling	103.63	103.65	103.60	103.63	0.024
	%Erosion	178.97	176.83	175.51	177.10	0.853
480	Mass	1839.20	1766.80	1739.20	1781.73	21.579
	%Swelling	103.65	103.48	103.42	103.51	0.050
	%Erosion	179.00	176.54	175.19	176.91	0.904
600	Mass	2010.10	1926.70	1905.70	1947.50	20.900

	%Swelling	104.04	103.85	103.80	103.89	0.048
	%Erosion	179.67	177.17	175.84	177.56	0.901
720	**Mass**	1883.60	1812.20	1801.70	1832.50	15.658
	%Swelling	103.75	103.58	103.56	103.63	0.036
	%Erosion	179.17	176.72	175.44	177.12	0.875
Dried Mass		172.70	170.60	169.40	170.90	0.794
Time (min)	**Parameter**	**M.G5.5.10**				
		Run 1	**Run 2**	**Run 3**	**Average**	**SD**
Initial mass		250.30	249.70	251.20	250.40	0.751
30	**Mass**	1367.50	1301.80	1284.30	1317.87	16.788
	%Swelling	102.58	102.43	102.39	102.47	0.039
	%Erosion	175.63	173.93	175.60	175.05	0.852
60	**Mass**	1421.70	1404.10	1348.80	1391.53	28.989
	%Swelling	102.71	102.67	102.54	102.64	0.067
	%Erosion	175.84	174.33	175.86	175.34	0.776
90	**Mass**	1446.30	1375.30	1353.30	1391.63	19.236
	%Swelling	102.77	102.60	102.55	102.64	0.045
	%Erosion	175.94	174.22	175.88	175.34	0.845
120	**Mass**	1621.20	1564.30	1515.60	1567.03	28.938
	%Swelling	103.17	103.04	102.93	103.05	0.067
	%Erosion	176.63	174.96	176.52	176.04	0.797
180	**Mass**	1711.20	1663.00	1628.30	1667.50	21.451
	%Swelling	103.38	103.27	103.19	103.28	0.050
	%Erosion	176.99	175.35	176.97	176.43	0.824
240	**Mass**	1541.40	1503.40	1495.10	1513.30	9.112
	%Swelling	102.99	102.90	102.88	102.92	0.021
	%Erosion	176.31	174.72	176.44	175.83	0.869
360	**Mass**	1465.70	1469.00	1460.40	1465.03	4.304
	%Swelling	102.81	102.82	102.80	102.81	0.010
	%Erosion	176.01	174.59	176.30	175.63	0.863
480	**Mass**	1642.20	1573.00	1500.20	1571.80	41.689
	%Swelling	103.22	103.06	102.89	103.06	0.096
	%Erosion	176.71	175.00	176.46	176.06	0.755
600	**Mass**	1774.60	1741.00	1743.70	1753.10	6.352
	%Swelling	103.53	103.45	103.46	103.48	0.014
	%Erosion	177.24	175.66	177.42	176.77	0.894
720	**Mass**	1562.00	1525.30	1501.30	1529.53	15.226
	%Swelling	103.04	102.95	102.89	102.96	0.033

	%Erosion	176.40	174.81	176.46	175.89	0.840
Dried Mass		171.20	169.80	171.50	170.83	0.857
Time (min)	**Parameter**	**M.G10.5.5**				
		Run 1	**Run 2**	**Run 3**	**Average**	**SD**
Initial mass		250.40	251.10	250.30	250.60	0.404
30	**Mass**	1257.10	1251.00	1222.60	1243.57	14.728
	%Swelling	102.29	102.27	102.21	102.26	0.033
	%Erosion	174.30	178.06	175.80	176.05	1.237
60	**Mass**	1051.80	1039.50	1019.60	1036.97	10.832
	%Swelling	101.82	101.79	101.75	101.79	0.025
	%Erosion	173.50	177.22	175.01	175.24	1.215
90	**Mass**	1247.40	1227.40	1223.80	1232.87	4.565
	%Swelling	102.27	102.22	102.21	102.23	0.010
	%Erosion	174.26	177.96	175.81	176.01	1.191
120	**Mass**	1234.10	1213.10	1214.40	1220.53	3.970
	%Swelling	102.24	102.19	102.19	102.21	0.009
	%Erosion	174.21	177.91	175.77	175.96	1.183
180	**Mass**	724.70	675.90	654.40	685.00	15.713
	%Swelling	101.08	100.97	100.92	100.99	0.036
	%Erosion	172.24	175.78	173.58	173.87	1.197
240	**Mass**	664.70	688.00	667.70	673.47	10.461
	%Swelling	100.94	100.99	100.95	100.96	0.024
	%Erosion	172.00	175.83	173.63	173.82	1.218
360	**Mass**	341.40	352.90	354.70	349.67	2.550
	%Swelling	100.21	100.23	100.24	100.23	0.006
	%Erosion	170.75	174.50	172.41	172.56	1.170
480	**Mass**	637.10	588.60	571.60	599.10	13.877
	%Swelling	100.88	100.77	100.73	100.79	0.032
	%Erosion	171.90	175.44	173.26	173.53	1.188
600	**Mass**	765.70	737.30	714.50	739.17	13.734
	%Swelling	101.17	101.11	101.05	101.11	0.031
	%Erosion	172.40	176.03	173.82	174.08	1.207
720	**Mass**	555.10	552.50	542.90	550.17	5.007
	%Swelling	100.69	100.69	100.66	100.68	0.011
	%Erosion	171.58	175.29	173.14	173.34	1.189
Dried Mass		170.40	174.10	172.00	172.17	1.167
Time (min)	**Parameter**	**M.G10.0.10**				
		Run 1	**Run 2**	**Run 3**	**Average**	**SD**
Initial mass		250.10	251.70	251.20	251.00	0.361
30	**Mass**	1303.40	1212.70	1202.60	1239.57	19.107

	%Swelling	102.49	102.28	102.25	102.34	0.045
	%Erosion	174.34	177.04	174.54	175.31	1.279
60	**Mass**	1296.30	1273.50	1216.80	1262.20	30.010
	%Swelling	102.47	102.42	102.29	102.39	0.071
	%Erosion	174.31	177.29	174.60	175.40	1.380
90	**Mass**	1409.20	1365.10	1341.40	1371.90	16.011
	%Swelling	102.74	102.64	102.58	102.65	0.038
	%Erosion	174.76	177.66	175.10	175.84	1.317
120	**Mass**	1459.10	1402.80	1417.80	1426.57	12.019
	%Swelling	102.86	102.73	102.76	102.78	0.028
	%Erosion	174.96	177.82	175.41	176.06	1.244
180	**Mass**	898.50	865.50	874.70	879.57	7.144
	%Swelling	101.53	101.46	101.48	101.49	0.017
	%Erosion	172.71	175.62	173.22	173.85	1.243
240	**Mass**	1008.60	980.60	983.90	991.03	5.333
	%Swelling	101.79	101.73	101.74	101.75	0.013
	%Erosion	173.15	176.09	173.66	174.30	1.258
360	**Mass**	1398.70	1460.40	1457.60	1438.90	11.689
	%Swelling	102.72	102.86	102.86	102.81	0.028
	%Erosion	174.72	178.05	175.57	176.11	1.304
480	**Mass**	891.90	882.80	865.90	880.20	9.100
	%Swelling	101.52	101.50	101.46	101.49	0.022
	%Erosion	172.68	175.69	173.18	173.85	1.297
600	**Mass**	961.80	916.60	820.10	899.50	51.493
	%Swelling	101.68	101.58	101.35	101.54	0.122
	%Erosion	172.96	175.83	173.00	173.93	1.441
720	**Mass**	1168.20	1151.60	1121.50	1147.10	16.236
	%Swelling	102.17	102.13	102.06	102.12	0.038
	%Erosion	173.79	176.79	174.22	174.93	1.328
Dried Mass		170.10	173.10	170.70	171.30	1.249
Time (min)	**Parameter**	**M.G15.0.5**				
		Run 1	**Run 2**	**Run 3**	**Average**	**SD**
Initial mass		250.40	251.20	251.10	250.90	0.153
30	**Mass**	1164.10	1143.20	1085.10	1130.80	30.599
	%Swelling	102.14	102.10	101.96	102.07	0.072
	%Erosion	175.28	169.48	175.27	173.34	2.950
60	**Mass**	1166.20	1114.90	1083.90	1121.67	20.137
	%Swelling	102.15	102.03	101.96	102.04	0.047
	%Erosion	175.29	169.37	175.26	173.31	3.004
90	**Mass**	1069.50	1042.90	1038.20	1050.20	6.047

	%Swelling	101.92	101.86	101.85	101.88	0.014
	%Erosion	174.90	169.09	175.08	173.02	3.046
120	Mass	1137.90	1180.40	1151.60	1156.63	15.382
	%Swelling	102.08	102.18	102.11	102.13	0.036
	%Erosion	175.17	169.62	175.54	173.44	3.000
180	Mass	1447.80	1411.90	1382.40	1414.03	17.680
	%Swelling	102.81	102.73	102.66	102.73	0.041
	%Erosion	176.42	170.52	176.47	174.47	3.025
240	Mass	1259.60	1257.00	1242.00	1252.87	7.748
	%Swelling	102.37	102.36	102.33	102.35	0.018
	%Erosion	175.66	169.92	175.90	173.83	3.038
360	Mass	1368.80	1359.70	1341.70	1356.73	9.651
	%Swelling	102.62	102.60	102.56	102.60	0.023
	%Erosion	176.10	170.32	176.30	174.24	3.040
480	Mass	1426.10	1354.60	1325.60	1368.77	22.004
	%Swelling	102.76	102.59	102.52	102.62	0.052
	%Erosion	176.33	170.30	176.24	174.29	3.028
600	Mass	1502.50	1466.20	1433.50	1467.40	19.235
	%Swelling	102.94	102.85	102.78	102.86	0.045
	%Erosion	176.64	170.73	176.67	174.68	3.023
720	Mass	1290.60	1265.90	1263.20	1273.23	5.192
	%Swelling	102.44	102.38	102.38	102.40	0.012
	%Erosion	175.79	169.95	175.99	173.91	3.065
Dried Mass		171.60	166.00	171.90	169.83	2.994

Time (min)	Parameter	M.G15.0.5				
		Run 1	Run 2	Run 3	Average	SD
Initial mass		250.20	250.90	251.30	250.80	0.265
30	Mass	1323.30	1290.90	1304.30	1306.17	8.328
	%Swelling	102.51	102.44	102.47	102.47	0.020
	%Erosion	175.50	176.40	175.63	175.84	0.395
60	Mass	1112.00	1126.50	1090.60	1109.70	17.962
	%Swelling	102.02	102.05	101.97	102.01	0.042
	%Erosion	174.65	175.73	174.77	175.05	0.494
90	Mass	1065.40	1062.20	1073.80	1067.13	5.822
	%Swelling	101.91	101.90	101.93	101.91	0.014
	%Erosion	174.47	175.47	174.70	174.88	0.402
120	Mass	1216.90	1171.00	1174.10	1187.33	8.675
	%Swelling	102.26	102.16	102.16	102.19	0.020
	%Erosion	175.08	175.91	175.11	175.37	0.411
180	Mass	1377.60	1367.60	1359.60	1368.27	4.823

	%Swelling	102.64	102.62	102.60	102.62	0.011
	%Erosion	175.72	176.71	175.85	176.09	0.440
240	**Mass**	1217.80	1229.00	1198.10	1214.97	15.472
	%Swelling	102.27	102.29	102.22	102.26	0.036
	%Erosion	175.08	176.15	175.20	175.48	0.485
360	**Mass**	1124.10	1109.00	1105.40	1112.83	3.717
	%Swelling	102.05	102.01	102.00	102.02	0.009
	%Erosion	174.70	175.66	174.83	175.07	0.428
480	**Mass**	1340.30	1294.60	1283.50	1306.13	11.317
	%Swelling	102.55	102.45	102.42	102.47	0.027
	%Erosion	175.57	176.41	175.55	175.84	0.439
600	**Mass**	1416.40	1356.70	1321.80	1364.97	22.912
	%Swelling	102.73	102.59	102.51	102.61	0.054
	%Erosion	175.88	176.66	175.70	176.08	0.484
720	**Mass**	1159.10	1189.70	1174.10	1174.30	8.949
	%Swelling	102.13	102.20	102.16	102.16	0.021
	%Erosion	174.84	175.99	175.11	175.31	0.460
Dried Mass		171.20	172.20	171.40	171.60	0.416

Table B.V: Friability parameters and data

Sample	Parameters	1	2	3	Ave	SD
M.G5.3.5	W0	3.00	3.00	3.01	3.00	0.005
	W1	2.84	3.01	3.01	2.96	0.100
	%Friability	**5.33**	**0.00**	**0.00**	**1.78**	**3.079**
M.G5.5.10	W0	3.00	3.00	3.00	3.00	0.001
	W1	3.00	2.99	3.01	3.00	0.008
	%Friability	**0.00**	**0.37**	**0.00**	**0.12**	**0.212**
M.G10.5.5	W0	3.00	3.00	3.00	3.00	0.001
	W1	3.01	3.01	3.01	3.01	0.003
	%Friability	**0.00**	**0.00**	**0.00**	**0.00**	**0.000**
M.G10.0.10	W0	3.00	3.00	3.00	3.00	0.001
	W1	2.98	2.99	2.98	2.98	0.005
	%Friability	**0.63**	**0.47**	**0.87**	**0.66**	**0.201**
M.G15.0.5	W0	3.00	3.00	3.01	3.00	0.002
	W1	3.01	3.01	3.02	3.01	0.005
	%Friability	**0.00**	**0.00**	**0.00**	**0.00**	**0.000**
M.G15.3.10	W0	3.00	3.00	3.00	3.00	0.002
	W1	3.01	3.04	3.01	3.02	0.015
	%Friability	**0.00**	**0.00**	**0.00**	**0.00**	**0.000**

C.G.5.5.5	W0	3.00	3.00	3.00	3.00	0.001
	W1	2.91	2.97	2.95	2.94	0.027
	%Friability	**2.87**	**1.10**	**1.90**	**1.96**	**0.885**

Table B.VI Disintegration times

Samples	**Disintegration time (s)**						**Ave**	**SD**
	Vessel 1	**Vessel 2**	**Vessel 3**	**Vessel 4**	**Vessel 5**	**Vessel 6**		
M.G5.3.5	241.80	247.80	259.20	240.60	252.00	249.00	248.40	6.852
M.G5.5.10	300.00	258.00	313.80	420.60	378.00	480.00	358.40	83.090
M.G10.5.5	420.00	510.00	486.00	498.00	540.00	486.00	490.00	39.739
M.G10.0.10	275.40	336.00	288.00	258.00	330.00	354.00	306.90	38.313
M.G15.0.5	600.00	606.00	564.00	570.00	330.00	384.00	509.00	120.085
M.G15.3.10	300.60	270.00	510.00	396.00	450.00	330.00	376.10	92.595
C.G5.5.5	210.00	270.00	330.00	300.00	294.00	198.00	267.00	52.547

ANNEXURE C

DISSOLUTION STUDIES

LINEARITY AND VALIDATION

Table C.I: Linearity and validation data for gliclazide in acidic medium

Medium	Acidic	**Day**	1	**Run**	1	**Intraday**
Standard	**Gliclazide ($\mu g.ml^{-1}$)**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25.1
1	2.01	0.06	0.00	0.08	**Regression**	
2	5.02	0.19	0.00	0.05		
3	10.04	0.39	0.00	0.04		
4	20.08	0.74	0.00	0.03	**m**	0.04
5	30.12	1.13	0.06	4.01	**c**	-0.00
6	40.16	1.49	0.0	0.06	**r**	0.9998
Medium	Acidic	**Day**	1	**Run**	2	**Intraday**
Standard	**Gliclazide ($\mu g.ml^{-1}$)**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25.1
1	2	0.54	0.00	0.04	**Regression**	
2	5	0.095	0.00	0.04		
3	10	0.46	0.00	0.02		
4	20	0.83	0.00	0.00	**m**	0.19
5	30	1.20	0.00	0.01	**c**	-0.10
6	40	1.59	0.00	0.10	**r**	0.9999
Medium	Acidic	**Day**	1	**Run**	3	**Intraday**
Standard	**Gliclazide ($\mu g.ml^{-1}$)**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25.1
1	2.01	0.06	0.01	0.10	**Regression**	
2	5.02	0.10	0.00	0.00		
3	10.04	0.43	0.12	0.20		
4	20.08	0.81	0.46	0.00	**m**	0.18
5	30.12	1.23	0.00	2.00	**c**	-0.10
6	40.16	1.50	1.29	1.07	**r**	0.9997
Medium	Acidic	**Day**	2	**Run**	1	**Interday**
Standard	**Gliclazide ($\mu g.ml^{-1}$)**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25.1
1	2.01	0.08	0.01	12.63	**Regression**	
2	5.02	0.21	0.00	0.19		
3	10.04	0.43	0.01	1.06		
4	20.08	0.82	0.03	2.41	**m**	0.04
5	30.12	1.20	0.21	12.40	**c**	0.02
6	40.16	1.59	0.00	0.21	**r**	0.9997
Medium	Acidic	**Day**	3	**Run**	1	**Interday**

Standard	Gliclazide (µg.ml^{-1})	Average Absorbance	SD	%RSD	Mass (mg)	25.1
1	2.01	-0.04	0.00	-0.19	**Regression**	
2	5.02	0.08	0.00	0.09		
3	10.04	0.30	0.00	0.22		
4	20.08	0.67	0.00	0.26	**m**	0.04
5	30.12	1.06	0.00	0.01	**c**	-0.11
6	40.16	1.46	0.00	0.11	**r**	0.9999

Table C.II Linearity and validation data for gliclazide in alkaline medium

Medium	Alkaline	**Day**	1	**Run**	1	**Intraday**
Standard	**Gliclazide (µg.ml^{-1})**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25
1	2	0.00	0.00	7.19	**Regression**	
2	5	0.15	0.00	0.33		
3	10	0.32	0.01	4.29		
4	20	0.70	0.00	0.22	**m**	0.03
5	30	1.07	0.00	0.04	**c**	-0.06
6	40	1.49	0.00	0.05	**r**	0.9995
Medium	Alkaline	**Day**	1	**Run**	2	**Intraday**
Standard	**Gliclazide (µg.ml^{-1})**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25
1	2	0.01	0.00	0.01	**Regression**	
2	5	0.23	0.00	0.09		
3	10	0.33	0.00	2.70		
4	20	0.59	0.00	0.00	**m**	0.19
5	30	1.10	0.02	0.01	**c**	-0.30
6	40	1.53	0.01	0.00	**r**	0.992
Medium	Alkaline	**Day**	1	**Run**	3	**Intraday**
Standard	**Gliclazide (µg.ml^{-1})**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25.1
1	2.01	0.18	0.00	0.03	**Regression**	
2	5.02	0.24	0.00	0.30		
3	10.04	0.33	0.00	0.87		
4	20.08	0.77	1,00	0.99	**m**	0.1532
5	30,12	1.01	0.20	0.01	**c**	-0.2698
6	40.16	1.40	0.00	0.00	**r**	0.9997
Medium	Alkaline	**Day**	2	**Run**	1	**Interday**
Standard	**Gliclazide (µg.ml^{-1})**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	24.9

1	1.992	0.17	0.00	0.33	**Regression**	
2	4.98	0.27	0.00	0.04		
3	9.96	0.43	0.00	0.05		
4	19.92	0.77	0.00	0.05	**m**	0.03
5	29.88	1.08	0.01	0.49	**c**	0.10
6	39.84	1.46	0.00	0.15	**r**	0.9996
Medium	Alkaline	**Day**	3	**Run**	1	**Interday**
Standard	**Gliclazide ($\mu g.ml^{-1}$)**	**Average Absorbance**	**SD**	**%RSD**	**Mass (mg)**	25
1	2	0.00	0.00	3.30	**Regression**	
2	5	0.11	0.00	0.33		
3	10	0.33	0.00	0.04		
4	20	0.69	0.00	0.01	**m**	0.04
5	30	1.07	0.01	0.50	**c**	-0.06
6	40	1.42	0.15	7.30	**r**	0.9997

DISSOLUTION DATA

Table C.III: Dissolution data for bead formulations and Diamicron®

Time (min)	M.G5.3.5			M.G5.5.10			M.G10.5.5			M.G10	
	Ave	SD	%RSD	Ave	SD	%RSD	Ave	SD	%RSD	Ave	SD
0	0.00	0.000	0	0.00	0.000	0.00	0	0	0	0	0
2.5	3.55	1.314	36.99	3.07	0.263	8.58	19.97	1.074	5.38	5.93	0.22
5.0	6.11	0.933	15.28	4.80	0.771	16.06	21.60	0.659	3.05	7.54	0.94
7.5	8.86	0.889	10.03	7.22	1.639	22.71	23.44	0.825	3.52	9.86	0.76
15	11.88	2.333	19.63	13.62	2.828	20.76	26.80	3.898	14.54	11.07	0.89
30	16.84	2.983	17.71	26.71	9.634	36.07	31.70	3.947	12.45	16.56	1.10
60	20.38	4.393	21.56	42.06	2.831	6.73	37.33	1.876	5.03	19.93	1.43
90	26.53	3.096	11.67	48.04	2.457	5.11	45.88	0.979	2.13	26.48	1.96
120	30.58	1.891	6.18	55.03	5.574	10.13	51.90	3.122	6.02	34.22	0.61
180	32.19	2.223	6.91	59.66	3.082	5.17	54.96	3.104	5.65	39.62	3.41
240	39.73	2.516	6.33	63.26	3.535	5.59	64.90	4.356	6.71	44.16	1.41
360	44.41	2.899	6.53	68.63	2.061	3.00	66.53	2.965	4.46	69.14	5.56
480	59.04	10.281	17.41	84.77	9.409	11.10	76.50	11.730	15.33	81.41	1.99
600	87.02	7.824	8.99	94.29	2.784	2.95	90.93	6.453	7.10	87.17	0.58
720	92.81	4.433	4.78	97.55	2.058	2.11	98.86	0.424	0.43	95.96	1.51
735	100.00	0.000	0.00	100.00	0.000	0.00	100.00	0.000	0.00	100.00	0.00
Time (min)	M.G15.0.5			M.G15.3.10			C.G5.5.5			Diamic	
	Ave	SD	%RSD	Ave	SD	%RSD	Ave	SD	%RSD	Ave	SD
0	0	0	0	0	0	0	0	0	0	0	0
2.5	11.33	2.061	18.19	2.92	0.379	12.97	32.63	9.765	29.93	11.92	4.84

5.0	13.09	2.118	16.18	4.89	1.356	27.73	39.57	7.155	18.08	12.54	1.31
7.5	15.27	1.481	9.70	6.45	0.622	9.65	44.57	7.746	17.38	19.43	4.61
15	16.10	1.376	8.55	8.95	2.372	26.49	60.44	11.27 7	18.66	22.62	2.76
30	18.89	1.002	5.30	14.65	4.239	28.94	63.88	7.676	12.02	25.29	1.67
60	23.81	1.320	5.54	22.17	1.648	7.43	66.62	8.967	13.46	28.35	2.37
90	27.86	0.806	2.89	31.67	0.602	1.90	69.37	7.784	11.22	36.91	7.24
120	32.51	2.732	8.40	35.95	4.587	12.76	70.87	8.215	11.59	37.62	1.35
180	34.66	4.384	12.65	43.13	3.708	8.60	74.67	8.698	11.65	45.51	4.35
240	42.60	3.490	8.19	65.77	3.910	5.94	78.94	9.059	11.48	74.64	0.85
360	56.30	5.872	10.43	73.23	6.101	8.33	81.85	8.301	10.14	77.18	2.30
480	67.27	4.423	6.57	82.71	3.994	4.83	88.55	8.407	9.49	83.48	4.25
600	86.71	8.099	9.34	84.54	7.178	8.49	93.03	3.613	3.88	88.70	6.58
720	92.46	5.926	6.41	92.70	5.834	6.29	94.64	3.849	4.07	95.07	1.53
735	100.0 0	0.000	0.00	100.0 0	0.000	0.00	100.00	0.000	0.00	100.00	0.00