Formulation of a multiple-unit pellet solid oral delivery system for metformin and gliclazide

KC Ngoy
ORCiD 0000-0002-9092-0382

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Supervisor: Prof JH Steenekamp
Co-supervisor: Prof JH Hamman

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Student Number: 23460873

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ABSTRACT

Non-compliance is one of the contributing factors leading to poor treatment response in patients with chronic conditions such as diabetes mellitus (DM), due to the complex regimens often used in the management of these conditions. Fixed-dose combinations (FDCs) simplify medication regimens where different medicines are needed for the treatment of a single disease. The preparation of multiple-unit pellet system (MUPS) dosage forms allow the incorporation of different incompatible drugs in one dosage form and the minimisation of side-effects and the possibility to improve patient compliance amongst other benefits.

In this study, a FDC MUPS capsule containing metformin and gliclazide was developed. A factorial design was used to formulate different bead formulations differing with respect to filler, binder and disintegrant. The amount of the active ingredients (metformin and gliclazide) used in the preparation of beads was varied between 5 and 10% w/w. The fillers used were Pharmacel® (microcrystalline cellulose (MCC) and MicroceLac® (MCC-lactose)). The disintegrant used was Ac-di-sol® (super-disintegrant) at a concentration level of either 0.5 or 1% w/w. Kollidon® VA 64 was used as binder at either a 3 or 5% w/w concentration level. The bead formulations were characterised with respect to flow rate, critical orifice diameter (COD), Hausner's ratio and % compressibility.

After flowability characterisation, the bead formulations were assayed (for metformin and gliclazide content) and formulations with an assay value of ≥ 90% (for both active ingredients) were selected and filled into hard gelatin capsules to render FDC dosage forms for metformin-gliclazide. These capsule formulations were evaluated with respect to mass variation, disintegration time and dissolution behaviour.

The flowability results indicated that all the bead formulations exhibited good to excellent flow. All capsule formulations complied with the specifications as set by the British Pharmacopoeia (BP) regarding mass variation and disintegration time.

All the formulations exhibited average percentage dissolution values of 92.43 – 101.12% and 87.18 – 97.91% after 360 min for metformin and gliclazide, respectively. A marked slower and erratic initial dissolution rate for gliclazide, regardless of the filler (Pharmacel® or MicroceLac®) or excipients used, was observed. All the capsule formulations exhibited more than 80% dissolution for metformin within 30 min from the start of the dissolution study. Metformin therefore exhibited a higher and faster dissolution rate compared to gliclazide. The extent of metformin and gliclazide dissolution ($AUC_{(0-360)}$) for both metformin and gliclazide were similar in all the formulations with no statistically significant differences (ANOVA, $p > 0.05$).

Results from this study indicated that the excipients used in this study had no pronounced influence on the physical capsule properties as well as the release of the active ingredients from the dosage form. However, the marked slower and erratic dissolution behaviour of gliclazide in comparison to metformin as noted in this study, may in all likelihood be attributed to the difference in solubility between these two drugs

It is evident from this study that a MUPS FDC capsule dosage form containing metformin and gliclazide that is able to render both drugs pharmaceutically available in solution, could be prepared successfully, although a higher drug load of one or both drugs should be considered in a future study.

Keywords: Multiple-unit pellet system (MUPS); fixed-dose combination (FDC); metformin; gliclazide; patient compliance

1 CHAPTER 1: INTRODUCTION, PROBLEM STATEMENT, AIM AND OBJECTIVES

1.1 INTRODUCTION

1.1.1 Diabetes mellitus

Diabetes mellitus (DM) is defined as a condition characterised by higher than normal blood glucose levels due to the absence of pancreatic insulin secretion or inadequate insulin secretion with or without concurrent impairment of insulin action. The disease is characterised by altered metabolism of lipids, carbohydrates and protein, hyperglycaemia and an increased risk of complications resulting from the vascular effects of the disease (Gilman *et al*., 2001). DM is currently classified into four categories: type 1, type 2, gestational DM and DM related to other causes. Other causes of DM include drug therapy, pancreatectomy, non-pancreatic diseases and pancreatitis. Any abnormality in glucose levels noted for the first time in pregnancy is referred to as gestational DM (Katzung *et al*., 2015).

Type 1 DM is an absolute or severe insulin deficiency due to selective β-cell destruction, while type 2 DM is characterised by tissue resistance to the action of insulin combined with a relative deficiency in insulin. Insulin produced by type 2 DM patients is insufficient to overcome the tissue resistance, therefore elevated blood glucose levels are seen in these patients. Besides abnormal blood glucose levels, fat metabolism is affected in diabetic patients that results in an increase in free fatty acid flux and triglyceride levels as well as low levels of high-density lipoprotein (HDL). The mainstay of treatment in type 1 DM is parenterally administered insulin, but type 2 DM can be treated by seven categories of oral anti-diabetic agents: insulin secretagogues (sulfonylureas, meglitinides, and D-phenylalanine derivatives), biguanides, thiazolidinediones, alpha-glucosidase inhibitors, incretin-based therapies, amylin analogues, and bile acid-binding sequestrants (Nankar *et al*., 2013).

Metformin is regarded as first line therapy for type 2 DM, however, due to difficulties encountered in terms of an acceptable therapeutic response over a prolonged period of treatment in the presence of advanced disease damage to the insulin producing cells; multiple medicine products may be required to achieve glycaemic control. Therefore, the use of combination therapy such as biguanides (metformin) and sulfonylureas (gliclazide) is frequently required (Katzung *et al*., 2015). Metformin and gliclazide have been used in combination as one of the pillars of anti-diabetic therapy for many years. Gliclazide stimulates insulin secretion by closing of ATP-sensitive potassium channels in the pancreatic β-cells and it is classified as a second generation sulfonylurea with a decreased tendency of inducing hypoglycaemic episodes. Metformin activates

the enzyme AMP–activated protein kinase and as a consequence reduces hepatic glucose production (Xin *et al*., 2016).

Numerous undesirable symptoms/consequences that are related to type 2 DM have been identified such as depression, anxiety, premature morbidity and mortality due to poor health status that leads to unemployment, loss of productivity and an increase in medical cost. A surge in the prevalence of DM (especially type 2) has been observed in regions where it was once rare, specifically in Africa amongst others. DM in Africa has become a burden for the young working population, which has resulted in a decrease outcome in productivity. This is an undesirable situation for a continent with far-reaching economic implications (Dixon *et al*., 2013). Different approaches may be used to improve glycaemic control in DM, which includes the combination of different anti-diabetic drugs in fixed-dose combination products.

1.1.2 Fixed-dose combination regimes

A fixed-dose combination (FDC) is a product containing two or more active ingredients in fixed proportions in a single dosage unit such as a capsule or tablet. Fixed-dose combination therapeutic regimes have shown benefits like improving patient compliance due to the reduction of medication burden, simplifying drug regimens and optimising the treatment of various diseases (Taupitz *et al*., 2013). Furthermore, FDC therapy is less costly (Barner, 2011).

1.1.3 Multiple-unit dosage forms

A dosage form in which multiple discrete units are combined into a single dosage unit, e.g. compressed into a tablet or filled into a hard gelatin capsule, is known as a multiple-unit dosage form. Each constituting part in the dosage form contains a fraction of the active ingredient (Kumar *et al*., 2011) According to Dey (2008), the reduction of systemic toxicity, predictability of gastric emptying, lowering of the risk of gastrointestinal irritation and consequently an increase in bioavailability provided by a multiple-unit dosage form proves its benefits over single-unit dosage forms. Additional advantages of multiple-unit dosage forms include:

- improved active ingredient stability as incompatible actives may be incorporated in a single dosage form without reacting with each other,
- the possibility to modify the release pattern,
- extended patent protection, globalisation of a product and overcoming competition,
- flexibility in dosage form design,
- less inter- and intra-subject variability,
- ease in combining pellets/particles with unlike composition or release pattern, and

- an increase in patient comfort and compliance (Ozarde *et al.*, 2012).

Despite the mentioned advantages, multiple-unit dosage forms have the following potential disadvantages: segregation during manufacturing, relatively low drug loading, a proportionally high need for excipients, a large number of process variables, high cost of production, need of advanced technology, multiple formulation steps and trained/skilled personnel needed for manufacturing (Patwekar *et al.*, 2012).

Two types of multiple-unit particle drug delivery systems can be distinguished namely beads/pellets and granules. For the purpose of this study, the focus will be directed to beads/pellets. Beads (or pellets) are spherical agglomerates of powder particles that can be used to formulate multiple-unit dosage forms. Pellets as a drug delivery system offers many benefits including better flow properties, less gastro-intestinal tract irritation and a lower risk of side effects, a less friable dosage form and a narrow particle size distribution. Pellets can be produced by employing different techniques or methods including spraying of a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer by layer, spraying of a melt of fats and waxes from the top into a cold towel (spray-congealing), spray-drying of a solution or a suspension of the drug, spraying of a binder solution into a whirling powder mass using a fluidised bed and extrusion-spheronisation. Extrusion-spheronisation involves the preparation of a wet powder mass, shaping of the wet mass into cylinders (extrudate), breaking the extrudate and rounding of the particles into spheres (pellets/beads) and lastly drying of the pellets. The pellets may be coated with a polymer film with the purpose of controlling drug release. The produced beads with the correct particle size, layering and coating can consequently be processed into a solid dosage form (e.g. tablets or capsules) rendering an effective multiple-unit dosage form (Vervaet *et al*., 1995).

1.2 PROBLEM STATEMENT

The oral route is the preferred route of administration for various therapeutic agents due to the ease and comfort of medication administration (Li *et al*., 2013). DM and associated complications have become a worldwide burden due to its impact on the productivity, economy, medical cost and poor health status of patients and society. Effective treatment of type 2 DM is critical for an optimised treatment outcome, which often requires administration of more than one drug. A multiple-unit, fixed-dose combination containing metformin and gliclazide will contribute to improve patient compliance and potentially decrease side-effects, which can lead to a better therapeutic outcome.

1.3 AIM AND OBJECTIVES

The aim of this study was to prepare beads that contain metformin and beads that contain gliclazide and to combine them into a multiple-unit solid oral dosage form. In order to achieve this aim, the following objectives were set:

- Development and validation of a high performance liquid chromatographic (HPLC) method for the analysis of metformin and gliclazide;
- Preparation of powder mixture formulations intended for bead preparation using a factorial design;
- Preparation of two different bead formulations, containing metformin and gliclazide respectively by means of extrusion-spheronisation.
- Characterisation of the formulated beads with regard to powder flow (e.g. bulk density, tapped density, Hausner's ratio, Carr's index, flow rate and critical orifice diameter) and particle size;
- Filling of the different bead formulations into hard gelatin capsules (i.e. to form multiple-unit pellet system (MUPS) capsules); and
- Evaluation of the capsules with regard to weigh variation, disintegration, and dissolution (drug release behaviour).

1.4 OUTLINE OF THE CHAPTERS

The dissertation will be divided into the following chapters:

- Chapter 1: Introduction, problem statement, aim and objectives.
- Chapter 2: Literature overview.
- Chapter 3: Experimental methods.
- Chapter 4: Results and discussion.
- Chapter 5: Summary and future prospects.

2 CHAPTER 2: FIXED-DOSE COMBINATIONS AND MULTIPLE-UNIT PELLET DOSAGE FORMS

2.1 INTRODUCTION

Compliance with drug treatment by patients is an important factor for successful treatment of chronic conditions. There is a possibility for non-compliance to arise as the treatment regime becomes more complex. Fixed-dose combinations (FDCs) are becoming more popular as they simplify medication regimens where different medicines are administered for the treatment of a single disease. This is done by reducing the number of pills to be taken by the patient (Bangalore *et al*., 2007).

Pharmaceutical pellets are produced primarily for the purpose of oral controlled release dosage forms having gastro-resistant or sustained release properties. For such purposes, coated pellets are usually administered encapsulated in hard gelatin capsules or as disintegrating tablets that quickly release their contents in the stomach. The popularity in the development of pellets as dosage forms is increasing due to the flexibility in terms of targeted delivery to a specific part of the gastrointestinal tract or flexibility to modify drug release properties (Jawahar *et al*., 2012).

2.2 FIXED-DOSE COMBINATIONS (FDCs)

2.2.1 Definition

A fixed combination dosage form is a dosage form containing two or more active pharmaceutical ingredients (APIs) in a fixed proportion (Taupitz *et al*., 2013).

2.2.2 Value in long term (chronic) drug therapy

The oral route of drug administration is arguably preferred by the majority of patients and is also associated with the best patient compliance due to notable advantages such as feasibility in the whole range of patient ages, reproducibility of administration, ease-of use, and minimal invasiveness (Li *et al*., 2013). In addition, it is possible to formulate modified release dosage forms for this route of drug administration. Moreover, drugs can be formulated in such a way that they are released in the stomach or in different areas of the small intestine and/or the colon to adjust the absorption site or attain localised delivery (Mahato, 2007). Unfortunately, some challenges have to be overcome if oral drug delivery is to be used, among others; the presence of digestive enzymes, the mucus barrier, poor aqueous solubility and chemical stability of many drugs in the

acidic gastric environment. However, the oral route is unsuitable in patients who are unconscious, have ileus or are vomiting (Sosnik *et al*., 2016).

Irrespective of the mentioned challenges, the advantages of oral drug delivery still outweighs the disadvantages; therefore, it remains the preferred route in patients affected by chronic diseases (Verma *et al*., 2001).

FDCs have been found valuable for the management of chronic diseases such as asthma, diabetes, hypertension and hyperlipidaemia, as they are effective and a convenient alternative to administer multiple drugs in a single dosage form. FDCs present an improvement in patient compliance and therefore also for therapeutic outcomes. Furthermore, they reduce the overall costs of the treatment compared to regimens consisting of dosage forms containing single APIs. In chronic diseases, the possibility for non-compliance increases with each additional medication product added to a treatment regime, while the potential for medication errors also increase. FDCs simplify the medication regimen by reducing the number of dosage units and thus improve compliance (Bangalore *et al*., 2007).

Examples of commercially available FDCs products with their active ingredients are presented in Table 2.1**.**

Table 2.1: Examples of available fixed dose combinations (FDCs) (adapted from Vijayakumar et al., 2017)

Active pharmaceutical ingredients	Strengths
Acarbose + metformin	50 mg/500 mg
Rosiglitazone + metformin	4 mg/2 g
Sitagliptin + metformin	100 mg/1000 mg and 100 mg/2000 mg
Glimepiride + metformin	1 mg/500 mg and 2 mg/500 mg
Glibenclamide + metformin	5 mg/500 mg
Glyburide + metformin	2.5 mg/500 mg and 5 mg/500 mg
Vildagliptin + metformin	50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg
Pioglitazone + metformin	30 mg/50 mg
Repaglinide + metformin	1 mg/500 mg and 2 mg/500 mg
Mitiglinide + metformin	10 mg/500 mg
Empagliflozin + linagliptin	10 mg/5 mg and 25 mg/5 mg
Glipizide + metformin	2.5 mg/250 mg, 2.5 mg/500 mg and 5 mg/500 mg
Rosiglitazone + glimepiride	4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg and 8 mg/4 mg
Pioglitazone + glimepiride	30 mg/2 mg and 30 mg/4 mg
Saxagliptin + metformin	5 mg/500 mg, 2.5 mg/1000 mg and 5 mg/1000 mg
Perindopril + indapamide	4 mg/1.25 mg
Tenofovir disoproxil furamate + emtricitabine + efavirenz	300 mg/200 mg/600 mg
Fenoterol + iprotropium bromide	1.25 mg/4 ml/0.5 mg/4 ml
Trimethoprim + sulphamethoxazole	80 mg/ 400 mg
Ritonavir + lopinavir	20 mg/ml/80 mg/ml
Bromhexine + salbutamol	4 mg/5 ml/2 mg/5 ml
Rifampicin + isoniazid	150 mg/75 mg and 60 mg/60 mg
Rifampicin + isoniazid + pyrazinamide	150 mg/75 mg/400 mg

2.2.3 Advantages

FDCs are especially suited for patients taking different medicines due to simplification of drug administration and improvement of compliance. FDCs therefore renders the benefit of taking more than one medication without taking additional dosage forms such as tablets or capsules (Bailey *et al*., 2009). Furthermore, fixed-dose combination regimes are an attractive option, as they improve treatment efficacy in many cases due to the dual mechanism of action of the APIs,

targeting multiple effector mechanisms. In general, FDCs offer the advantages of simplicity, convenience, tolerability and cost-effectiveness of treatment (Rosenthal *et al*., 2006).

In terms of treatment efficacy, a combination of two oral antiplatelet agents namely dipyridamole and aspirin showed a better efficacy than the co-administration of these drugs in different dosage forms. Sometimes, drugs are combined just to enhance the effectiveness of one of the drugs in the combination, the combination of amoxicillin and potassium clavulanate serve as an example in this instance. Since potassium clavulanate is an inhibitor of β-lactamases, it protects amoxicillin from degradation by β lactamases produced by many microbial organisms. The antibacterial spectrum of amoxicillin is consequently effectively extended. Another FDC that contains buprenorphine and naloxone is used to prevent the misuse of buprenorphine, an opioid analgesic. The combination of this opioid with naloxone prevents the usual euphoria associated with buprenorphine use. The combination with, naloxone an opioid antagonist will generate withdrawal symptoms when the combination (buprenorphine/naloxone) is used (Desai *et al*., 2013).

As indicated in the preceding sections, an obvious advantage of FDCs is treatment simplification, and as a consequence both prescription errors and the need for supervision during dosing are reduced. Furthermore, the use of FDCs has the potential to simplify the drug supply management and fixed-dose combinations can reduce out-of-stock situations. Associated benefits include an improvement in the management of drug adverse reactions, ordering, distribution, procurement and storage. In some conditions such as tuberculosis where drug resistance is more likely to be seen and where drug unavailability and lower compliance rates result in a dramatic fall in cure rates, FDCs play an important role. It decreases the emergence of drug resistance by preventing monotherapy, ensuring delivery to the patient of the correct dose of all drugs, thereby reducing, and preventing drug resistance (Blomberg *et al*., 2003).

It is thus evident that the advantages of FDCs are very notable and play an important role in patient adherence therefore improving the therapeutic outcome. To highlight the advantages of FDCs, the benefits of FDCs in disease management is discussed using the following conditions as examples: diabetes mellitus, hypertension and tuberculosis.

2.2.3.1 FDCs in diabetes mellitus (DM)

In order to manage hyperglycaemia in type 2 diabetes, a combination of two or more glucose-lowering drugs is often necessary. By doing so, glycaemic control is improved because different pathophysiological aspects of the disease are therefore addressed, such as α-cell dysfunction, insulin resistance, β-cell dysfunction, and defects of nutrient metabolism affecting liver, adipose and muscle tissue (Bailey *et al*., 2009). The use of FDCs provide a reduced incidence of side effects like hypoglycaemia and weight gain. Furthermore, an improved adherence may in turn

lead to better glycaemic control and implies less drug wastage and greater opportunity for added medication to achieve their therapeutic potential thereby reducing the incidence of possible complications associated with diabetes (Melikian *et al*., 2000). This is particularly evident when using metformin and a sulfonylurea as an FDC, since the efficacy of sulfonylureas begins to plateau at half of the maximum recommended dose. Therefore, up titration to the maximal dose of a sulfonylurea is associated with less effectiveness and a higher rate of adverse effects compared to the addition of a second agent (Bailey *et al*., 2009).

Compared with individual-dose combinations (i.e. dual therapy, separate products each containing an active ingredient) and monotherapy, the glycaemic control has been shown to improve not only with dual therapy but also with FDC therapy. Although the use of two agents may achieve better glycaemic control, studies have shown that medication adherence typically decreases with the addition of another agent. It has been shown that the use of dual or triple therapy and regimens that require more frequent administration than once per day are associated with lower adherence rates (Bell *et al*., 2013). In addition, the complications and comorbidities related to type 2 diabetes mellitus (T2DM) such as hypertension and dyslipidaemia necessitate additional therapies, which leads to a variety of medications in any diabetic patient's regimen. Most of the time, the frequency of dosing and/or the specific timing of medication prescribed, whether it is to be taken with or without food is the challenge confronting patients who need multiple agents to manage their disease. Considering the importance of glycaemic control, especially early glycaemic control in the prevention of long-term diabetic microvascular complications, poor medication adherence poses a major obstacle for the achievement of optimal outcomes. FDCs present an alternative to separately dispensed medication that is advantageous to medication adherence. By means of FDCs, the frequency of missed doses is reduced because of the number of medications and the dosing or timing schedule that is simplified. Furthermore, greater efficacy may be achieved by lower doses of two agents when using an FDC in comparison to combining single medications with a higher or maximal dose of the single agents because the risk of an adverse effect reduces by using lower doses of agents in combination in comparison to higher doses of the same ingredients (Bell *et al*., 2013).

From a practical perspective, FDCs should offer a financial advantage for patients, because they are typically less costly than a combination of the comprising separate agents, thus, co-payments can be avoided. Ultimately, an improved adherence to anti-diabetic medication may result in fewer hospital admissions and reduced overall healthcare costs among T2DM patients (Bell *et al*., 2013).

2.2.3.2 FDCs in hypertension (high blood pressure or high BP)

According to several studies, it was shown that there is a tendency of an increase in hypertension in developed countries. However, the low- and middle-income countries are also involved in the prevalence of this condition. Hypertension is among others, the major cause of disability and a leading cause for death in the world. It is associated with stroke, coronary artery disease, renal dysfunction and congestive heart failure. In addition, hypertension is the cause of acute myocardial infarction incidences in many cases (Li *et al*., 2016). Hypertension is well managed when various physiological blood pressure (BP) mechanisms and pathways are targeted and this can be achieved with multidrug therapy, which offers multiple mechanisms of action. It follows that single agents in the treatment of hypertension are usually less efficacious than antihypertensive medication combinations that target more than one mechanism. The result of a multi-mechanism approach in the treatment of hypertension has the potential to maximise BP lowering and can neutralise counter regulatory mechanisms that would otherwise lead to the persistence of high BP (Rosenthal *et al*., 2006).

FDCs reduce adverse effects; this is evident when using a combination of a diuretic with an angiotensin converting enzyme (ACE) inhibitor. When using this combination, certain adverse effects of a diuretic may be reduced. Potassium depletion is usually seen when certain diuretics are used alone. The inclusion of an ACE inhibitor attenuates the metabolic effects, reverse the potassium depletion and to some extent offset the glucose intolerance effects of diuretics in an FDC. With dihydropyridine calcium antagonists, pedal oedema is one of the common adverse effects which is related to arteriolar dilatation caused by these drugs, resulting in intracapillary pressure hypertension. Pedal oedema has been shown to be dose related; therefore, the addition of an ACE inhibitor will result in post-capillary venous dilation and thereby returning intra-capillary pressure to normal (Bangalore *et al*., 2007).

2.2.3.3 FDCs in tuberculosis (TB)

With the goal to cure each patient and thereby reducing the mortality and morbidity of diseases, patients are treated quickly and effectively with anti-TB drugs to reduce the transmission of tubercle bacteria and limit the emergence of more drug resistant strains. To achieve these objectives, a multi-drug regime is given to patients and the treatment should therefore be applied under ideal conditions, which is practically challenging due to many obstacles. Amongst others, these obstacles appear to be the reason for unsuccessful therapy. The TB burden is almost entirely carried by poor people; this condition affects the productivity and the economy of the society thereby promoting poverty. The lack of compliance with treatment by patients; the repeated interruptions of treatments due to the high cost of the drugs and the failure to comply

because of the complexity of the multi-drug regimen lead to drug resistant mutations of TB bacteria. Because of the above-mentioned difficulties, FDC regimes have been of great value in the treatment of TB in order to limit additional drug resistance that could have escalated. Especially with TB treatment, the main aspect of FDCs is to reduce the risk of giving too low doses of individual drugs, since sub-therapeutic concentrations of the drugs may lead to treatment failure and a rise in drug resistance. (Laing *et al*., 2000).

Patients that are in the intensive phase of TB treatment need to ingest more than 10 tablets per day, sometimes as many as 16-17 a day depending on the treatment regime in use. FDCs specifically offer a simplified therapy in this scenario because it reduces the number of pills to three or four per day only. Patients prefer three or four pills versus a hand-full of tablets and/or capsules, which consequently increases the compliance. FDC regimens result in efficient drug supply management; it makes the calculation of drug needs, ordering, procurement, distribution and storage much easier (Blomberg *et al*., 2003).

FDCs also have an advantage in terms of the frequency of “out of stock situations” especially for TB. Out of stock situations usually occur due to too small quantities of medicines ordered, delay in receipt of orders from suppliers and insufficient buffer stocks. However, ordering too much of a medicine may result in medicine stocks reaching expiry dates before being used or before the available stock is replaced. The use of FDCs is therefore justified by the simplified treatment, minimum prescription errors and improved patient compliance that they offer (Blomberg *et al*., 2003).

2.2.4 Cost efficiency

Studies that examined pharmacy retail prices regarding medication cost savings showed that FDC products were less expensive than the corresponding combinations of single products (Barner, 2011:1282). By means of FDCs both patients’ and institutions’ cost are reduced. Due to a decrease in the number of co-payments or the size of the co-payments of FDC prescriptions, the patient out-of-pocket cost is also reduced compared to the components of single products prescribed together. However, because co-payments for brand-name drugs may be noticeably higher than those for generic agents, such cost savings may not be realised for brand-name-only FDCs containing otherwise generically available single component agents. FDCs can also decrease institutional costs by restructuring inventory, logistical and administrative processes. As such, savings achieved from increased utilisation of FDCs may prevail over the investments needed to heighten their prevalence (Bangalore *et al*., 2007). The direct and indirect cost savings with FDCs may be significant, due to the medication compliance improvement that they bring about, which is translated into a better therapeutic outcomes (Bangalore *et al*., 2007).

2.2.5 Patient compliance

By definition patient compliance, or adherence is considered as the extent to which a patient's behaviour corresponds with agreed recommendations from a healthcare provider and implicates taking medication as prescribed, on time, and at the correct dose and following the recommended lifestyle (Osterberg *et al*., 2005). With the use of appropriate monitoring, treatment adjustment and guidance, physicians can help patients achieve better therapeutic outcomes. However, even if the healthcare provider prescribed appropriate therapy, many patients are still failing to reach their needed outcomes. The patient is ultimately responsible for following a treatment regimen. A sub-optimal patient compliance contributes to treatment failure in over half of cases rather than an inadequate regimen. There are many possible reasons for non-compliance and lack of persistence with treatment, including poor drug tolerability, financial constraints, scepticism about treatment benefits, and the need for multiple agents or complex treatment regimens. Conditions that have co-morbidities, such as DM, further increase the patient's pill burden. A complex treatment regimen is not only inconvenient for the patient, but can also upsurge problems related to health literacy, such as processing, obtaining and understanding dosing regimens and self-management (Khouri *et al*., 2007).

There is substantial evidence suggesting that poor compliance increases healthcare costs and substantially worsen diseases and contribute to the number of deaths. Furthermore, because of the increased number of days missed due to inadequate treatment or poor compliance, productivity is therefore inevitably affected (Blomberg *et al*., 2003).

It is, generally recognised that simpler therapeutic regimens with less frequent administration may be preferred by patients, the introduction of FDC dosage forms could therefore promote compliance (Rosenthal *et al*., 2006).

2.2.6 Disadvantages of FDCs

At some point, the use of FDCs may limit the ability to customise dosage and administration regimens. Furthermore, it should be noted that it is not always possible to titrate the dose or split the timing of doses. FDC therapy may represent an over-treatment for some patients who may be controlled with a single agent (Khouri *et al*., 2007).

FDC products may not always be appropriate for patients. Costs may be similar for patients who are already taking one or more branded medicines, but costlier if they are currently using multiple generics. The fact that combination products are fixed-doses, in some cases present as a disadvantage as physicians lose some level of flexibility when a combination product is desired but a patient requires an unavailable dosage strength. For instance, metformin is contraindicated

in men and women when the serum creatinine is 1.5 mg/dl and 1.4 mg/dl, respectively. In this case, using an FDC containing metformin could be challenging or even not usable (Desai *et al*., 2013).

Knowing that FDCs contain multiple drugs in one solid dosage form (tablets or capsules), it can sometimes be a problem for elderly and paediatric patients due to the size of the tablet or capsule presenting problems with swallowing. For example, metformin as a main pillar of therapy in T2DM is usually employed in a dose range of 200 - 500 per dose. An addition of any anti-diabetic agent to it may result in an increase in the tablet or capsule size that can be too big to swallow easily.

Combination products are not always available in every possible dosing combination of their comprising drugs. In addition, FDCs make it more difficult to determine the agent within the combination that is responsible for the adverse effect if the patient experiences an adverse effect. Although combination products are known to have fewer side-effects, some rare events, such as a hypersensitivity reaction or side-effect that is not commonly associated with certain drug classes may occur. It is therefore possible that an FDC can cause a side-effect that is not a reported side-effect for a particular active ingredient in the FDC (Bangalore *et al*., 2007).

Formulary restrictions, such as listing FDCs as second- or third-line therapies or excluding them from the listings are associated with FDCs and are usually done with the intention to reduce utilisation and costs. To ensure that FDCs are included in the list of covered drugs, the formulary list need to be updated regularly. Basing prescribing decisions on drug price alone, as with co-payments may lead to higher overall healthcare expenses, inefficiency and equity problems (Khouri *et al*., 2007).

Numerous factors may enlighten the market discordance of FDCs that we experience. For example, FDCs are not always straightforward to manufacture, and substantial technical expertise and resources may be required to create stable FDC tablets and capsules (Desai *et al*., 2013).

In addition, additional phase 3 clinical trials are sometimes required to demonstrate the FDC's efficacy and safety in order for them to be approved. The decision of whether new trials are needed is determined on an individual basis for each proposed product, according to the FDA (Orloff,2005).

A limited number of FDCs have been developed, mostly because of issues such as differences in pharmacokinetics, the cumulative nature of adverse effects with multiple drugs, other limitations and potential drug interactions. All forms of combination therapy require special vigilance to comply with the contraindications; precautions and monitoring that apply to all agents in the

combination (Khouri *et al*., 2007). Furthermore, potential incompatibilities between the APIs and the excipients in FDCs must also be considered. It should also be clear that certain medications require different dosing schedules that would confound or impede the development of a corresponding FDC (Khouri *et al*., 2007).

A complex approach is also needed to promote the use of FDCs after their approval. Prescribers just like patients may not be aware of all available FDCs. In addition, prescribers may not always be aware of all the drugs taken by their patients, they may choose to initiate patients on single active medicines in order to identify the causing adverse event drug through de-challenge and re-challenge (Barner *et.al*., 2011).

2.3 MULTIPLE-UNIT PELLET SYSTEMS (MUPS)

A dosage form in which multiple discrete units are combined into a single dosage form e.g. pellets compressed into a tablet or filled into a hard gelatin capsule, is known as a multiple-unit dosage form. Multiple-unit pellet systems (MUPS) is a drug delivery system that offers the opportunity to modify drug release. This is usually achieved by the use of a polymer coating on the units comprising the dosage form or employing a polymer to form a matrix. Polymer coated pellets are compacted into tablets either alone or with a blend of excipients and matrix pellets containing excipients that retard drug release by being contained within the pellet structure (Ozarde *et al*., 2012). However, there are some MUPS that are formulated without the purpose of controlling the release of the active ingredient such as plain uncoated pellets that are compacted into tablets or filled into capsules.

An ideal MUPS tablet has the following properties:

1 the drug release is not affected by the compaction process,

2 pellet compacts possess optimum physical strength to withstand mechanical shocks.

3 the compacted pellets should not fuse into a non-disintegrating matrix during compaction. The dosage form must disintegrate rapidly into individual pellets in gastrointestinal fluids.

4 the surface of the compacted tablets should be smooth and elegant and devoid of pinholes and other imperfections and should facilitate ease of film coating if needed.

In addition, with MUPS containing reservoir-type coated pellets, the polymeric coating must be able to withstand the compression force; it may deform, but it should not rupture (Bhad et al., 2010).

2.3.1 Types of MUPS

MUPS are usually distinguished in two categories namely: MUPS containing uncoated and coated pellets (Kallakunta *et al*., 2017). The uncoated pellets are frequently prepared by the extrusion-spheronisation process. As mentioned in the previous section, plain uncoated pellets do not necessary control the release of the active ingredient. However, drug release may be modified in uncoated pellets depending on the incorporated excipients (Kallakunta *et al*., 2017). MUPS comprising coated pellets are prepared by coating the required polymer on the pellets in a layer wise manner (Kallakunta *et al*., 2017).

Beads are used to produce multiple-unit pellet systems (MUPS) such as beads compressed into tablets (MUPS tablets) or hard gelatin capsules filled with the beads (MUPS capsules) (Mahrous *et al*., 2010).

2.3.2 Advantages of MUPS

Conventional solid oral dosage forms such as tablets or capsules render very limited control over drug release and as a consequence to achieve an effective concentration at the target site, a repeated dosing with sometimes excessive doses is required. In some cases, this results in unpredictable, constantly changing, and often sub- or supra-therapeutic plasma concentrations. An ideal oral drug delivery system should steadily deliver over a prolonged period, a reproducible and measurable amount of drug to the target site. Controlled release (CR) delivery systems usually provide minimal side-effects and reduce the frequency of administration due to the uniform concentration of the drug at the absorption site and the maintenance of plasma concentrations at a certain level (Mahrous *et al*., 2010). Controlled release of an active pharmaceutical ingredient (API) into the body predictably and gradually over a 12 to 24 hour period with a simplified dose frequency of once or twice a day is advantageous as it is associated with improved patient compliance. The improved patient compliance can be attributed to a simplified dosing schedule, greater convenience, reduced side-effects and greater effectiveness, especially in the treatment of chronic conditions (Verma *et al*., 2001).

2.3.2.1 Pharmacodynamic and pharmacokinetic advantages

Uniform drug absorption is facilitated due to rapid and uniform gastric emptying and subsequently uniform drug dissolution of pellets in the gastrointestinal tract due to their small size and larger surface area, which results in controlled and consistent pharmacological action (Bhad *et al*., 2010).

The possibility of dose dumping (in the stomach) and incomplete drug release is further minimised due to the fact the total drug dose is divided between the pellets and the likelihood of release failure of all the pellets at the same time is highly unlikely in comparison to a conventional single-unit modified release dosage form such as a tablet. Owing to the small size of pellets/beads, rapid but uniform transit of pellets contained in MUPS from the stomach into small intestine is obtained, and thus better and uniform drug absorption, greater bioavailability, a reduction in inter- and intra-subject variability in drug absorption and a smaller possibility of localised irritation are usually encountered. MUPS, therefore offer a shorter lag time, lower variability and more homogenous individual plasma profiles as compared to single unit formulations (Bhad *et al*., 2010).

2.3.3 Disadvantages of MUPS

Multiple-unit dosage forms have the following potential disadvantages: segregation during manufacturing, low drug loading, the possibility of a high quantity of excipients, large number of process variables, high cost of production, the need of advanced technology, multiple formulation steps and trained/skilled personnel needed for manufacturing (Patwekar *et al*, 2012). In general, the manufacturing of tablets/capsules from multiple-units such as pellets, the following are considered as complicating factors or disadvantages (depending on the dosage form):

1. The compaction of pellets into tablets requires complex machinery (Patwekar *et al*, 2012).

2. The scale-up and process development is more time consuming and challenging (Ozarde *et al*., 2012).

3. During a tablet compression cycle, the development of an electrostatic charge on pellet surfaces can interfere with their flow; however, talc at a concentration of 1% w/w is usually added to solve this problem (Palash *et al*., 2011).

4. Due to the segregation phenomenon, MUPS may present higher variations in tablet or capsule content/weight. De-mixing is usually due to differences in density, surface, shape and size between pellets and extragranular tableting excipients. However, uniformity of mass and content can be achieved if pellets with a narrow size distribution are compressed together with additives of similar size and shape. In order to obtain, an optimum MUPS, the ratio of excipients to pellets is equally important besides addressing the role of particle and pellet shape, size and density. To avoid segregation, a threshold of at least 50% w/w pellet content has to be attained in any tableting or capsule blend. Variation may reduce with the use of a higher amount of pellets (Dash *et al*., 2012).

5. After compaction into tablets or filling into capsules, a change in drug release characteristics may occur. The major challenge in compaction of reservoir pellets into MUPS tablets is damage to the coating with a subsequent loss of the controlled release, taste masking or stabilising properties. To maintain the desired drug release properties of the subunits, the selection of the external additives, the type and amount of coating agent and the rate and magnitude of the pressure applied must be considered carefully. Furthermore, formulation scientists must have a comprehensive knowledge of how other excipients and/or process-related parameters will affect the performance of that formulation as a drug delivery system as well as how that formulation will behave during tableting (Dash *et al*., 2012).

The increase in the number of operations involved in the compaction of pellets have resulted in a growing need for new theories and methodologies, which describe the physical properties of pellets and their relation to the compression/consolidation processes. In order to predict more accurately the tableting behaviour of the pellets and its optimisation, a more in-depth understanding of the compaction process and the development and refinement of methods for determination of physical properties of pellets are needed (Mangesh *et al*., 2010).

2.3.4 Pharmaceutical pellets (beads)

Beads (or pellets) are spherical agglomerates of powder particles formed by appropriate techniques and processing equipment. Depending on the method and equipment used, pharmaceutical pellets are usually produced in sizes ranging from 0.1 – 2 mm and each have their own properties contributing to the release kinetics of the final dosage form (Mahrous *et al*., 2010).

The spherical shape and size of beads are a very important advantage when manufacturing tablets and other dosage forms due to better flow properties. A pharmaceutical dosage form can be formulated with a higher drug load by means of beads and the volume or size ratio of the beads can also be controlled. Drug release can be delayed or modified for a prolonged effect in the human body and film coating and powder layering of beads are relatively easy to do. There is a lower chance of dose dumping, but irritation of the mucosa in certain areas of the body can occur (Gandhi *et al*., 1999). By embedding the drug in a matrix type bead or coating the beads with a thin layer of polymer coating a prolonged pharmacological effect can be established (Howard *et al*., 2006).

Beads have numerous pharmacokinetic and biopharmaceutical advantages over conventional tablets and they are being successfully used. For immediate release products, the larger surface area of pellets enables better dissolution, distribution, and absorption. Pellets offer the advantage

of incorporating chemically incompatible products to be formulated into pellets and delivered in a single dosage form by encapsulating them. A dye material can be used to colour the coating material so that the beads of different coating thickness will be darker in colour and distinguishable from those having fewer coats. Beads or granules of different thickness of coatings can be blended together in the desired proportions to give the desired effect. The rate at which the drug/contents are released from the coated particles is therefore controlled by the thickness of the coat over the drug pellets (Palash *et al*., 2011).

The ability to incorporate high levels of active ingredients without producing excessively large particles is the major advantage over other methods of producing drug-loaded spheres or pellets (Ozarde *et al*., 2012).

2.3.4.1 Methods for bead preparation

A range of techniques is available for pellet manufacturing. Different layering processes have been used over the years. In recent years, cryopelletisation and hot melt extrusion, freeze pelletisation and extrusion-spheronisation processes have also been used to produce sphere-shaped pellets.

2.3.4.1.1 Layering

The layering process involves the deposition of consecutive layers of drug from solution/suspension, or dry powder on nuclei, which may be granules or crystals of the same material or inert starter seeds. Layering can broadly be classified into two categories: powder layering and solution/suspension layering (Jawahar *et al*., 2012).

2.3.4.1.2 Freeze pelletisation

Freeze pelletisation is a technique in which a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. It is a simple and novel technique for producing spherical matrix pellets containing active ingredients. It is an inexpensive, simple and reproducible technique for producing pellets with varying properties (Cheboyina *et al*., 2004).

2.3.4.1.3 Cryopelletisation

Cryopelletisation as a technique involves the production of pellets by allowing droplets of liquid formulation such as solution, emulsion or suspension to encounter liquid nitrogen as a solidifying medium. To remove water or organic solvents, the resulting particles are then freeze-dried or lyophilised. As indicated, this process requires liquid nitrogen, which has a temperature of -196°C;

this is the major limitation to this process. Furthermore, the impaction of liquid or semi-solid droplets on the surface of the liquid nitrogen creates surface irregularities in the pellets. Furthermore, pellets produced by freeze-drying are highly porous and may not be spherical (Ozarde *et al*., 2012).

2.3.4.1.4 Hot-melt extrusion

Hot melt extrusion (HME) is a method developed by researches as a new modified method for preparing matrix pellets for controlled release drug delivery systems in order to overcome the disadvantages associated with spheronisation and wet mass extrusion processes. In this method; a thermal agent is softened or is melted during the process to obtain matrix pellets (Ozard *et al*., 2012). HME technology is mainly employed in amorphous drug-in-drug formulations. HME technology is used to prepare both immediate and sustained release formulations. This technique is suitable in the formulation for the preparation of FDC products containing one or two drugs at a high dose. This method uses the reduction of polymer viscosity at higher temperatures and this results in a surface area with improved compression characteristics of the granules containing drug and polymer. The processing temperatures are typically set between the melting temperature of the drug substance and the glass transition temperature (Tg) of the polymer. In most cases, the drug substance remains in the crystalline state. Numerous polymers are used in this technique such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and Poloxamer® (Desai *et al*., 2013).

2.3.4.1.5 Extrusion-spheronisation

Extrusion-spheronisation was initially developed as a pelletisation technique to prepare multi-particulates for controlled drug release applications. This technique is becoming popular for the production of beads due to its advantages such as production of relatively dense and homogeneous particles with a low surface porosity (Mallipeddi *et al*., 2009).

It is particularly useful to prepare dense pellets/beads with a high drug loading for controlled release oral solid dosage forms with a low amount of excipients. Extrusion-spheronisation is basically a two-step process involving the extrusion of a wet mass in the first step followed by spheronisation to produce uniform sized spherical particles, called matrix pellets, spheroids, beads or pellets depending upon the materials as well as the process used for extrusion-spheronisation. The ability to incorporate high levels of active ingredients without producing excessively large particles is the main advantage over other methods for producing drug-loaded spheres or pellets (minimal excipients are necessary). Potential applications are many but relate mainly to improved processing and controlled drug release. The processing steps in the extrusion-spheronisation production process are described below (Dukie-Ott *et al*., 2009).

2.3.4.1.5.1 Dry mixing

Dry mixing of all ingredients is performed in the first step. Different mixers may be employed, e.g. a twin shell blender, high speed mixer, plane tray mixer and tumbler mixer (Ozard *et al*., 2012).

2.3.4.1.5.2 Wet massing and extrusion

Following mixing of the dry powders, the powder blend is wet massed and extruded. Wet massing of the powder blend is done to produce a sufficient plastic mass for extrusion. Extrusion is a method of applying pressure to a mass until it moves through an orifice or defined opening, and produces rod shaped particles of uniform diameter from the wet mass (Dukie-Ott *et al*., 2009).

2.3.4.1.5.3 Spheronisation

The function of the fourth step in the process (i.e. spheronisation) is to round off the rods produced by extrusion into spherical particles. The transition from rods to spheres during spheronisation occurs in various stages. If the mass is too dry, spheres will not form and the rods will only transform as far as dumbbells. The rounding of the extrudate into spheres is dependent on frictional forces generated by particle-particle and particle-equipment collisions (Muley *at el*., 2016).

2.3.4.2 Excipients for bead preparation

Different types of excipients are used in the formulation of beads and MUPS. Table 2 lists the typical excipients used in the formulation of beads and MUPS.

Table 2.2: List of possible excipients used in bead preparation (adapted from Ozard *et al.,* 2012)

Excipient type (% w/w)	Preferred	Particularly preferred	Most preferred
Filler (20 to 90)	Lactose, cellulose, starch, phosphate salts, mannitol, maltose, maltodexin, sorbitol, sucrose	Lactose, cellulose, starch phosphate salts	Cellulose, lactose
Binder (0.5 to 25)	Dextrin, dextrates, dextrose, cellulose derivatives, gelatin, gums, polyvinylpyrrolidone, starch, sucrose	Cellulose derivatives, polyvinylpyrrolidone starch	Polyvinylpyrrolidone cellulose derivatives
Disintegrant (1 to 25)	PVP, agar, bentonite, Carboxymethyl-cellulose, sodium alginates, starch	PVP, Carboxymethylcellulose	PVPP, Carboxy-methylcellulose
Lubricant (0.2 to 10)	Magnesium stearate, hydrogenated castor oil, glycerylester, polyethylene, glycol, sodium stearyl fumarate, stearic acid, talc	Magnesium stearate, hydrogenated castor oil, sodium stearyl fumarate	Magnesium stearate, hydrogenated castor oil

Excipient type (% w/w)	Preferred	Particularly preferred	Most preferred
Flow control agent (0.1 to 15, based on the weight of the film coated tablet)	Colloidal silica, precipitated silica, starch, talc, stearic acid, palmitic acid, pulverized cellulose	Colloidal silica, precipitated silica	Colloidal silica
Colorants (0.01 to 5 based on the weight of the film coated tablet)	FD&C and D&C blue, green, orange, red, violet, yellow, E 100 to 180	FD&C and D&C blue, green, titanium dioxide E 171, E 127 erythrosine	Titanium dioxide E 171
Other excipients (0.1 to 10, based on the weight of the film coated tablet)	Triethyl citrate, dibutyl sebacate, propylene glycol, diethyl phthalate, dibutyl phthalate, glyceryl monostearate, tri-acetin, stearic acid	Triethyl citrate, dibutyl sebacate, glyceryl monostearate, stearic acid	Propylene glycol, triethyl citrate, dibutyl sebacate

2.3.4.2.1 Fillers

Fillers are added to formulations (especially for very low dose drugs) for acceptable size tablet preparation or capsule filling for ease of handling by the patient. Lactose, dextrose, dicalcium phosphate, starches, microcrystalline cellulose (MCC), sucrose, sorbitol, and mannitol are commonly used as diluents. Dicalcium phosphate absorbs less moisture than lactose and is therefore used in dosage forms containing hygroscopic drugs such as pethidine hydrochloride. Microcrystalline cellulose is a very popular diluent in formulations intended for tableting or capsule filling (Mahato *et al*., 2007).

Microcrystalline cellulose (MCC) is included in most formulations processed by means of extrusion-spheronisation, because it provides the proper rheological properties to the wetted mass for successful extrusion and spheronisation. MCC possesses good binding properties that

provide cohesiveness to a wetted mass and for this reason it is seen as the golden standard as extrusion-spheronisation aid. MCC facilitates extrusion by improving the plasticity of the wetted mass and consequently enhance spheronisation since it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity. Moreover, it prevents phase separation during extrusion and spheronisation by controlling the movement of water through the plastic mass (Abdul *et al*., 2010). Due to these properties, MCC-based pellets produced via extrusion-spheronisation have a low friability, high density, good sphericity and smooth surface properties (Dukie-Ott *et.al*., 2009).

2.3.4.2.2 Binders, disintegrants and other excipients

Binding agents (adhesives) are used to promote cohesive compacts during bead preparation, promoting the strength and integrity of the beads. Binders are added in either dry or liquid form. Examples of binders include starch, PVP, gelatin, alginic acid derivatives, cellulose derivatives, sucrose and glucose. The binder affects the dissolution rate and consequently the release of the drug and therefore special consideration is required during the formulation process. The most effective dry binder is microcrystalline cellulose (Mahato *et al*., 2007).

Disintegrants are added during bead/pellet formulation to facilitate and promote the disruption of pellets. Croscarmellose sodium and sodium starch glycolate are frequently used as disintegrants (Muley *at el*., 2016).

Other excipients such as lubricants, separating agents, spheronisation enhancers and release modifiers may also be added to bead/pellet formulations. Lubricants are added to reduce friction between individual particles or between the particles and the surfaces of the processing equipment. Magnesium stearate are frequently used as a lubricant. Separating agents are employed in pellet formulations to promote the separation of pellets into distinct units during the pelletisation process – talc may be used for this purpose. Spheronisation enhancers such as microcrystalline cellulose is used to facilitate the production of spherical pellets, while a release modifier is used to obtain modified release from the pellet formulation. Ethylcellulose and shellac serve as examples of release modifiers (Muley *at el*., 2016).

2.4 SUMMARY

Although FDCs present certain disadvantages concerning the flexibility of dosing and size limitations with regard to the ease of swallowing, especially for elderly and paediatric patients, FDCs are very useful especially for patients taking multiple medicines as they simplify the medication regimen by reducing the number of pills and thus improve compliance.

Solid oral dosage forms may be manufactured as single-unit systems or multiple-unit pellet systems (MUPS). Broadly, three types of MUPS can be distinguished namely: MUPS containing uncoated, coated and matrix pellets and these multiple-units can be compressed into tablets or filled into hard gelatin capsules. Multiple-unit dosage forms offer numerous benefits such as the minimisation of side effect such as dose dumping and incomplete drug release. MUPS results in better and uniform drug absorption, greater bioavailability and a smaller possibility of localised irritation.

Multiple-unit dosage forms might be associated with some challenges such as the manufacture that is expensive, time consuming, technically more complicated and low drug loading, but has been found to be an attractive drug delivery system in terms of drug therapy due to the numerous benefits they possess over the single-unit dosage forms.

3 CHAPTER 3: EXPERIMENTAL METHODS

3.1 INTRODUCTION

Just like any other solid oral dosage form, the safety, effectiveness and reproducibility of pharmacological response is very important whenever capsules are prepared for medicinal use. Capsules should therefore be appropriate and safe for human consumption and they should also contribute to the stability of the active ingredient. All formulations that are intended for filling into capsules should be capable of being filled uniformly to give a reliable product and must release the active ingredient in a form that is ready for absorption. The choice and combination of excipients and quantities of the excipients are therefore important considerations when formulating powders intended for capsule filling to ensure good flow to produce capsules that will comply with specifications of the official pharmacopoeias. Powder flow is the factor that contributes the most to the uniform filling of capsules because all capsule filling machines operate by measuring volumes of powders with the objective of making powders act like liquids (Aulton *et al*., 2013). The formulation and preparation of beads is one of the methods that can be used to improve powder flowability (Aulton *et al*., 2013).

In this chapter, the materials used in the study are listed and the experimental methods that were used to analyse, formulate, manufacture and evaluate pellet/beads and MUPS capsules are described.

3.2 HIGH PRESSURE LIQUID CHROMATOGRAPHY (HPLC) ANALYTICAL METHOD

Samples intended for assay of drug content and dissolution samples were analysed by means of a validated HPLC method. The method was developed and validated by the student at the Analytical Laboratory of the North-west University under guidance of Prof JL du Preez.

3.2.1 HPLC system

The HPLC system used consisted of an Agilent 1100 series high pressure liquid chromatograph with a gradient pump, Chemstation, Rev. A.08.03 data acquisition software, UV detector, and autosampler (Agilent Technologies, Japan). As mobile phase consisting of 15% v/v of acetonitrile/0.005 M saltonic sulphur sodium in water with a pH adjusted to 3.5 was used for the first 5 minutes followed by 85% v/v of acetonitrile in water. An injection volume of 50 µl was used and a flow rate of 1 ml/min and UV detection at 230 nm were employed. A Venusil XBP C18, 150

x 4.6 nm column was used for this method. The total run time was 12 min and the retention times were about 4.4 and 7.1 min for metformin and gliclazide, respectively.

3.2.2 Preparation of stock solutions

A weight of 55 mg of metformin and 10 mg of gliclazide raw material were weighed on an analytical balance (Sartorius BP211D, Sartorius Balances, Sartorius, Germany). The metformin and gliclazide were quantitatively transferred to a 100 ml volumetric flask and dissolved in a 50:50 mixture of methanol and water. The 50:50 mixture of methanol and water was used to fill up the volumetric flask to volume (i.e. 100 ml).

3.2.3 Validation

3.2.3.1 Linearity

To determine linearity over the expected concentration range of different metformin and gliclazide concentrations, different concentrations were prepared by diluting the stock solution (prepared as described in section 3.2.2 above). The dilution was done as follows: different volumes of the stock solution (2, 3, 4, 5, 6, 7, 8 and 9 ml) were pipetted into 10 ml volumetric flasks respectively and filled up to volume (10 ml) with a 50:50 mixture of methanol and water. The diluted solutions were injected in the HPLC instrument for analysis. The instrument response (peak area) versus concentration was plotted on a graph and the line was evaluated for a linear relationship between metformin/gliclazide concentration and peak area by using linear regression.

3.2.3.2 Accuracy

Accuracy was determined by analysing three solutions with a low, intermediate and a high concentration of metformin and gliclazide, respectively. The standard solutions were prepared with a concentration of 150, 300 and 500 µg/ml for metformin and a concentration of 30, 70 and 100 µg/ml for gliclazide. Three sample solutions of each concentration were taken, giving a total of nine samples for analysis. The sample solutions were injected in the HPLC instrument for analysis.

3.2.3.3 Precision

Precision was determined on two levels, namely inter-day and intra-day precision. A low, intermediate and high concentration of metformin/gliclazide were analysed for both levels.

3.2.3.3.1 Intra-day precision

Intra-day precision was determined by preparing 3 sets of 3 samples with known metformin/gliclazide concentrations and they were analysed on the same day.

3.2.3.3.2 Inter-day precision

Inter-day precision was determined by preparing 3 sets of 3 samples with known metformin/gliclazide concentrations and they were analysed on two (2) separate days.

3.3 Materials

Information on the excipients used in manufacturing the beads as well as the active ingredients that were used in the study are given in Table 3.1.

Table 3.1: List of materials used in the study

Material type	Material name	Batch/Lot number	Supplier
Active ingredients	Metformin hydrochloride	Batch: 20160515	DB Fine, South Africa
	Gliclazide hydrochloride	Batch: 20161025	DB Fine, South Africa
Fillers	MicroceLac® 100	Lot no: 416 300	MEGGLE, Germany
	Pharmacel®101	Lot no: 60839C	Warren Chemical Specialities, South Africa
Disintegrant	Ac-di-sol®	Lot no: T017C	FMC, Ireland
Binder	Kollidon® VA64	Lot no: 93520356PO	BASF, South Africa

3.4 METHODS

3.4.1 Formulation variables

Due to the fact that the preparation of beads by means of extrusion-spheronisation depends on formulation composition as well as formulation variables, the formulation of powder mixtures intended for bead formulation containing both metformin and gliclazide was conducted by employing a full factorial design. The variables and levels involved in the factorial design are shown in Table 3.2.

Table 3.2: Variables and levels of the factorial design for the powder formulations intended for bead manufacturing

		Diluent A (Pharmacel® 101)		Diluent B (Microcelac®)	
		Disintegrant			
		Ac-di-Sol® (0.5% w/w)	Ac-di-sol® (1.0% w/w)	Ac-di-Sol® (0.5% w/w)	Ac-di-sol® (1.0% w/w)
		Drug load			
		5% w/w	10% w/w	5% w/w	10% w/w
Binder	Kollidon® VA64 (3% w/w)	X	X	X	X
	Kollidon® VA64 (5% w/w)	X	X	X	X

The experimental layout as indicated in Table 3.2 was used to prepare beads containing metformin and beads containing gliclazide, respectively. In the following sections (Sections 3.4.2 – 3.4.5) a brief discussion is given to indicate the rationale behind the selection of the active ingredients as well as the excipients used for the formulation of the beads.

3.4.2 Selection of active ingredients

Metformin and gliclazide were used as model drugs in all the capsule formulations in a concentration of 5% and 10% w/w. Metformin was specifically selected based on the fact that it is regarded as first line therapy for type 2 DM (Wang *et al*., 2017). Metformin activates the enzyme, AMP–activated protein kinase and consequently reduces hepatic glucose production (Chi *et al*., 2017). However, due to difficulties encountered in terms of an acceptable therapeutic response over a prolonged period of treatment in the presence of advanced disease damage; multiple medicine products may be required to achieve glycaemic control. Therefore, the use of combination therapy such as biguanides (metformin) and sulfonylureas (gliclazide) is frequently required (Masharani *et al*., 2015). Metformin and gliclazide have been used as the pillars of the anti-diabetic therapy for many years. Gliclazide on the other hand was specifically selected because it stimulates insulin secretion by closing of ATP-sensitive potassium channels in the pancreatic beta cells and it is classified as a second-generation sulfonylurea with a decreased tendency of inducing hypoglycaemic episodes and weight gain (Leiter *et al*., 2016).

3.4.3 Selection of fillers

Microcrystaline cellulose (MCC) based pellets produced via extrusion-spheronisation have a low friability, high density, good sphericity and smooth surface properties. With the intention to have the desired beads/pellets with the mentioned characteristics; MCC based fillers namely: Pharmacel®101 (microcrystalline cellulose) and MicroceLac® 100 (microcrystalline cellulose and lactose) were selected for the preparation of the different bead formulations. MCC fillers provide good rheological properties to the wetted mass for successful extrusion and spheronisation. For this reason; they are incorporated in most bead formulations intended to be produced via extrusion-spheronisation. MCC fillers give cohesiveness to the wetted mass due to their good binding properties. Furthermore, they are known to facilitate extrusion, improving wetted mass plasticity and enhancing spheronisation as they absorb and retain a large quantity of water due to their large surface area and high internal porosity. MCC fillers prevent phase separation during extrusion or spheronisation for they control the movement of water through the plastic mass (Dukic-Ott *et al*., 2009).

3.4.4 Selection of disintegrant

It is important when formulating beads to be filled into capsules to include a disintegrant in the formulation; in order for the beads to break down into smaller particles in the gastro-intestinal tract to render primary particles with the purpose of increasing the surface area available for drug release and dissolution. Ac-di-sol® was selected as disintegrant in this study. The disintegrant was used in two different concentrations, namely 0.5 and 1% w/w. Ac-di-sol® is classified as a super-disintegrant, which is commonly used because of its excellent performance in solid dosage forms as disintegrant. When it comes into contact with water, it swells to a large extent — the disintegration is initiated as soon as the dosage form comes into contact with an aqueous environment, breaking the dosage form into smaller fragments or particles and consequently rendering primary particles (Srinarong *et al.,* 2009).

3.4.5 Selection of binder

Binders are included in bead formulations to provide better mechanical strength to the beads. Therefore, the inclusion of a binder might be necessary for the successful formulation of beads to be filled into capsules. Kollidon® VA 64 was used as a binder at a concentration of 3 and 5% w/w depending on the formulation. Kollidon® VA 64 was selected based on its versatility as a binder in solid oral dosage form formulations (Mellert *et al.,* 2004).

3.5 FORMULATION AND PREPARATION OF POWDER MIXTURES

3.5.1 Formulation and composition of powder mixture

In Table 3.3, the abbreviations that were used to identify the different formulations during the powder flow studies are given. These abbreviations were used to refer to and distinguish between the different formulations during the relevant discussions. In Table 3.4, the abbreviations that were used to identify the different capsule formulations used during the discussions of the encapsulated formulations are given. These abbreviations were used to refer to and distinguish between the different capsule formulations during the relevant discussions.

Table 3.3: Table of abbreviations used to identify the different bead formulations for flow characterisation

Abbreviation	Description
MMF1	Microcelac® beads containing metformin formula 1
MGF1	Microcelac® beads containing gliclazide formula 1
MMF2	Microcelac® beads containing metformin formula 2
MGF2	Microcelac® beads containing gliclazide formula 2
MMF3	Microcelac® beads containing metformin formula 3
MGF3	Microcelac® beads containing gliclazide formula 3
PMF1	Pharmacel® 101 beads containing metformin formula 1
PGF1	Pharmacel® 101 beads containing gliclazide formula 1
PMF2	Pharmacel® 101 beads containing metformin formula 2
PGF2	Pharmacel® 101 -gliclazide containing beads formula 2
PMF3	Pharmacel® 101 beads containing metformin formula 3
PGF3	Pharmacel® 101 beads containing gliclazide formula 3

Table 3.4: Table of abbreviations identifying different formulations used in the figures and tables in chapter 4 to explain the results of particle size analysis, scanning electron microscopy and capsules evaluation tests

Abbreviation	Description
MF1	Microcelac® beads containing metformin and gliclazide formula 1 capsule
PF1	Pharmacel® 101 beads containing metformin and gliclazide formula 1 capsule
MF2	Microcelac® beads containing metformin and gliclazide formula 2 capsule
PF2	Pharmacel® 101 beads containing metformin and gliclazide formula 2 capsule
MF3	Microcelac® beads containing metformin and gliclazide formula 3 capsule
PF3	Pharmacel® 101 beads containing metformin and gliclazide formula 3 capsule

3.5.2 Preparation of the powder mixtures

To prepare the powder mixtures (100 g) as indicated in Table 3.2, the ingredients were weighed off accurately and precisely with a Mettler Toledo® electronic balance (Mettler, Germany, Model MS205DU) and transferred to glass bottles, sealed with Parafilm® and fitted with screw caps.

The mixing process of the dry powders and beads is a critical step in the formulation process of solid oral pharmaceutical products such as tablets and capsules. During the mixing process, it is important that homogeneous dispersion of the particles of every active pharmaceutical ingredient (API) and/or excipient is achieved to provide a batch of dosage form units with a uniform concentration of the API and excipients in each dosage (Ervasti *et al*., 2015).

The Turbula® mixer (Type T2C, Willy A Bachofen, Germany) (See Figure 3.1) was used as mixer to perform all the mixing operations during this study. After the powder mixtures were mixed using a Turbula® T2B mixer (WA, Bachofen, Switzerland) at 69 rpm for 7 min, they were stored in a dark cabinet at room temperature until bead preparation.

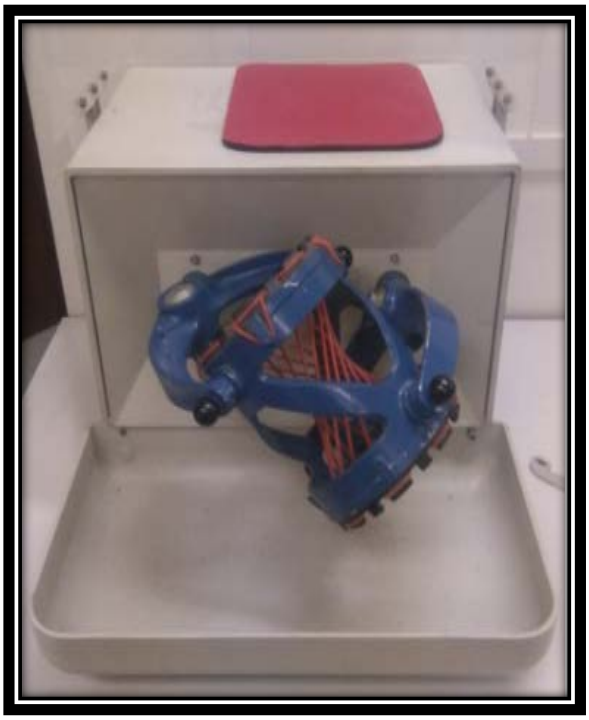

Figure 3.1: Image depicting the Turbula® mixer used to prepare the different powder and bead mixtures in this study

3.6 PREPARATION OF BEADS

Bead production is one of the effective methods known to improve the flowability of powder mixtures, as they improve particle size and shape uniformity. Beads were produced by means of extrusion-spheronisation. After mixing as indicated in Section 3.5.2, the powder mixtures were transferred to a clean mortar. Distilled water was the only wetting liquid used in all formulations. For the MicroceLac® formulations, the volume of wetting liquid varied between 24 and 33 ml for 100 g of powder mixture depending on the active ingredient used. For the Pharmacel® formulations, the volume of wetting liquid ranged between 80 and 100 ml for 100 g of powder mixture depending on the active ingredient used. While stirring continuously, the powder mixture in the mortar with a pestle, the wetting liquid was added very slowly to it with the aid of a burette.

The wetting of the powder mass continued until the desirable texture was obtained, the wetted powder mass was then added to the pan of the Caleva® Extruder (Type 20 Caleva®, Caleva Process Solutions, England) and fed into the extruder. Extrusion was done at 35 rpm using a 1 mm screen.

The extrusion process gave spaghetti-like strands in the bottom pan (See Figure 3.2a), which were subsequently added to the multi-bowl Caleva® spheroniser (Caleva Process Solutions, England) (See Figure 3.2b). The strands were then spheronised into uniform pellets/beads using

the spheronising procedure. The spheroniser was set at 2005 rpm for 10 min. Upon collection of the beads, they were freeze dried using a VirTis® bench top freeze drier (SP Industries Company, USA). The beads were freeze dried for 72 h and stored in a cool, dry and dark cabinet until filling into capsules (See Figure 3.2c).

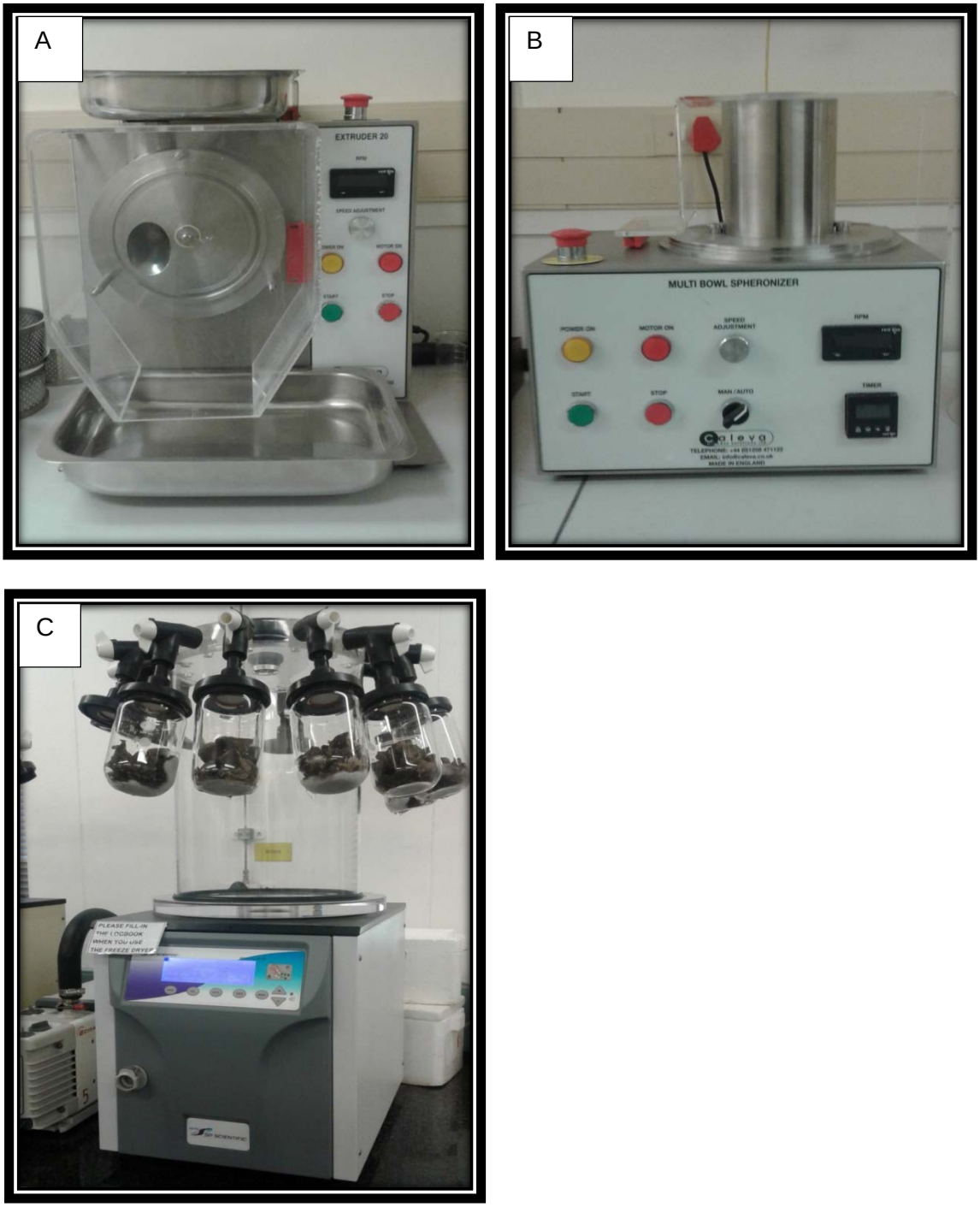

Figure 3.2: Images depicting the a) Caleva® Extruder, b) Caleva® Spheroniser, c) VirTis® bench top freeze drier

3.7 CHARACTERISATION OF BEAD FORMULATIONS

3.7.1 Particle size analysis

The flow behaviour of powders or beads is influenced by the shape and size of their particles. It is therefore important to characterise the shape and size of particles (Horiba Instruments, 2016).

The particle size of the bead formulations was determined by means of laser diffraction with a Malvern® Mastersizer 2000 (Malvern Instruments Ltd©, UK) fitted with a Hydro 2000MU dispersion unit. A volume of 100 ml ethanol was used to fill the small volume dispersion unit. To compensate for electrical interference as well as possible interference from the dispersion medium, a background measurement was taken. The bead sample was added to the dispersion unit upon completion of the background measurement. An obscuration of between 3 and 10% was obtained by adding a sufficient quantity of the sample. The particle size of the sample was measured after a suitable obscuration was obtained. Each measurement consisted of 12000 sweeps.

3.7.2 Flow properties

The flow rate, critical orifice diameter, compressibility (Carr's index and Hausner ratio), bulk and tapped density of the bead formulations were determined according to the methods and specifications of the British Pharmacopeia (BP), which are described in the following sections. All experiments were conducted in triplicate.

3.7.2.1 Density

The bulk and tapped density of the bead formulations were determined by pouring a pre-determined mass of the bead formulation (50 g) into a 250 ml graduated cylinder, and then the unsettled apparent volume (V_0) it occupied was measured and noted. The cylinder containing the bead sample was placed on an Erweka® Tapped Density Tester (SVM 121/221, Germany) to be tapped for 180 s. The tapped volume (V_{tap}) was noted and the respective densities (bulk and tapped) were calculated using Equations 1 and 2.

$$\rho_{bulk} = \frac{M}{V_\circ} \qquad \text{Equation 1}$$

Where ρ_{bulk} is the bulk density of the powder bead sample,

M is the mass of the bead sample, and

$V_\circ$ is the bulk volume of the bead sample.

$$\rho_{tap} = \frac{M}{V_{tap}}$$ Equation 2

Where ρ_{tap} is the tapped density of the bead sample,

M is the mass of the bead sample, and

V_{tap}, is the tapped volume of the bead sample (Aulton *et al*., 2013).

3.7.2.1.1 Carr's index

Carr's index (or % compressibility) is an indirect method used to determine the flowability of a powder. This test was conducted according to the specifications of the BP (2017). A compressibility of less than 17% indicates a good flow, whereas a compressibility of greater than 21% indicates a poor flow (Aulton *et al.*, 2013). To calculate Carr's index, Equation 3 was used.

$$\%\ compressibility = \frac{\rho tap - \rho bulk}{\rho tap}\ x\ 100$$ Equation 3

3.7.2.1.2 Hausner ratio

The Hausner ratio gives an indirect indication of the inter-particulate friction of powder particles. More friction or less friction between the particles will indicate poor or better powder flow respectively. This test was conducted according to the specifications of the BP (2017). In Figure 3.3, the Erweka® Tapped Density Tester is depicted.

Equation 4 was used to calculate the Hausner ratio (Staniforth and Aulton, 2013).

$$Hausner\ ratio = \frac{\rho tap}{\rho bulk}$$ Equation 4

Figure 3.3: Image depicting the Erweka® Tapped Density Tester

3.7.2.2 Flow rate

Flow rate of the bead formulations was measured with an Erweka® GTL powder and granulate flow tester (Type GTL, Erweka® GmbH, Heusenstamm, Germany). A 100 g sample of each bead formulation was used to fill the hopper, fitted with a closed shutter at the bottom. The shutter was opened and the time required to complete the discharge of the bead mass through an orifice (10 mm) was noted. This study was conducted according to the specifications of the BP (2017). Flow rate of the bead mass was calculated using equation 5.

$$\mathrm{F} = \frac{M}{t} \qquad \text{Equation 5}$$

Where F is the flow rate expressed in $g.s^{-1}$ or $ml.s^{-1}$,

t, the time in seconds(s), and

M, the mass.

In Figure 3.4, the Erweka® GTL powder and granulate flow tester is depicted.

Figure 3.4: Image depicting the Erweka® GTL powder and granulate flow tester

3.7.2.3 Critical orifice diameter (COD)

An apparatus consisting of tapered copper disks of different sized orifices was used to measure the critical orifice diameter (COD). Each disc had a different diameter size. The disks were stacked on top of each other to form a funnel-like shape with the largest diameter opening facing upwards. At the bottom of the stack, a shutter is fitted that can be opened to allow powder flow. A cylinder with the pre-determined bead mass (100 g) was placed on top of the stacked disks. The discs were held on top of a stand at a fixed height placed on a flat surface. When no bead flow occurred through the disc at the bottom of the stack (upon opening of the shutter), the disc was removed from the stack leaving a disc with a larger opening at the bottom of the stack. Removal of discs continued until flow of the bead sample occurred. When the beads were flowing through the disc at the bottom of the assembly, the diameter of the disc was recorded, which represented the COD. The test was done in triplicate and according to the specifications of the BP (2017).

In Figure 3.5, the copper discs and the shutter used and the COD apparatus with funnel fitted to the top are depicted.

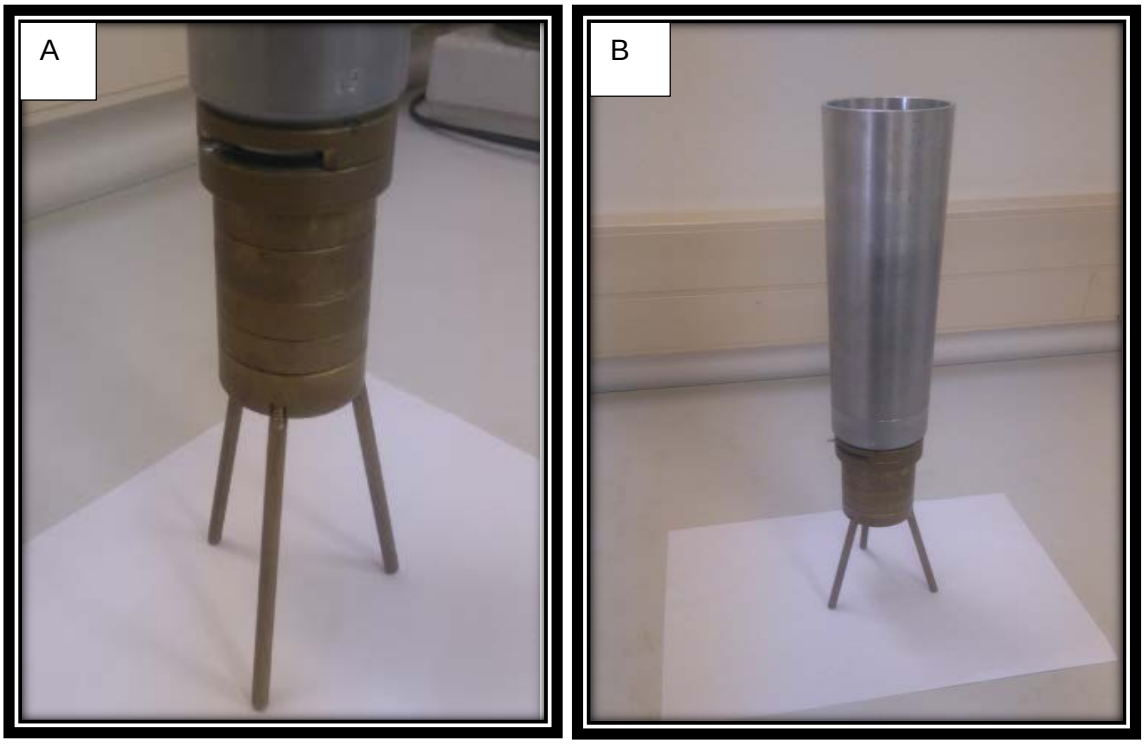

Figure 3.5: Images depicting the A) copper discs and the shutter used, B) COD apparatus with funnel fitted to the top

3.8 ASSAY OF THE BEAD FORMULATIONS

3.8.1 Assay of gliclazide containing beads

The gliclazide bead samples were prepared as indicated in sections 3.8.1.1 and 3.8.1.2 for the 5% and 10% w/w gliclazide containing bead formulations respectively.

3.8.1.1 Beads containing 5%w/w gliclazide

In theory, the 5% w/w gliclazide beads contained 5 g of gliclazide per 100 g of beads, thus: 500 mg of beads theoretically contained 25 mg of gliclazide.

Approximately 500 mg of beads were accurately weighed, crushed and powdered in a mortar with a pestle, then approximately 150 mg of the powdered beads were transferred quantitatively to a 100 ml volumetric flask with methanol (Associated chemical enterprise; Johannesburg, South Africa) to dissolve the gliclazide. The ultrasonic bath was used to facilitate the dissolution of the gliclazide in the volumetric flask. The volumetric flask was allowed to cool down to room temperature before filling the volumetric flask to volume (100 ml). The dissolved sample was filtered using a syringe filter (fitted with a 0.45 µm membrane filter) to remove any undissolved

excipient. The filtered sample was injected in the HPLC (high pressure liquid chromatography) for analysis. The % gliclazide content was determined using the following equation:

$$\% \text{ gliclazide content} = \frac{Experimental\ concentration}{Theoritical\ concentration} \times 100 \qquad \text{Equation 6}$$

3.8.1.2 Beads containing 10%w/w gliclazide

In theory, the 10% w/w gliclazide beads contained 10 g of gliclazide per 100 g of beads, thus: 250 mg of beads theoretically contained 25 mg of gliclazide.

Approximately 250 mg of beads were weighed, crushed and powdered in a mortar with a pestle, then approximately 75 mg of the powdered beads were transferred quantitatively to a 100 ml volumetric flask with methanol to dissolve the gliclazide. The ultrasonic bath was used to facilitate the dissolution of the gliclazide in the volumetric flask. The volumetric flask was allowed to cool down to room temperature before filling the volumetric flask to volume (100 ml). The dissolved sample was filtered using a syringe filter (fitted with a 0.45 µm membrane filter) to remove any undissolved excipient. The filtered sample was injected in the HPLC (high pressure liquid chromatography) for analysis. The % gliclazide content was determined using the following equation 6.

3.8.2 Assay of metformin beads

The metformin bead samples were prepared as indicated in sections 3.8.2.1 and 3.8.2.2 for the 5% and 10% w/w metformin containing bead formulations respectively.

3.8.2.1 Beads containing 5%w/w metformin

In theory, the 5% w/w metformin bead formulations contained 5 g of metformin per 100 g of beads, thus 500 mg of beads theoretically contained 25 mg of metformin.

Approximately 500 mg of beads were weighed, crushed and powdered in a mortar with a pestle, then approximately 300 mg of the powdered beads were transferred quantitatively to a 100 ml volumetric flask with methanol to dissolve the metformin. The ultrasonic bath was used to facilitate the dissolution of the mixture in the volumetric flask. The volumetric flask was allowed to cool down to room temperature before filling the volumetric flask to volume (100 ml). The dissolved sample was filtered using a syringe filter (fitted with a 0.45 µm membrane filter) to remove any undissolved excipient. The filtered sample was injected in the HPLC (high pressure liquid chromatography) for analysis. The % metformin content was determined using equation 6.

3.8.2.2 Beads containing 10%w/w metformin

In theory, the 10% w/w metformin bead formulations contained 10 g of metformin per 100 g of beads, thus 250 mg of beads theoretically contained 25 mg of metformin.

Approximately 500 mg of beads were weighed, crushed and powdered in a mortar with a pestle, then approximately 150 mg of the powdered beads were transferred quantitatively to a 100 ml volumetric flask with methanol to dissolve the metformin. The ultrasonic bath was used to facilitate the dissolution of the mixture in the volumetric flask. The volumetric flask was allowed to cool down to room temperature before filling the volumetric flask to volume (100 ml). The dissolved sample was filtered using a syringe filter (fitted with a 0.45 µm membrane filter) to remove any undissolved excipient. The filtered sample was injected in the HPLC (high pressure liquid chromatography) for analysis. The % metformin content was determined using equation 6.

3.9 FILLING OF THE BEADS INTO CAPSULES

The combination of gliclazide and metformin beads were done to be in agreement with the ratio of the conventional tablets containing 500 mg of metformin and 80 mg of gliclazide (500:80; 6.25:1).

Due to the amount of beads that needed to be encapsulated, size 000 hard gelatin capsules were used to encapsulate the bead formulations. Based on the assay results, the bead formulations from the factorial design with an assay percentage of above 90% were selected for encapsulation into hard gelatine capsules. Based on the results, six (6) formulations containing 10% w/w of the active ingredients (metformin and gliclazide) were selected for the capsule filling. With the intention of having 3.5 mg of gliclazide and 62.5 mg of metformin in a single capsule, approximately 0.04 g of gliclazide and 0.55 g of metformin containing beads (depending of the assay % of each formulation) were weight off using a Mettler Toledo® electronic balance (Mettler, Germany, Model MS205DU). After the weighing off, the formulations were mixed in a weighing vessel and then encapsulated manually by hand.

3.10 EVALUATION OF THE MUPS CAPSULES

The MUPS capsules were evaluated with regards to morphology (beads), weight variation, disintegration and dissolution behaviour as described in the following sections.

3.10.1 Scanning electron microscopy

The morphology and internal structure of the content (beads) of the different MUPS capsule formulations were investigated using scanning electron microscopy. An FEI Quanta®250 Environmental Scanning Electron Microscope with a Field Emission Gun (FEI®, Netherlands) was employed to capture micrographs.

All the samples were mounted onto aluminium sample mounts prior to capturing the micrographs, using adhesive tape and coated under vacuum with carbon before being sputter-coated with gold-palladium to minimize surface charging.

3.10.2 Mass variation

Twenty (20) capsules were selected randomly from each formulation, dusted and cleaned with a brush before weighing. To weigh each capsule individually, a Metter Toledo® balance (Mattler, Germany, Model MS205DU) was used. After weighing the capsule, it was emptied completely, the shell of the capsule was weighed. The mass of the capsule content was obtained by calculating the difference between the capsule mass with its contents and its shell. The average weight of the capsules' contents was calculated and the mass variation was determined according to the specifications of the British Pharmacopoeia (2017: Appendix XII C).

The standard deviation (SD) and the percentage relative standard deviation (%RSD) were also calculated. The percentage relative standard deviation (%RSD) was calculated using equation 7.

$$\%\ RSD = SDAverage\ x\ 100 \qquad \textit{Equation 7}$$

3.10.3 Disintegration

To evaluate the disintegration, six capsules from each formulation was used to conduct the test, using a disintegration tester (Type ZT 323, Erweka®, Germany) with distilled water as the disintegration medium. The temperature was kept at 37± 0.5°C with a thermostat and the thermostat was fitted to the test unit to regulate the temperature throughout the testing period. The time it took for the capsules to disintegrate was recorded as defined by the British Pharmacopoeia (2017: Appendix XII A).

In Figure 3.7, the six-tube disintegration apparatus is depicted.

Figure 3.7: Image depicting the six-tube disintegration apparatus

3.10.4 Dissolution behaviour

Dissolution studies were conducted using the USP paddle method. A six-station dissolution apparatus (Type Vankel® 7900, Vankel, USA) was used for the dissolution studies. Samples were taken manually and filtered through 0.45 µm filters. The samples were analysed by means of HPLC.

Phosphate buffer (pH = 6.8) was used as dissolution medium at a constant temperature of 37 ± 0.5°C. The stirring rate was set at 50 rpm. Samples of 5 ml was drawn at pre-determined time intervals of 2.5, 5, 10, 15, 30, 60, 90, 120, 150, 180, 240 and 360 min after adding capsules to the dissolution vessels. After the withdrawal at 360 min, the stirring rate was increased to 100 rpm for a further 15 min, and then the last sample was collected. The withdrawn samples were analysed by means of HPLC. The percentage drug release was plotted as a function of time to graphically illustrate the drug release behaviour of the MUPS capsules.

In Figure 3.8, the Vankel® dissolution apparatus is depicted.

Figure 3.8: Image depicting the Vankel® 700 dissolution apparatus

4 CHAPTER 4: BEADS/PELLETS FORMULATION AND EVALUATION RESULTS

4.1 INTRODUCTION

Every step undertaken during the formulation and production process of dosage forms can influence the properties of the intended final dosage form. For this reason; it is important to evaluate and to carefully consider every step during the formulation and production process of dosage forms to obtain a dosage form with an optimal performance (Tejedor *et al.,* 2015).

In this study, two different fillers namely, Pharmacel® 101 and MicroceLac® were employed to prepare two different types of beads with two different API's (i.e. metformin and gliclazide). Bead formulations were prepared as indicated in Table 3.2. Based on assay results, selected bead formulations (if the API content was > 90%) of both metformin and gliclazide were encapsulated together (FDC) in size 0 capsules and these solid oral dosage forms were evaluated with respect to weight variation, disintegration and dissolution behaviour to characterise the FDC combination.

In this chapter, the validation results of the HPLC analytical method used to quantify the assay and dissolution samples with regard to metformin and gliclazuide content as well as the flowability results of different pellet/bead formulations are presented. Furthermore, results concerning the characterisation of the physical properties and dissolution behaviour of the capsules filled with different beads/pellets formulations are presented.

4.2 HIGH PRESSURE LIQUID CHROMATOGRAPHY (HPLC) ANALYTICAL METHOD

4.2.1 Validation

4.2.1.1 Linearity

An example of a standard curve obtained during the validation of the analytical method is shown in Figures 4.1 for metformin and 4.2 for gliclazide. In Table 4.2 the regression results of the two standard curves (metformin and gliclazide, respectively) are given.

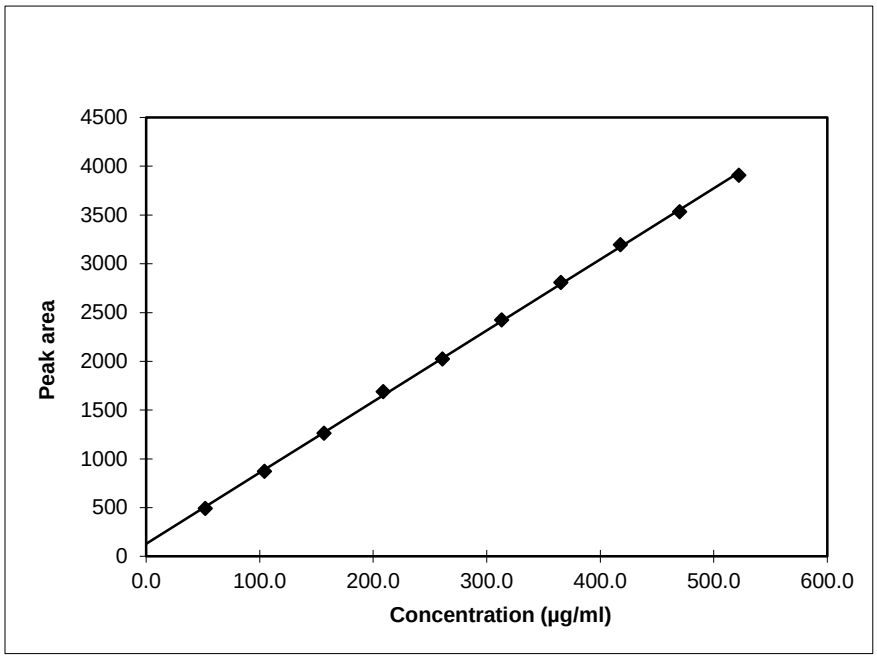

Figure 4.1: Example of a metformin standard curve obtained during validation of the analytical method

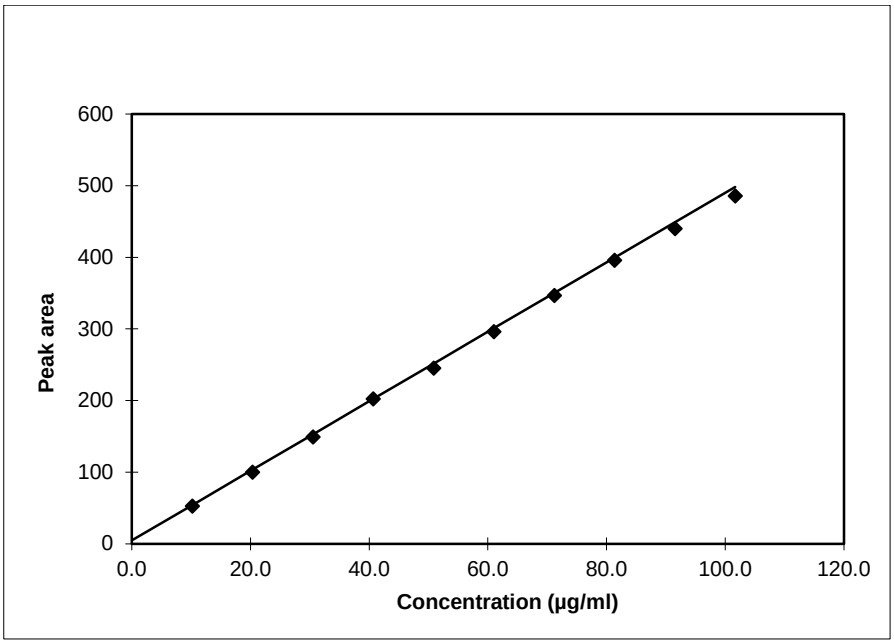

Figure 4.2: Example of a gliclazide standard curve obtained during validation of the analytical method

Table 4.1: Regression results obtained for both metformin and gliclazide standard curves during the validation of the analytical method

	Metformin curve	Gliclazide curve
Slope	7.286	4.765
Y-intercept	130.24	4.853
R-squared value (R^2)	1.000	1.000

From Figures 4.1, 4.2 and the regression results in Table 4.1, it is evident that a linear relationship existed between both metformin and gliclazide concentration and the instrument response (peak area) over the tested concentration range of 50-500 µg/ml and 10-100 µg/ml, for metformin and gliclazide, respectively.

4.2.1.2 Accuracy

The spiked concentration values, obtained concentration values as well as the percentage of metformin and gliclazide recovered are shown in Tables 4.2 and 4.3 for metformin and gliclazide, respectively. The mean metformin and gliclazide recovery and relevant statistics for each spiked metformin and gliclazide concentration are shown in Table 4.4.

Table 4.2: Spiked concentration values, obtained concentration values as well as the percentage of the metformin recovered

.	Metformin concentration (µg/ml)								
	Low			Intermediate			High		
Spiked conc.	150.72	151.35	150.21	351.68	353.15	350.49	502.40	504.50	500.70
Obtained conc.	152.3	154.8	150.7	353.7	353.7	355.7	506.9	498.5	506.8
% Recovery	101.0	102.3	100.3	100.6	98.0	101.5	100.9	98.8	101.2

Table 4.3: Spiked concentration values, obtained concentration values as well as the percentage of the gliclazide recovered

	Gliclazide concentration (µg/ml)								
	Low			Intermediate			High		
Spiked conc.	31.1	31.0	30.6	72.5	72.2	71.5	103.5	103.2	102.1
Obtained conc.	30.3	30.8	29.1	71.3	72.2	71.8	102.4	102.3	100.6
% Recovery	97.6	99.4	95.2	98.5	99.9	100.4	98.9	99.2	98.5

Table 4.4: The mean metformin and gliclazide recovery (%), standard deviation (SD) and percentage relative standard deviation (%RSD) for the spiked metformin and gliclazide concentration

	Metformin	Gliclazide
Mean	100.5	98.6
SD	1.3	1.5
%RSD	1.3	1.5

From the results in Tables 4.2, 4.3 and 4.4, it can be seen that the mean recovery was 100.5% and 98.6% for metformin and gliclazide respectively, and the %RSD (coefficient of variation) was less than 2% for both drugs. Therefore, the accuracy of the analytical method was considered acceptable.

4.2.1.3 Precision

Precision was evaluated on two different levels, i.e. intra-day precision and inter-day precision respectively.

4.2.1.3.1 Intra-day precision

The mean metformin and gliclazide recovery (%), standard deviation (SD) and percentage relative standard deviation (%RSD) are shown in Table 4.5.

Table 4.5: Mean metformin and gliclazide recovery (%), standard deviation (SD) and percentage relative standard deviation (%RSD)

	Metformin	Gliclazide
Mean	103.3	99.7
SD	1.5	1.5
%RSD	1.7	1.5

From the data in Table 4.5, it can be seen that the mean recovery was 100.5% and 99.7% for metformin and gliclazide, respectively and the %RSD (coefficient of variation) was less than 2% for both metformin and gliclazide. Therefore, the intra-day precision of the analytical method was considered acceptable.

4.2.1.3.2 Inter-day precision

The mean metformin and gliclazide recovery (%), standard deviation (SD) and percentage relative standard deviation (%RSD) are shown in Table 4.6.

Table 4.6: Mean metformin and gliclazide recovery (%), standard deviation (SD) and percentage relative standard deviation (%RSD) for three different days

	Metformin			Gliclazide		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Mean	103.01	104.36	102.01	99.13	103.63	105.51
SD	2.02	1.15	1.67	1.76	4.10	2.17
%RSD	1.96	1.10	1.7	1.78	3.96	2.06

From Table 4.6, it can be seen that the mean recovery ranged from 102.01 – 104.36% for metformin and 99.13 – 105.51% for gliclazide and the %RSD was not more than 5% for both drugs. Therefore, the inter-day precision of the analytical method was considered acceptable.

4.3 CHARACTERISATION OF BEADS

4.3.1 Assay results

Based on the assay results, formulations that exhibited an assay value ≥ 90% were selected for further investigation and the assay results of these formulations are reported in Table 4.7 for the different metformin and gliclazide containing bead formulations.

Table 4.7: The assay results of the different bead formulations prepared from MicroceLac® and Pharmacel®

Formulations	% Drug content	
	Metformin	Gliclazide
MicroceLac®		
MF1	94.06	98.47
MF2	91	99.03
MF3	90.23	101.06
MF4	81.02	97.92
Pharmacel®		
PF1	100.89	97.92
PF2	101.23	101.23
PF3	97.62	100.47
PF4	88.65	97.07

M= MicroceLac® P= Pharmacel®

4.3.2 Particle size analysis

A summary of the particle size data for the different beads formulations are presented in Table 4.8. In Figures 4.3 to 4.8, an example of the average particle size distribution histograms of the selected formulations is given.

Table 4.8: The particle size analyses results of the different MicroceLac® and Pharmacel® containing bead formulations

Formulation	Span	Average volume diameter D[4.3] (µm)	Median particle distribution d(0.5) (µm)
MicroceLac®			
MF1a	0.890	1050.999	1008.885
MF1b	0.736	1094.530	1062.425
MF1c	0.672	1107.921	1080.179
AVG	**0.764**	**1084.483**	**1053.617**
±SD	**0.091**	**24.300**	**30.303**
MF2a	0.591	1132.467	1109.212
MF2b	0.794	1067.594	1028.508
MF2c	0.602	1124.809	1101.270
AVG	**0.661**	**1108.290**	**1083.727**
±SD	**0.093**	**28.946**	**36.317**
MF3a	0.613	1112.568	1087.325
MF3b	0.635	1059.594	1031.269
Mf3c	0.632	1069.343	1041.266
AVG	**0.629**	**1080.501**	**1053.255**
± SD	**0.010**	**23.021**	**24.412**

Table 4.8 (cont): The particle size analyses results of the different MicroceLac® and Pharmacel® containing bead formulations

Formulation	Span	Average volume diameter D[4.3] (µm)	Median particle distribution d(0.5) (µm)
Pharmacel®			
PF1a	0.834	1004.642	960.283
PF1b	0.977	1003.610	951.156
PF1c	0.986	1001.020	949.228
AVG	**0.932**	**1003.091**	**953.965**
± SD	**0.070**	**1.524**	**4.822**
PF2a	0.741	1081.918	1048.318
PF2b	0.608	1108.325	1082.766
PF2c	0.628	1068.136	1040.260
AVG	**0.658**	**1086.126**	**1057.760**
± SD	**0.059**	**16.675**	**18.434**
PF3a	0.644	1034.805	1004.959
PF3b	0.850	969.255	921.786
PF3c	0.648	1027.564	997.220
AVG	**0.713**	**1010.542**	**978.648**
±SD	**0.096**	**29.343**	**37.517**

M= MicroceLac® P= Pharmacel®

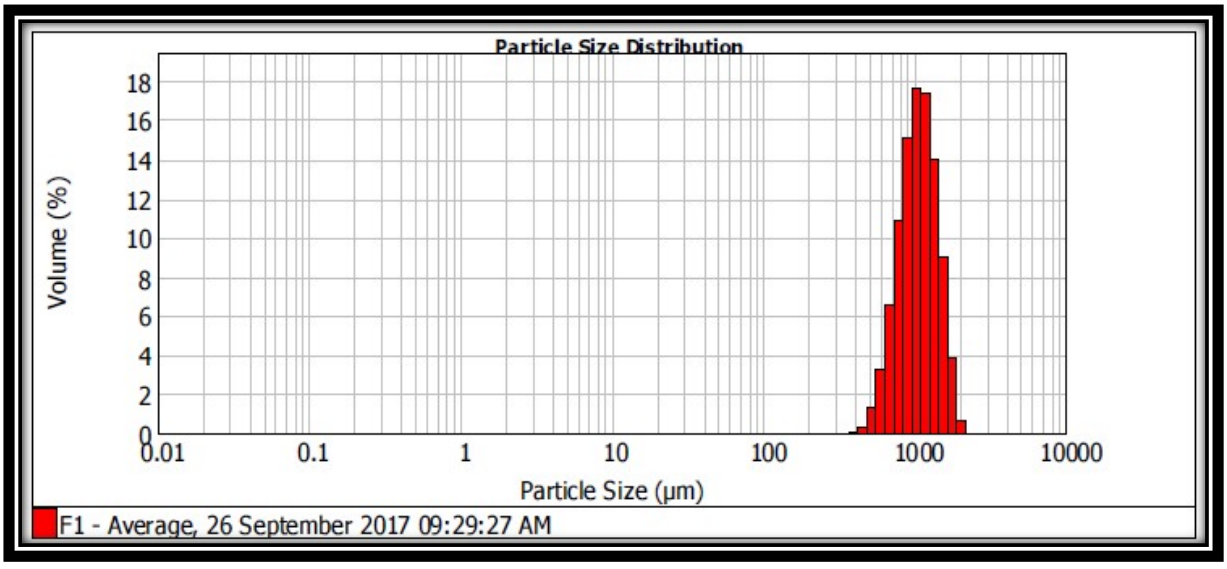

Figure 4.3: An example of the particle size distribution histogram for formula 1 (MF1)

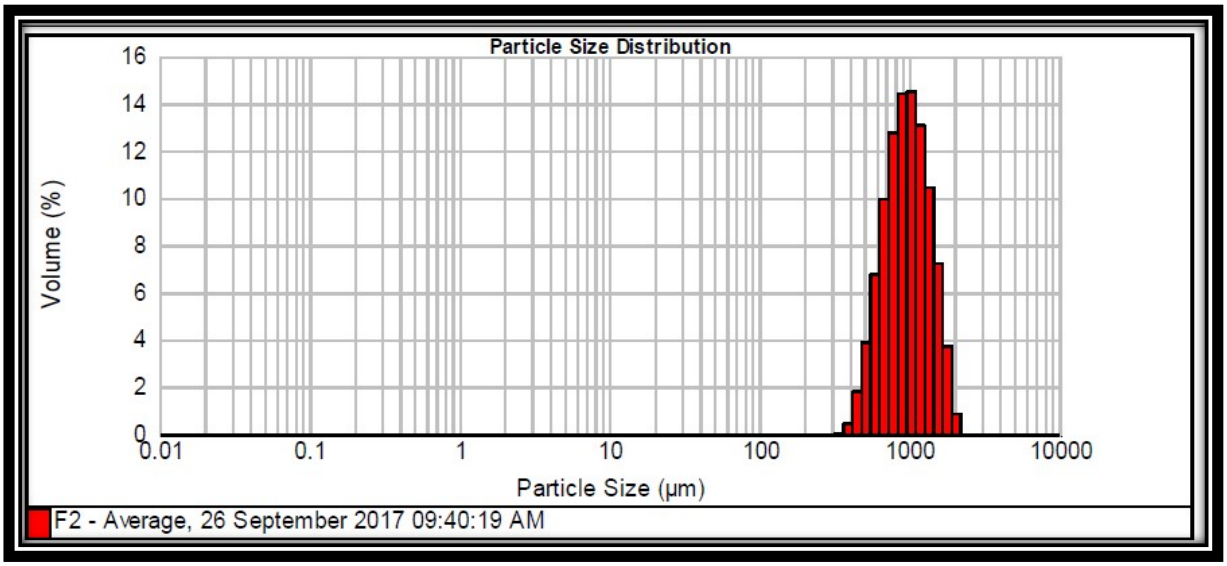

Figure 4.4: An example of the particle size distribution histogram for formula 2 (PF1)

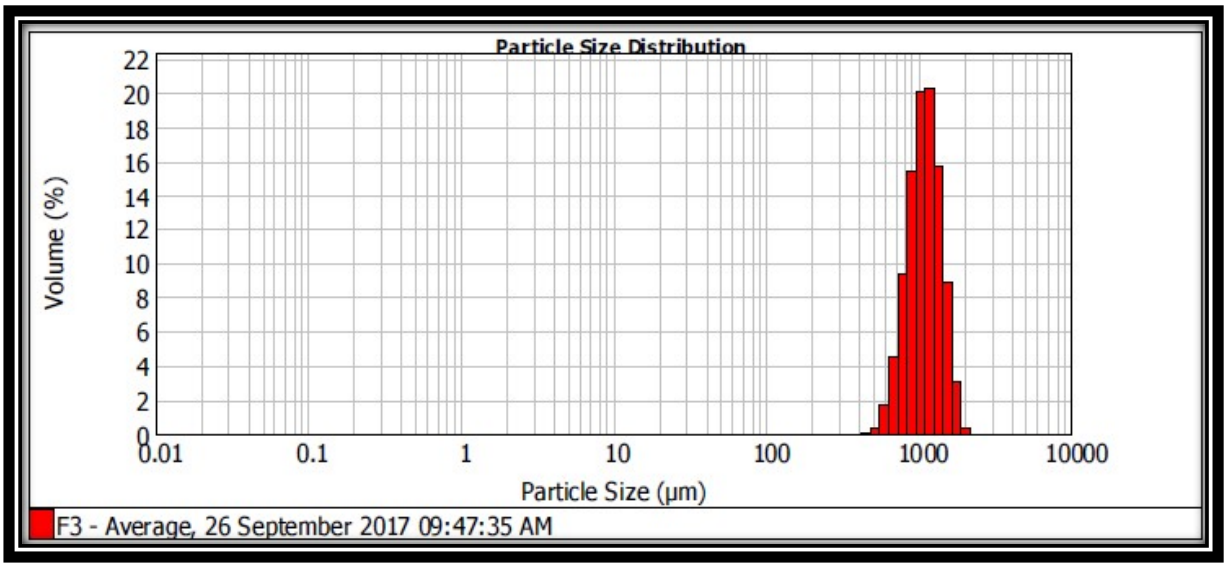

Figure 4.5: An example of the particle size distribution histogram for formula 3 (MF2)

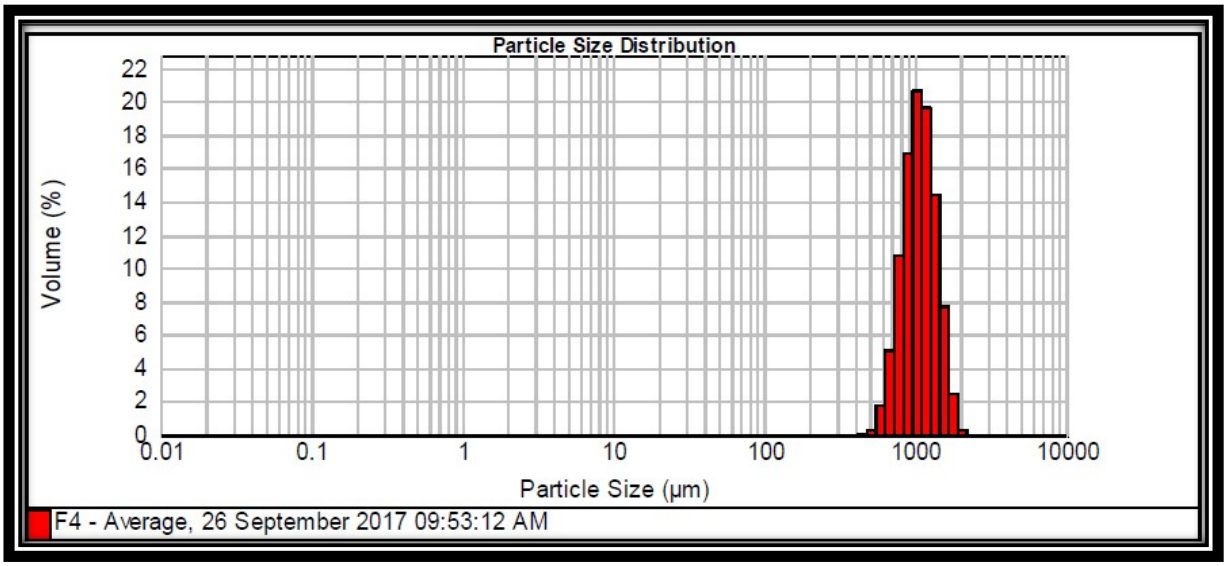

Figure 4.6: An example of the particle size distribution histogram for formula 4 (PF2)

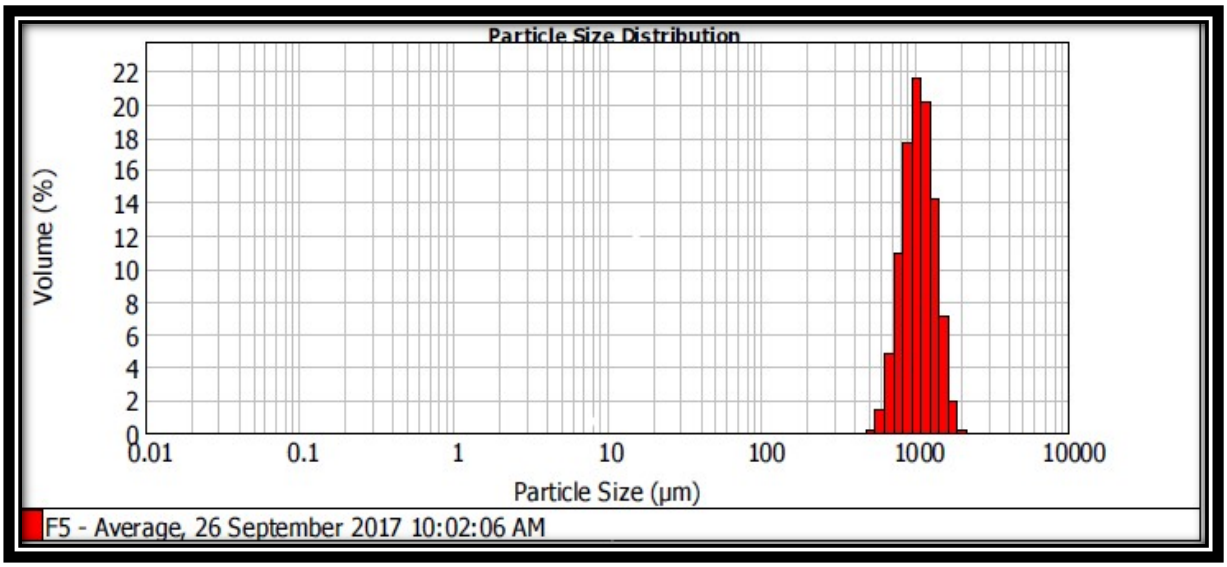

Figure 4.7: An example of the particle size distribution histogram for formula 5 (MF3)

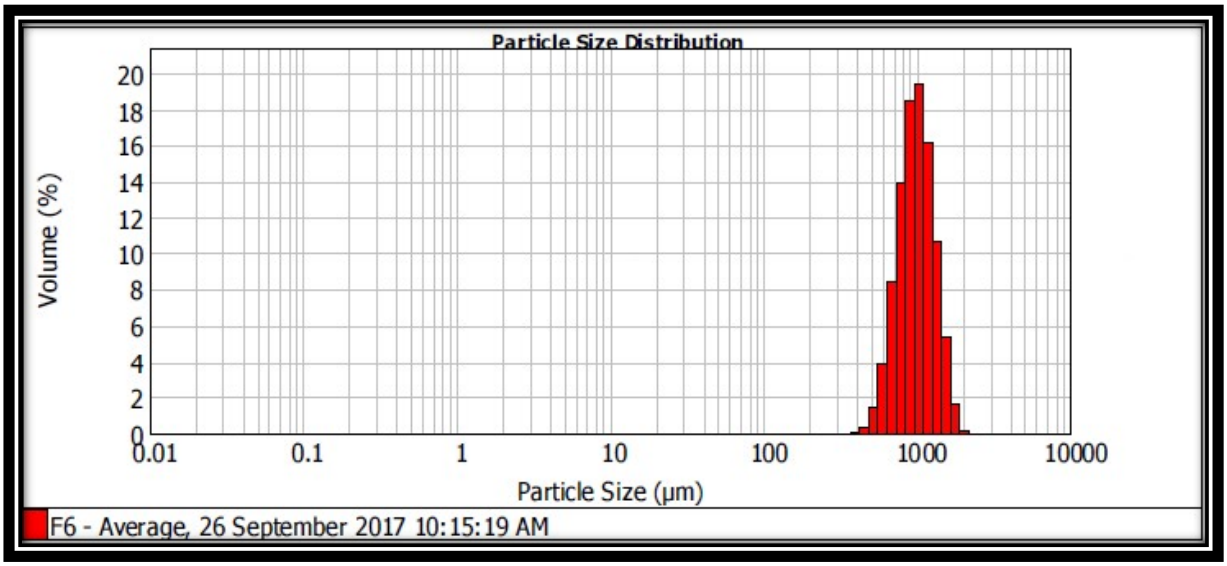

Figure 4.8: An example of the particle size distribution histogram for formula 6 (PF3)

It is evident from the data in Table 4.8 and Figures 4.3 to 4.8, that all the bead formulations exhibited similar particle size distributions. The similarity in particle size distribution is also reflected by the similarity in both the mean median (d(0.5)) and average particle size (D[4,3]) values for all the bead formulations. The median (d(0.5)) and average particle size (D[4,3]) for the different formulations ranged between 953.965 ± 4.822 – 1083.727 ± 36.317 µm and 1003.091 ± 1.524 – 1108.290 ± 28.946 µm respectively. Furthermore, the span values for all the formulations ranged between 0.658 ± 0.059 – 764 ± 0.091 — indicating a relatively narrow size distribution for all the bead formulations. The similarity in the particle size distributions is expected as all the formulations were prepared in the same way by means of extrusion-spheronisation using a 1.0 mm extrusion screen and spheronised at the same speed for the same time period. From the particle size data, it can be deduced that neither the API nor the excipients (type or concentration) had a pronounced influence on the particle size parameters and distribution of the beads.

4.3.3 Scanning electron microscopy

Micrographs of selected bead formulations investigated in this study are depicted in Figure 4.9 A - F.

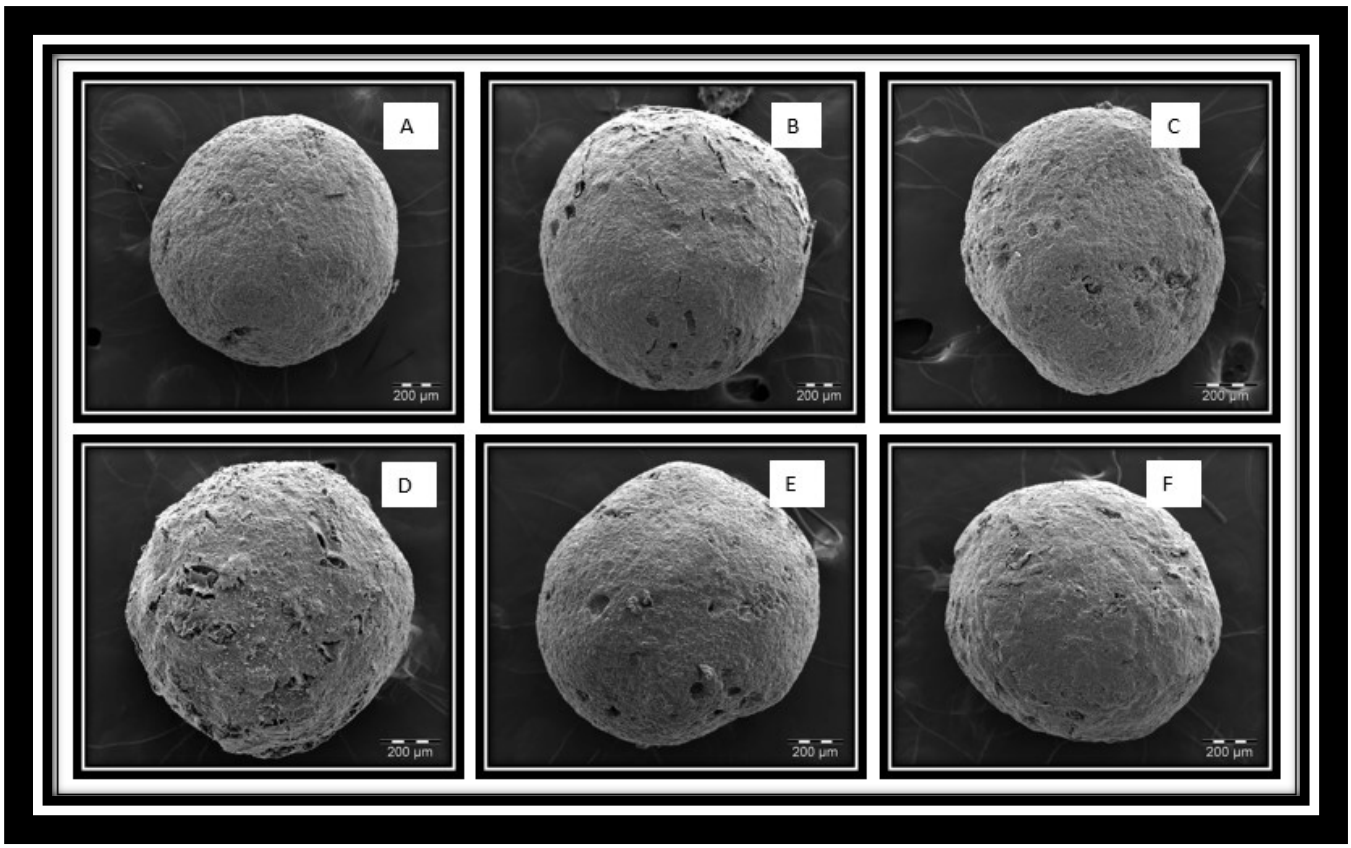

Figure 4.9: Micrographs depicting A) MicroceLac® -containing bead formula 1, B) Pharmacel® -containing bead formula 1 C) MicroceLac® -containing bead formula 2 D), Pharmacel® -containing bead formula 2, E) MicroceLac® -containing bead formula 3, F) Pharmacel® -containing bead formula 3

It is clear from the micrographs (Figure 4.9) that the different formulations prepared from the two different fillers (MicroceLac® and Pharmacel®) exhibited an overall similar shape and texture. However, the surface of the Pharmacel®-containing bead formulations (Figure 4.9 B, D and F) appears slightly flaky in comparison to the MicroceLac®-containing bead formulations. The flaky appearance might be related to the higher MCC content of the Pharmacel®-containing formulations. Irrespective of the filler, all the formulations exhibited a spherical or nearly spherical shape. From this observation, it can be concluded that neither the API nor the excipients had a pronounced effect on the spherical nature of the beads.

In Figure 4.10 A to F, an example of the internal structure of the bead formulations prepared from both fillers MicroceLac® (Figure 4.10 A, C and E) and Pharmacel® (Figure 4.10. B, D and E) used in this study is depicted.

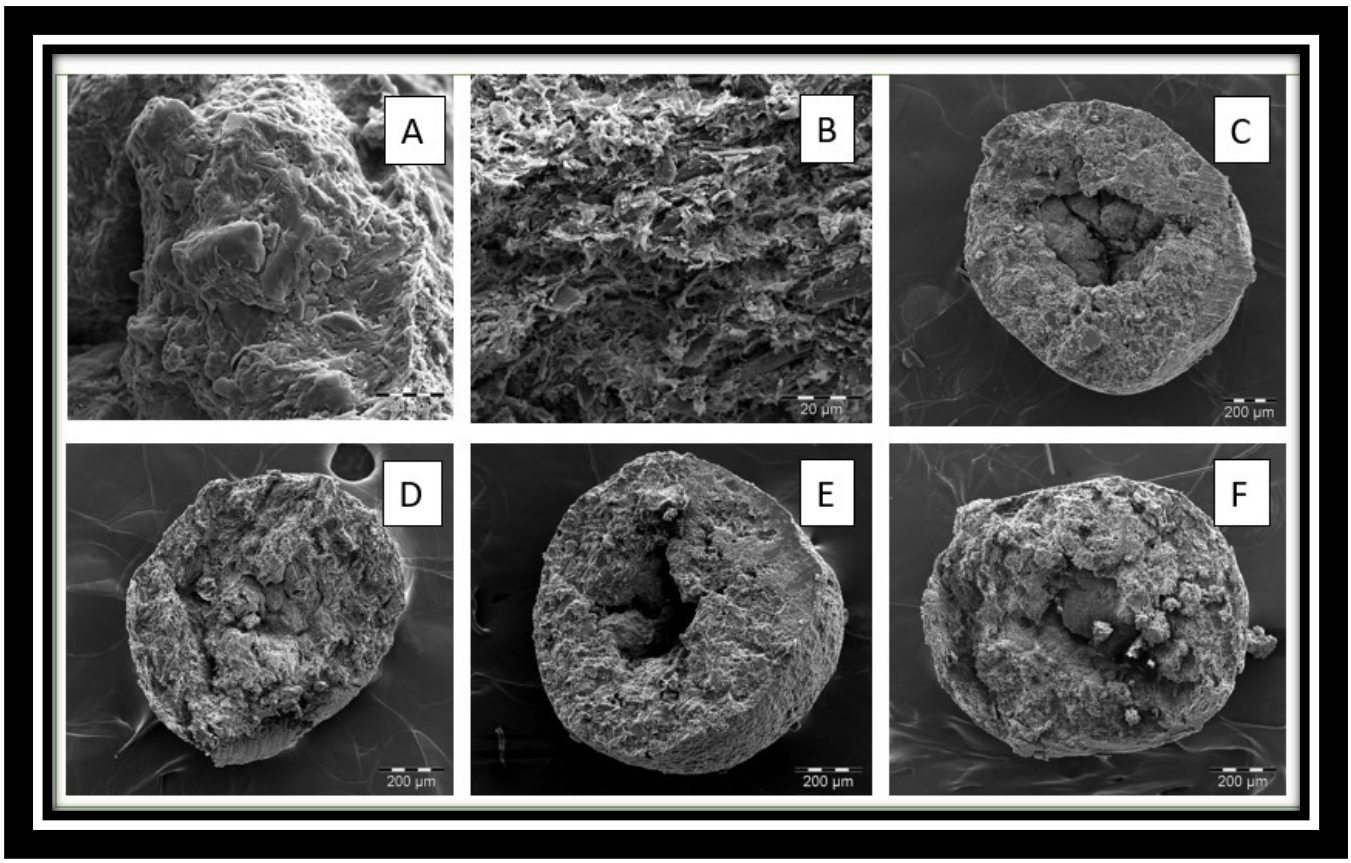

Figure 4.10: Micrographs depicting the internal structure of A, C and E) MicroceLac® -containing bead formula and B, D and F) Pharmacel® -containing bead formula

In Figure 4.10, it can be seen that formulations representing both Pharmacel® and MicroceLac® as filler exhibited an evenly dense structure inside the beads, with some pores and voids visible.

4.3.4 Powder (bead) flow properties

The flowability of the beads was characterised and evaluated in terms of the flow rate, critical orifice diameter (COD), Carr's index and Hausner ratio. A summary of the flowability data of the different pellet/bead formulations are presented in Table 4.9. Discussions of the flowability results are discussed in the following sections.

Table 4.9: Summary of the flowability results of pellet/bead formulations prepared from MicroceLac® and Pharmacel®

Formulation	Critical orifice diameter (mm)	Flow rate 10mm orifice (gram/sec)	± SD	Hausner ratio	± SD	Carr's index (%)	± SD
MicroceLac®							
MMF1	7.00	29.40	0.000	1.07	0.020	6	0.014
MMF2	7.00	29.40	0.000	1.15	0.017	13	0.013
MMF3	7.00	30.03	1.097	1.13	0.017	11	0.014
MGF1	7.00	28.87	0.924	1.04	0.020	4	0.018
MGF2	7.00	27.80	0.000	1.11	0.014	10	0.011
MGF3	7.00	27.30	0.866	1.06	0.021	6	0.019
Pharmacel®							
PMF1	7.00	22.70	0.000	1.07	0.006	6	0.006
PMF2	7.00	21.70	0.000	1.08	0.028	8	0.024
PMF3	7.00	23.07	0.635	1.07	0.038	7	0.033
PGF1	7.00	21.10	0.520	1.10	0.010	9	0.009
PGF2	7.00	19.20	0.000	1.07	0.009	7	0.008
PGF3	7.00	20.80	0.000	1.06	0.028	5	0.025

MM = MicroceLac® metformin, MG = MicroceLac® gliclazide, PM = Pharmacel® metformin, PG = Pharmacel® gliclazide

4.3.4.1 Flow rate

The flow rate data using a 10-mm orifice for different formulations are graphically depicted in Figure 4.11.

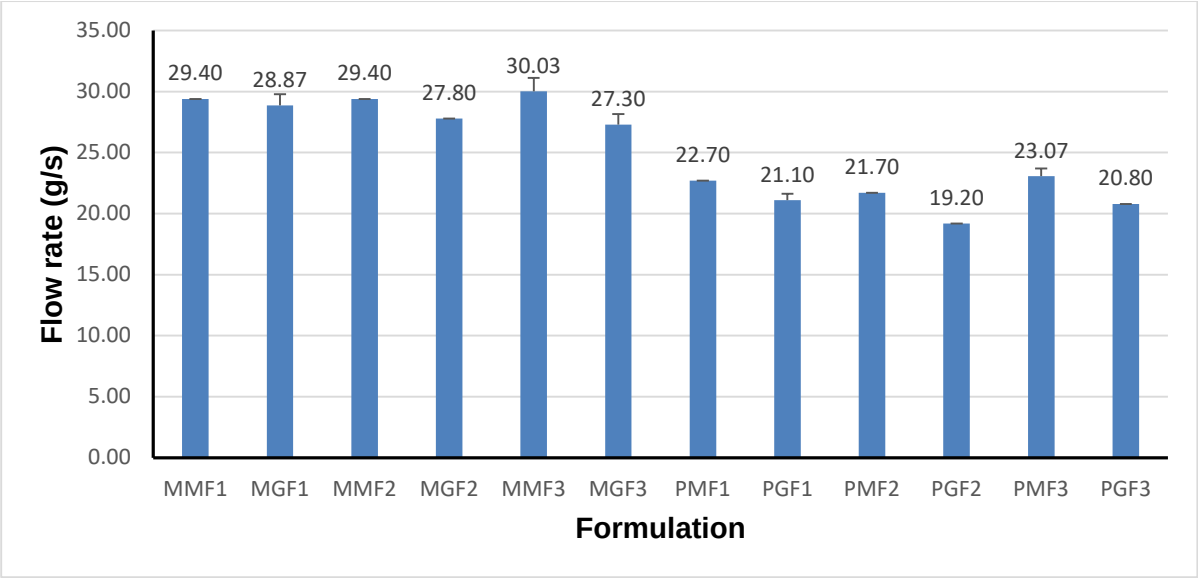

Figure 4.11: Flow rate of the different bead formulations (MM = MicroceLac® metformin, MG = MicroceLac® gliclazide, PM = Pharmacel® metformin, PG = Pharmacel® gliclazide)

In Table 4.10 an in-house, arbitrary classification of powder flow used in this study based on preliminary experiments is shown.

Table 4.10: An arbitrary classification of powder flow in this study is shown (Van der Merwe, 2015).

Classification of flow	Flow rate (g/s)
Excellent	8 and upwards
Good	5 – 7.99
Fair	2 – 4.99

All the bead formulations exhibited an excellent flow rate considering the flow rate results and the classification scale presented in Table 4.10. The Microcelac®-containing formulations exhibited average flow rate values between 27.30 and 30.03 g/s while the Pharmacel®-containing formulations exhibited average flow rate values between 19.20 and 23.07 g/s. No pronounced differences in terms of flow rate were observed between the different formulations. Once again, the similarity in flow rate for all the formulations can be attributed to the same manner in which the formulations were prepared. Furthermore, it is well known that an increase in sphericity and a smooth surface area are associated with a good flow behavior (Aulton, 2013). Although no pronounced differences in flow rate were observed, the Microcelac®-containing formulations exhibited a slightly better flow rate in comparison to the Pharmacel®-containing formulations. This slightly better flow rate might be attributed to the higher density of the Microcelac®-containing formulations. The density of Microcelac® and Pharmacel® is 0.5 g/ml and 0.2 g/ml, respectively (Shimizu *at el*., 2007).

4.3.4.2 Critical orifice diameter (COD)

The COD test results of the different formulations are graphically represented in Figure 4.12 and the criteria for the interpretation of COD results are indicated in Table 4.11.

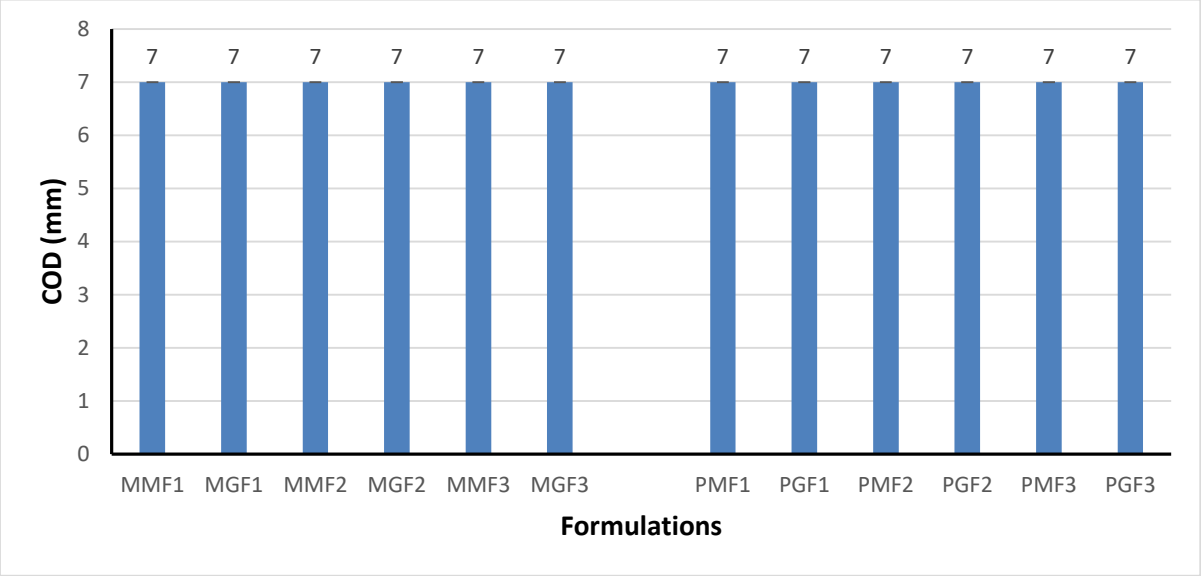

Figure 4.12: Critical orifice diameter results for all beads formulations (MM = MicroceLac® metformin, MG = MicroceLac® gliclazide, PM = Pharmacel® metformin, PG = Pharmacel® gliclazide)

In Table 4.11 an in-house, arbitrary classification is given with regards to critical orifice diameter based on preliminary experiments.

Table 4.11: Criteria for interpretation of the critical orifice diameter results

Classification of flow	COD (Critical orifice diameter) (mm)
Excellent	1 – 4
Good	5 – 8
Fair	8 – 12

All the bead formulations presented with the same COD value of 7 mm. All the MicroceLac®-containing bead formulations as well as all the Pharmacel®-containing bead formulations flowed through an orifice of 7 mm. The good flow properties could be attributed to the uniformity in particle size and shape for all the formulations (as evidenced from the particle size results as well as the SEM images). As discussed in the particle size results all formulations exhibited with an average particle size (D[4,3]) of between 1003.091 and 1108.290 µm. Similar to the flow rate results, the COD results could be explained by the fact that all the beads formulations were prepared under the same conditions and a 1 mm screen diameter perforation was used during the extrusion process of all the formulations as discussion in the section 3.5. From the COD results, it is evident that all the formulation from both diluents could be classified as free flowing according to the arbitrary flow property classification of the COD test given in Table 4.11.

4.3.4.3 Hausner ratio and Carr's index (% compressibility)

4.3.4.3.1 Hausner ratio

The Hausner ratio and the Carr's index (or % compressibility) data of the different formulations are presented in Figure 4.13 and 4.14 respectively.

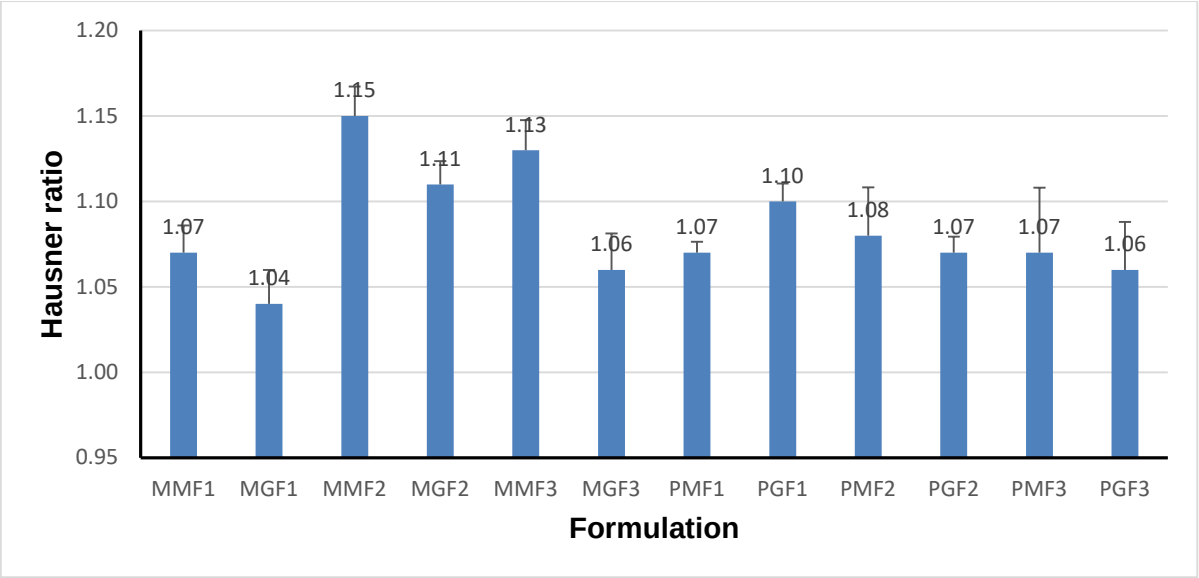

Figure 4.13: Hausner ratio values for all the bead formulations (MM = MicroceLac® metformin, MG = MicroceLac® gliclazide, PM = Pharmacel® metformin, PG = Pharmacel® gliclazide).

In Table 4.12, the criteria to interpret Hausner ratio values in terms of powder flow are given (BP, 2017 online).

Table 4.12: Criteria for interpretation of Hausner ratio values and Carr's index values in terms of powder flow classification

Classification of flow	Hausner ratio	Carr's index (% compressibility)
Excellent	1.00 – 1.11	1 – 10
Good	1.12 – 1.18	11 – 15
Fair	1.19 – 1.25	16 – 20

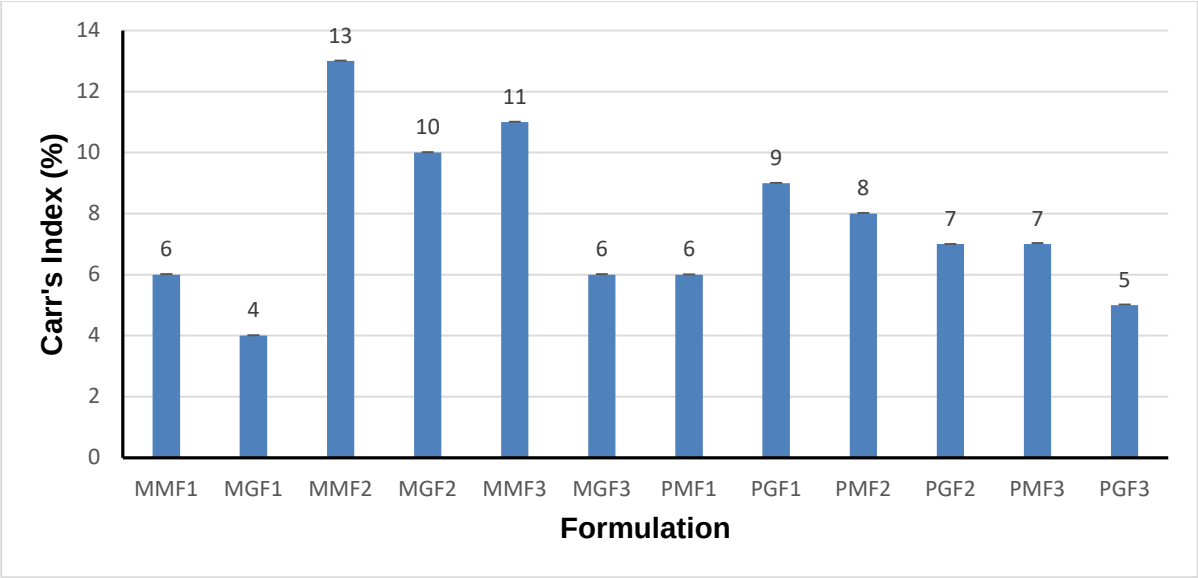

Figure 4.14: The % compressibility results for all bead formulations (MM = MicroceLac® metformin, MG = MicroceLac® gliclazide, PM = Pharmacel® metformin, PG = Pharmacel® gliclazide).

The MicroceLac®-containing beads formulations exhibited Hausner ratio values and Carr's index values between 1.07 – 1.15 and 4 – 13%, respectively. Both the Hausner ratio and Carr's index values indicated good to excellent flow. Similar to the MicroceLac®-containing bead formulations, the Pharmacel®-containing bead formulations exhibited Hausner ratio values and Carr's index values between 1.06 – 1.10 and 5 – 9%, respectively. Both the Hausner ratio and Carr's index values indicated excellent flow properties. From these results, it can be seen that although all the bead formulations exhibited good to excellent flow, the Pharrmacel®-containing formulations exhibited slightly better flow. This may be attributed to the inclusion of lactose in the co-processed filler, MicroceLac® (MCC-lactose). The lactose in the MicroceLac® might have caused cohesive forces between the particles and resulting in a decreased flow which consequently affected the Hausner ratio value negatively (Zhou *et al.,* 2011). The good to excellent flow can be explained as mentioned before, by the uniformity in terms of size, shape and structure of the beads.

4.5.5 Flowability properties summary

It is evident from the flow characterisation that all the bead formulations exhibited good to excellent flow properties. Considering the flow characterisation data from all the flow tests, the preparation of beads formulations resulted in good to excellent flowability, which is advantageous in the manufacturing of solid dosage forms such as capsules.

4.4 FIXED DOSE COMBINATION DOSAGE FORM (CAPSULE) EVALUATION

4.4.1 Mass variation

All capsule formulations for both MicroceLac® and Pharmacel® complied with the specifications for mass variation as set by the BP (2017). None of the capsule masses deviated by more than 7.5% from the average capsule mass for any of the formulations. In Table 4.14, the individual masses as well as average masses and standard deviation values are given.

Table 4.14: Average capsule mass values for all the formulations

Capsule nr.	MF1	PF1	MF2	PF2	MF3	PF3
1	0.66	0.57	0.61	0.57	0.64	0.6
2	0.65	0.59	0.63	0.56	0.64	0.58
3	0.65	0.57	0.64	0.57	0.62	0.57
4	0.65	0.58	0.62	0.57	0.64	0.57
5	0.65	0.58	0.62	0.57	0.64	0.58
6	0.66	0.58	0.63	0.58	0.64	0.58
7	0.65	0.58	0.63	0.56	0.63	0.59
8	0.65	0.59	0.60	0.56	0.65	0.58
9	0.65	0.56	0.64	0.57	0.65	0.58
10	0.65	0.58	0.62	0.58	0.64	0.63
11	0.65	0.58	0.64	0.58	0.64	0.63
12	0.62	0.57	0.65	0.58	0.64	0.6
13	0.65	0.59	0.61	0.57	0.62	0.59
14	0.64	0.57	0.61	0.58	0.62	0.59
15	0.65	0.57	0.61	0.57	0.62	0.6
16	0.65	0.58	0.62	0.58	0.63	0.58
17	0.66	0.57	0.61	0.58	0.64	0.6
18	0.65	0.60	0.61	0.54	0.64	0.6
19	0.65	0.58	0.62	0.57	0.64	0.6
20	0.65	0.58	0.62	0.57	0.64	0.61
Ave	**0.65**	**0.58**	**0.62**	**0.57**	**0.64**	**0.59**
SD	**0.008**	**0.009**	**0.013**	**0.010**	**0.009**	**0.017**

P= Pharmacel® and M= MicroceLac®

4.4.2 Disintegration time

In Table 4.15 the individual disintegration times as well as average values and standard deviations for the different capsule formulations are given.

From Table 4.15 it is clear that all the capsules from all the encapsulated formulation disintegrated within 15 min. Therefore, all the formulations complied with the specifications of the British Pharmacopoeia regarding disintegration of capsules (BP, 2017 online).

Table 4.15: Individual disintegration times as well as average disintegration and standard deviations for the capsules for all the formulations

Capsule nr.	MF1	PF1	MF2	PF2	MF3	PF3
1	208	302	247.2	371	192	436.2
2	208	302	395.4	371	309.6	436.2
3	271	335	483	371	383.4	570.6
4	271	482	483	437	383.4	624
5	327	482	483	502	483	624
6	371	678	483	502	483	624
AVE	**276.10**	**430.20**	**429.10**	**425.40**	**372.40**	**552.50**
SD	**64.541**	**147.307**	**95.754**	**64.322**	**110.630**	**92.429**

P= Pharmacel® and M= MicroceLac®

The MicroceLac®-containing beads formula 1 (MF1) had the shortest disintegration time and the Pharmacel®-containing bead formula 3 (PF3) had the longest disintegration time. However, all the formulations disintegrated within the required 15 minutes.

4.4.3 Capsule evaluation summary

Capsules were successfully filled with different beads formulations and all the formulations rendered capsules that complied with specifications as set by the BP (2017 online) regarding mass variation and disintegration time. No pronounced differences were noted between different formulations prepared from both MicroceLac® and Pharmacel® concerning the mass variation and the disintegration time results.

4.5 DISSOLUTION RESULTS OF THE DIFFERENT FORMULATIONS

In Figures 4.14 and 4.15 the percentage dissolution profiles for the capsules prepared from the MicroceLac®- and Pharmacel®-containing formulations are represented.

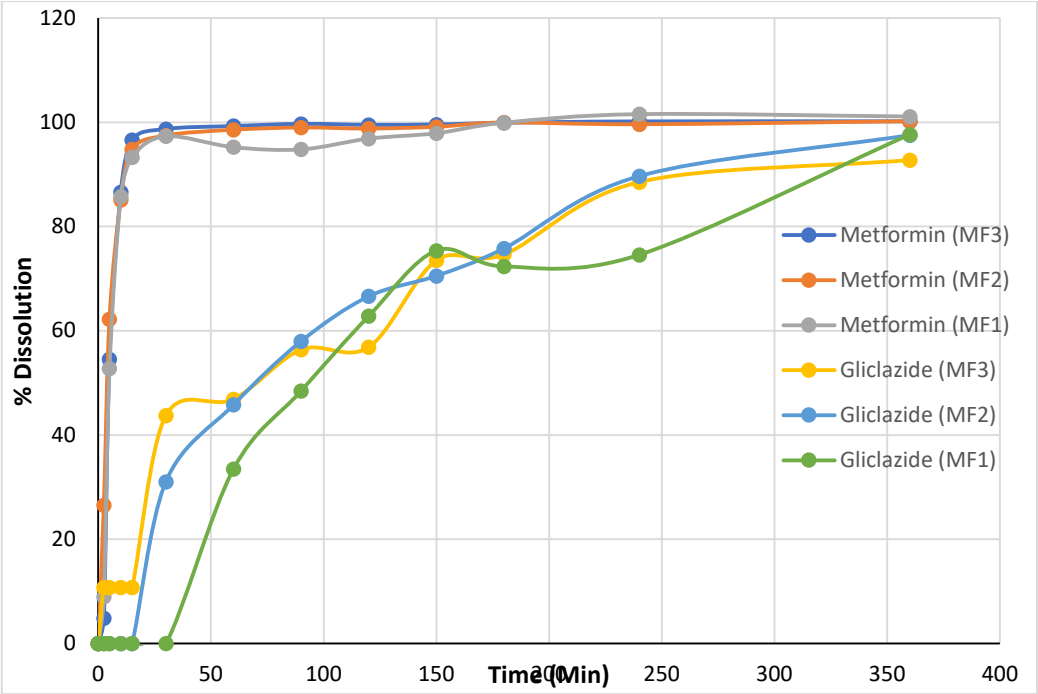

Figure 4.15: The dissolution profiles for metformin and gliclazide respectively for the capsules filled with MicroceLac®-containing beads

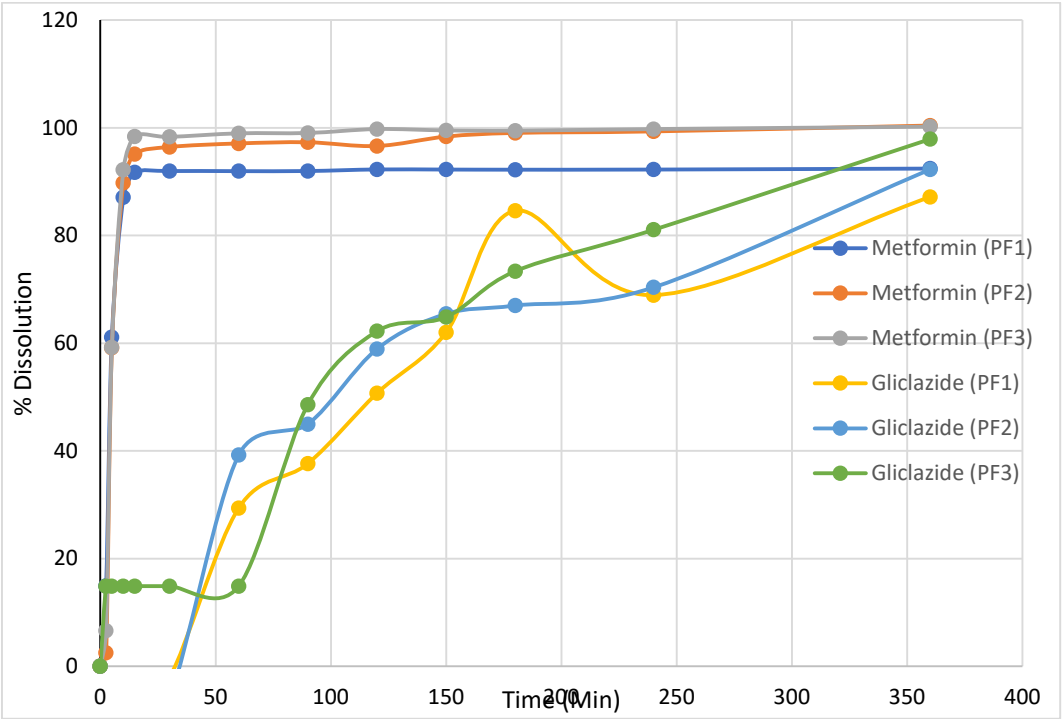

Figure 4.16: The dissolution profiles for metformin and gliclazide respectively for the capsules filled with Pharmacel®-containing beads

It is clear from Figures 4.15 and 4.16 that metformin exhibited a faster dissolution rate in comparison to gliclazide for all formulations irrespective of the formulation. All the capsule

formulations exhibited more than 80% dissolution for metformin within 30 min of the dissolution study. Metformin exhibited an average percentage dissolution ranging from 92.43 – 101.12 after 360 min depending on the formulation. The fast and complete or almost complete dissolution of metformin can be attributed to the high aqueous solubility of metformin. Metformin is classified as freely soluble in water (BP, 2017 online). In comparison to the metformin dissolution profiles, gliclazide exhibited a slower and more erratic profile. The gliclazide exhibited a slow initial dissolution rate evidenced by the fact that detectable gliclazide concentrations in the dissolution samples could only be observed after 15 to 35 min depending on the formulation. This was noted for all capsule formulations. The slow initial dissolution rate of glicalzide may be attributed to the poor solubility of gliclazide — indicated as practically insoluble in the water (BP, 2017 online). However, despite the slow onset of dissolution of gliclazide, the average percentage gliclazide dissolution ranged from 87.18 – 97.91% after 360 min depending on the formulation. The excipients used in the formulation of the different bead formulations (including the fillers, MicroceLac® and Pharmacel®) do not seem to have a pronounced influence either the dissolution of metformin or gliclazide. However, formula PF1 exhibited the lowest percentage dissolution for both metformin and gliclazide. The reason for this is not clear but it should be noted that formulation PF1 comprises a binder and a disintegrant at a concentration of 3% and 0.5%, respectively. The combination of the lowest disintegrant concentration (0.5% w/w) and a binder concentration of 3% w/w affected the dissolution rate for both drugs negatively.

In Table 4.16 the average AUC_{0-360} (%.min) for the different FDC formulations for metformin and gliclazide are given.

Table 4.16: The average AUC_{0-360} (%.min) of the different fixed dose combination capsule formulations for metformin and gliclazide

Formulations	Average $AUC_{(0-360)}$ (%.min)	SD	Average AUC_{0-360} (%.min)	SD
MF1	35022.54	1406.312	21914.07	1867.628
PF1	32742.14	1533.333	20548.10	1085.479
MF2	35212.99	43.959	25210.03	642.425
PF2	34905.22	83.811	20890.84	492.448
MF3	35305.50	194.588	25114.25	1760.644
PF3	35285.49	75.705	22841.16	383.666

P= Pharmacel® and M= MicroceLac®

The AUC_{0-360} of all the formulations for metformin ranged from 32742.14 to 35305.50 %.min. Minor differences were noted between the different formulations; however, these differences were not statistically significant (ANOVA, $p > 0.05$). The similarity in AUC value indicated that there was no statistically significant difference in the extent of metformin dissolution from the different

formulations indicating that none of the excipients (including the filler) had a pronounced influence on the extent of metformin dissolution.

The AUC_{0-360} values of all the formulations for metformin ranged from 32742.14 to 35305.50 %.min. Minor differences were noted between the different formulations; however, these differences were not statistically significant (ANOVA, $p > 0.05$). The similarity in AUC values and p values obtained indicated that there was no statistically significant difference in the extent of metformin dissolution from the different formulations indicating that none of the excipients (including the filler) had a pronounced influence on the extent of metformin dissolution.

The AUC_{0-360} values of all the formulations for gliclazide ranged from 20548.10 to 25210.03 %.min. Similar to metformin dissolution, minor differences were noted between the different formulations; however, these differences were not statistically significant (ANOVA, $p > 0.05$). The similarity in AUC value indicated that none of the excipients (including the filler) had a pronounced influence on the extent of metformin dissolution.

4.6 RESULTS SUMMARY

All the formulations exhibited good to excellent flow behavior and indicated therefore that these formulations may be used in the manufacture of solid oral dosage forms (e.g. capsules or tablets). All the FDC capsules disintegrated within 15 min as required by the BP and the mass variation between the capsules were very minor and acceptable as it complied with official specifications.

There was not a marked difference between the MicroceLac®-containing bead formulations and Pharmacel®-containing bead formulations concerning the dissolution behavior or the extent of dissolution for both metformin and gliclazide. All the formulations exhibited similar dissolution properties regardless of the filler used in their preparation. The capsule formulations exhibited an average percentage dissolution ranging from 92.43 – 101.12% and 87.18 – 97.91% for metformin and gliclazide, respectively. Metformin had a faster dissolution rate compared to that of gliclazide. All the formulations had a similar extent of dissolution for metformin and gliclazide as evidenced by the AUC_{0-360} values, although minor differences were noted. These differences were, however, not statistically significant. The differences in the dissolution behavior of metformin and gliclazide may be attributed to the difference in the solubility between these two drugs with metformin being freely water soluble while gliclazide is practically insoluble in water.

The results of this study indicated that an FDC solid oral dosage form containing metformin and gliclazide could be prepared successfully. that the FDC formulations were able to render both drugs pharmaceutically available in solution.

5 CHAPTER 5: SUMMARY AND FUTURE PROSPECTS

5.1 SUMMARY

Compliance to treatment by patients can be challenging especially when it comes to the management of chronic diseases due to the complexity of treatment. The popularity of fixed-dose combinations (FDC) is increasing as they simplify the treatment regimen by reducing the number of pills to be taken.

Considering that solid oral dosage forms such as capsules and tablets are generally well accepted by patients and is usually associated with a high degree of patient compliance, it consequently comprises a substantial part of the commercially available pharmaceutical dosage forms. It is important to keep on improving this well accepted dosage form to improve therapy and patient compliance even further.

In this study, a multiple-unit pellet system (MUPS capsules) dosage form containing metformin and gliclazide was developed. Thirty-two bead formulations were formulated varying with regard to the amount of disintegrant (Ac-di-sol®), binder (Kollidon® VA 64) and the type of filler (Pharmacel® or MicroceLac®). The bead formulations were prepared by extrusion-spheronisation and the different bead formulations were characterised in terms of flow properties since this is one of the most important aspects influencing the production and preparation of solid oral pharmaceutical dosage forms. Acceptable flowability of formulations intended for capsule filling is important in order to ensure uniform filling of capsules and contribute to a pharmaceutical product that is safe, reliable and effective. The flowability of the different formulations was characterised with regard to flow rate, critical orifice diameter (COD), Hausner's ratio and % compressibility (Carr's index). Besides flowability, the bead formulations were also assayed for metformin or gliclazide content. Based on the assay results, bead formulations with an assay value ≥ 90% were selected for further study. These bead formulations were encapsulated to render fixed-dose capsule formulations (metformin-gliclazide) that were evaluated with respect to mass variation, disintegration and dissolution behaviour.

Flow results indicated that it was clear that the preparation of beads did result in excellent/good flow as all the formulations exhibited a good to excellent flow and this may be explained with respect to the large and spherical or almost spherical shape of the beads.

All fixed-dose capsule formulations complied with regards to mass variation specifications of the BP (2017). There was no pronounced difference in the average disintegration time values recorded for both MicroceLac®- and Pharmacel®-containing capsules. All the capsules disintegrated within 15 min as required by the BP (2017). It was evident from the results that

neither the filler nor the concentration of the binder and disintegrant had a pronounced effect on the physical properties of the capsules.

All the formulations exhibited an average percentage dissolution of metformin and gliclazide ranging from 92.43 – 101.12 and 87.18 – 97.91%, respectively after 360 min depending on the formulation. There was not a pronounced difference in dissolution behaviour between the Pharmacel® and the MicroceLac®-containing capsule formulations. However, there was a marked slower initial dissolution rate for gliclazide regardless of the filler used (Pharmacel® or MicroceLac®), evidenced by the fact that gliclazide concentrations in the dissolution samples could only be detected after 15 to 35 min depending on the formulation. All the capsule formulations exhibited more than 80% dissolution for metformin within 30 min of the dissolution study. It was clear from the dissolution results that the choice of filler and the quantity of the other excipients such as disintegrant or binder did not have a significant effect on the extent of either metformin or gliclazide dissolution. The difference in $AUC_{(0-360)}$ between the formulations were minor with no statistical significance (ANOVA, $p > 0.05$). However, the solubility in water of the two drugs did influence their dissolution rate — metformin is very soluble in water and exhibited a higher and faster dissolution rate compared gliclazide which is practically insoluble in water.

The results of this study indicate that an FDC solid oral dosage form containing metformin and gliclazide that was able to render both drugs pharmaceutically available in solution could be prepared successfully.

5.2 FUTURE PROSPECTS

This study highlighted that it was possible to prepare an FDC of metformin and gliclazide, however, the following can be considered for future studies:

- Preparation of bead formulations containing a higher load of both metformin and gliclazide should be investigated.
- Preparation of a range of concentrations of FDC capsules should be attempted to render more flexibility in terms of dosages.
- Inclusion of excipients to modify the release of metformin and/or gliclazide to investigate the possibility to create modified release of either or both of the active ingredients.
- Investigate formulation strategies to improve the erratic and poor initial dissolution rate for gliclazide as observed in this study.
- Preparation of MUPS tablet formulations from the bead formulations of metformin and gliclazide.

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7 ANNEXURES

7.1 ANNEXURE A: PARTICLE SIZE DATA

7.1.1 MICROCELAC®-CONTAINING FORMULATIONS

7.1.1.1 Formulation 1

In the following Figures, the particle size distribution data for MicroceLac®-containing bead formula 1 (MF1) is given.

MASTERSIZER 2000

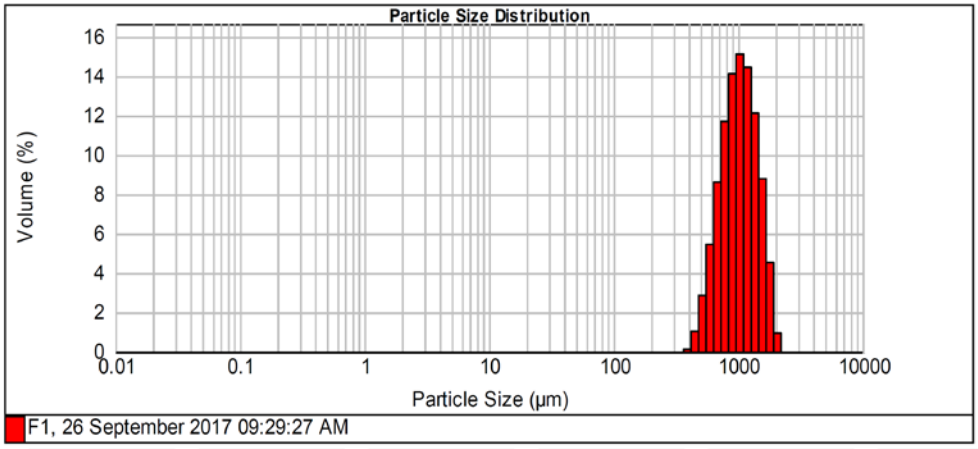
Result Analysis Report

Sample Name: F1	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:29:27 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:29:28 AM
Sample bulk lot ref: F1 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.0... um	**Obscuration:** 4.02 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.530 %	**Result Emulation:** Off

Concentration: 0.5490 %Vol	**Span :** 0.890	**Uniformity:** 0.271	**Result units:** Volume
Specific Surface Area: 0.00637 m²/g	**Surface Weighted Mean D[3,2]:** 942.220 um	**Vol. Weighted Mean D[4,3]:** 1050.999 um	

d(0.1): 636.663 um **d(0.5): 1008.885 um** **d(0.9): 1534.138 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	12.14
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.75
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	4.53
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.97
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.15	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	1.07	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	2.85	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	5.47	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	8.61	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	11.74	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	14.13	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.15	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	14.45		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	14.45		

Operator notes:

MASTERSIZER 2000

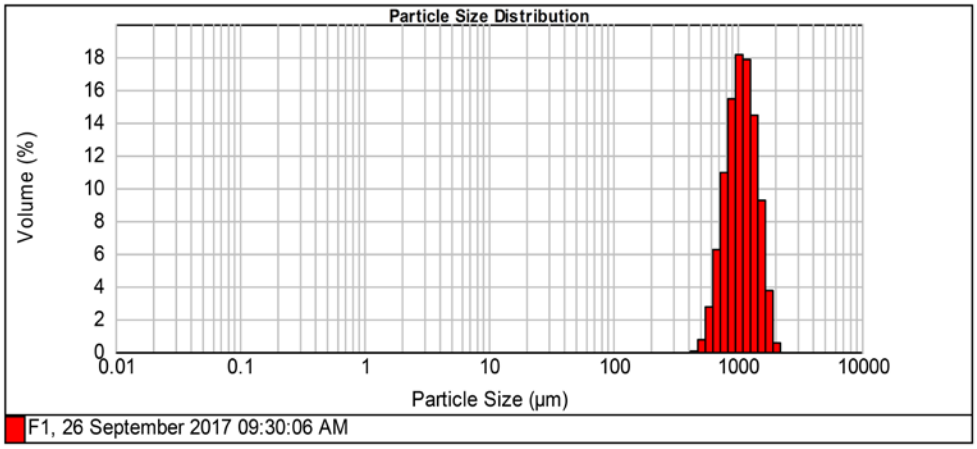
Result Analysis Report

Sample Name: F1	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:30:06 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:30:08 AM
Sample bulk lot ref: F1 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 9.66 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.499 %	**Result Emulation:** Off

Concentration: 1.4612 %Vol	**Span :** 0.736	**Uniformity:** 0.231	**Result units:** Volume
Specific Surface Area: 0.00592 m²/g	**Surface Weighted Mean D[3,2]:** 1013.213 um	**Vol. Weighted Mean D[4,3]:** 1094.530 um	

d(0.1): 727.904 um **d(0.5): 1062.425 um** **d(0.9): 1509.685 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	14.42
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	9.20
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	3.74
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.57
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.05	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.73	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	2.70	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	6.23	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	10.90	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.45	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	18.17		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	17.83		

Operator notes:

MASTERSIZER 2000

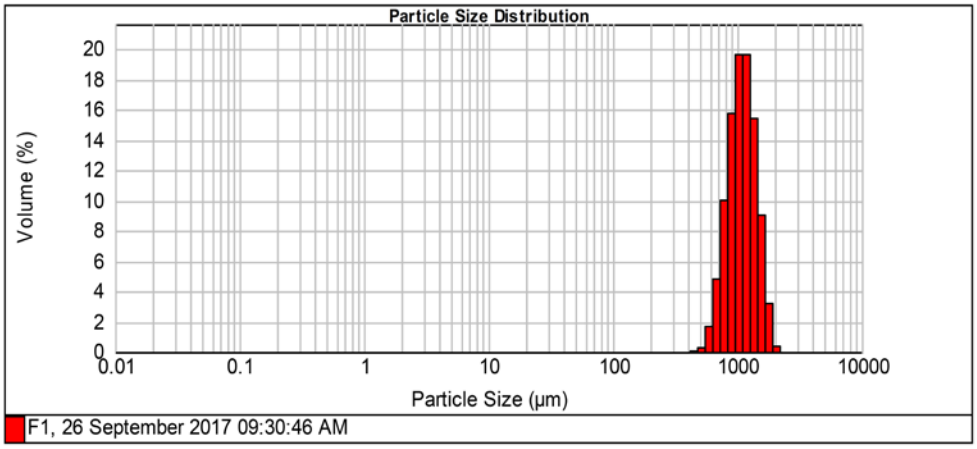
Result Analysis Report

Sample Name: F1	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:30:46 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:30:47 AM
Sample bulk lot ref: F1 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 24.15 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 6.209 %	**Result Emulation:** Off

Concentration: 4.0716 %Vol	**Span :** 0.672	**Uniformity:** 0.213	**Result units:** Volume
Specific Surface Area: 0.00578 m²/g	**Surface Weighted Mean D[3,2]:** 1037.697 um	**Vol. Weighted Mean D[4,3]:** 1107.921 um	

d(0.1): 765.207 um **d(0.5): 1080.179 um** **d(0.9): 1490.997 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	15.49
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	9.09
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	3.17
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.36
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.01	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.25	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.64	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	4.84	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	9.99	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.77	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	19.71		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	19.68		

Operator notes:

MASTERSIZER 2000

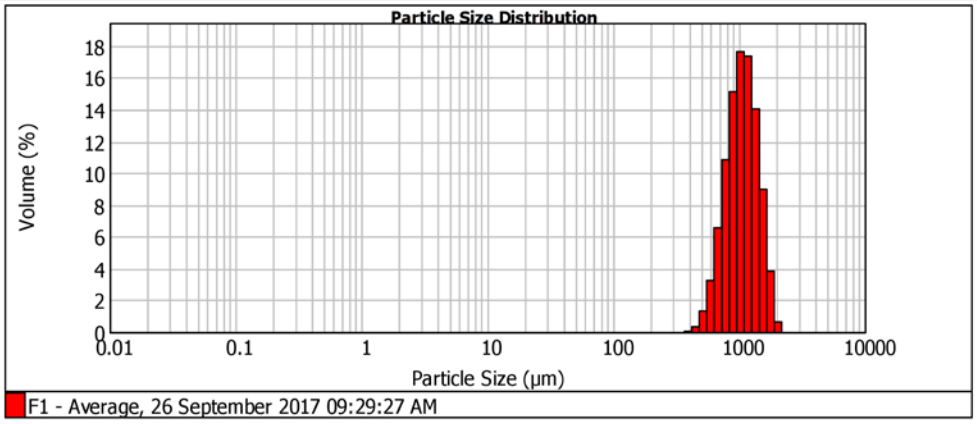
Result Analysis Report

Sample Name: F1 - Average	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:29:27 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:29:28 AM
Sample bulk lot ref: F1 (Sample 1)	**Result Source:** Averaged	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 12.61 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.746 %	**Result Emulation:** Off

Concentration: 2.0273 %Vol	**Span :** 0.764	**Uniformity:** 0.238	**Result units:** Volume
Specific Surface Area: 0.00602 m²/g	**Surface Weighted Mean D[3,2]:** 996.031 um	**Vol. Weighted Mean D[4,3]:** 1084.483 um	

d(0.1): 705.944 um **d(0.5):** 1053.617 um **d(0.9):** 1510.384 um



Size (µm)	Volume In %
0.010	0.00
0.011	0.00
0.013	0.00
0.015	0.00
0.017	0.00
0.020	0.00
0.023	0.00
0.026	0.00
0.030	0.00
0.035	0.00
0.040	0.00
0.046	0.00
0.052	0.00
0.060	0.00
0.069	0.00
0.079	0.00
0.091	0.00
0.105	0.00

Size (µm)	Volume In %
0.105	0.00
0.120	0.00
0.138	0.00
0.158	0.00
0.182	0.00
0.209	0.00
0.240	0.00
0.275	0.00
0.316	0.00
0.363	0.00
0.417	0.00
0.479	0.00
0.550	0.00
0.631	0.00
0.724	0.00
0.832	0.00
0.955	0.00
1.096	0.00

Size (µm)	Volume In %
1.096	0.00
1.259	0.00
1.445	0.00
1.660	0.00
1.905	0.00
2.188	0.00
2.512	0.00
2.884	0.00
3.311	0.00
3.802	0.00
4.365	0.00
5.012	0.00
5.754	0.00
6.607	0.00
7.586	0.00
8.710	0.00
10.000	0.00
11.482	0.00

Size (µm)	Volume In %
11.482	0.00
13.183	0.00
15.136	0.00
17.378	0.00
19.953	0.00
22.909	0.00
26.303	0.00
30.200	0.00
34.674	0.00
39.811	0.00
45.709	0.00
52.481	0.00
60.256	0.00
69.183	0.00
79.433	0.00
91.201	0.00
104.713	0.00
120.226	0.00

Size (µm)	Volume In %
120.226	0.00
138.038	0.00
158.489	0.00
181.970	0.00
208.930	0.00
239.883	0.00
275.423	0.00
316.228	0.00
363.078	0.07
416.869	0.34
478.630	1.30
549.541	3.26
630.957	6.56
724.436	10.88
831.764	15.12
954.993	17.67
1096.478	17.32
1258.925	17.32

Size (µm)	Volume In %
1258.925	14.02
1445.440	9.01
1659.587	3.81
1905.461	0.64
2187.762	0.00
2511.886	0.00
2884.032	0.00
3311.311	0.00
3801.894	0.00
4365.158	0.00
5011.872	0.00
5754.399	0.00
6606.934	0.00
7585.776	0.00
8709.636	0.00
10000.000	0.00

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 4
2017/10/19 03:47:38 PM

7.1.1.2 Formulation 2

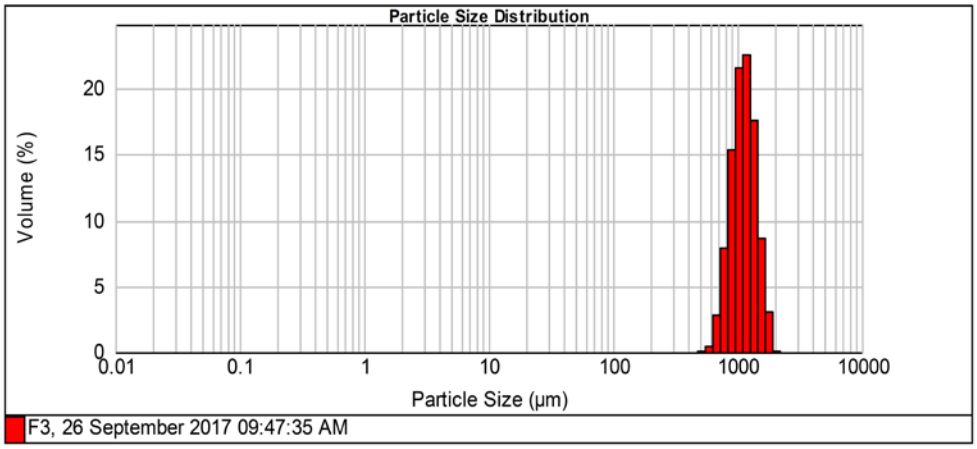
In the following Figures, the particle size distribution data for MicroceLac®-containing bead formula 2 (MF2) is given.

MASTERSIZER 2000

Result Analysis Report

Sample Name: F3	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:47:35 AM	
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:47:36 AM	
Sample bulk lot ref: F3 (Sample 1)	**Result Source:** Measurement		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 1.66 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 11.901 %	**Result Emulation:** Off
Concentration: 0.2551 %Vol	**Span :** 0.591	**Uniformity:** 0.189	**Result units:** Volume
Specific Surface Area: 0.00558 m²/g	**Surface Weighted Mean D[3,2]:** 1075.431 um	**Vol. Weighted Mean D[4,3]:** 1132.467 um	

d(0.1): 820.335 um **d(0.5): 1109.212 um** **d(0.9): 1476.200 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	17.62
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.63
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	3.03
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.05
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.04	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.44	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	2.75	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	7.87	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	15.34	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	21.62	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	22.61		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	22.61		

Operator notes:

MASTERSIZER 2000

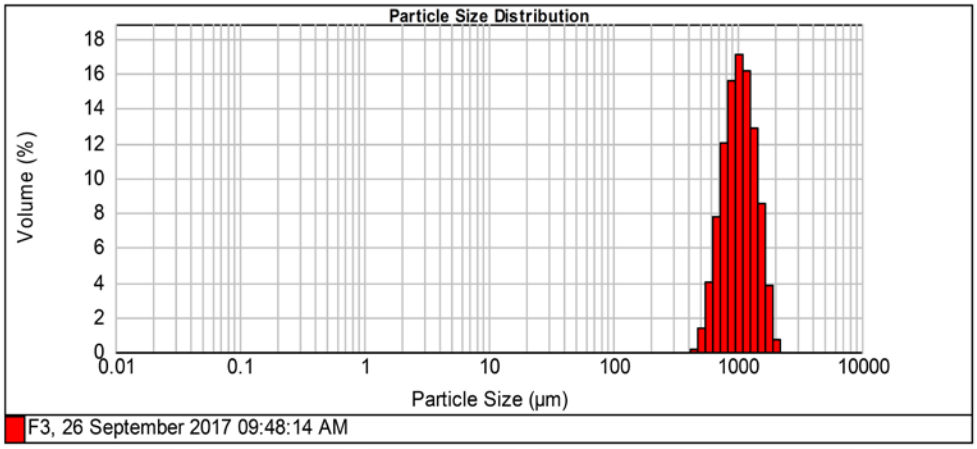
Result Analysis Report

Sample Name: F3	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:48:14 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:48:15 AM
Sample bulk lot ref: F3 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 0.86 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 10.529 %	**Result Emulation:** Off

Concentration: 0.1205 %Vol	**Span :** 0.794	**Uniformity:** 0.244	**Result units:** Volume
Specific Surface Area: 0.00613 m²/g	**Surface Weighted Mean D[3,2]:** 978.574 um	**Vol. Weighted Mean D[4,3]:** 1067.594 um	

d(0.1): 689.926 um **d(0.5):** 1028.508 um **d(0.9):** 1506.355 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	12.89
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.50
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	3.83
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.70
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.15	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	1.36	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	3.96	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	7.77	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	12.04	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.56	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	17.12		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	16.12		

Operator notes:

MASTERSIZER 2000

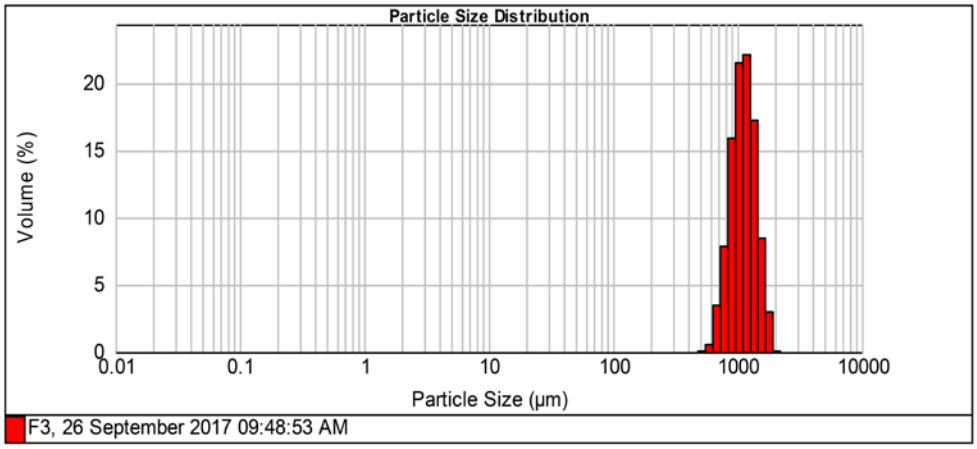
Result Analysis Report

Sample Name: F3	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:48:53 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:48:54 AM
Sample bulk lot ref: F3 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.63 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 9.356 %	**Result Emulation:** Off

Concentration: 1.0390 %Vol	**Span :** 0.602	**Uniformity:** 0.192	**Result units:** Volume
Specific Surface Area: 0.00563 m²/g	**Surface Weighted Mean D[3,2]:** 1066.092 um	**Vol. Weighted Mean D[4,3]:** 1124.809 um	

d(0.1): 809.676 um **d(0.5):** 1101.270 um **d(0.9):** 1472.274 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	17.15
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.43
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.97
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.05
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.06	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	0.57	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	3.45	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	7.90	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.90	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.40		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	22.11		

Operator notes:

MASTERSIZER 2000

Result Analysis Report

Sample Name:
F3 - Average

Sample Source & type:
CN

Sample bulk lot ref:
F3 (Sample 1)

SOP Name:
Consolate

Measured by:
Neil Barnard

Result Source:
Averaged

Measured:
26 September 2017 09:47:35 AM

Analysed:
26 September 2017 09:47:36 AM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Cyclohexane

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.426

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
10.595 %

Sensitivity:
Enhanced

Obscuration:
3.05 %

Result Emulation:
Off

Concentration:
0.4715 %Vol

Specific Surface Area:
0.00578 m²/g

Span :
0.661

Surface Weighted Mean D[3,2]:
1038.147 um

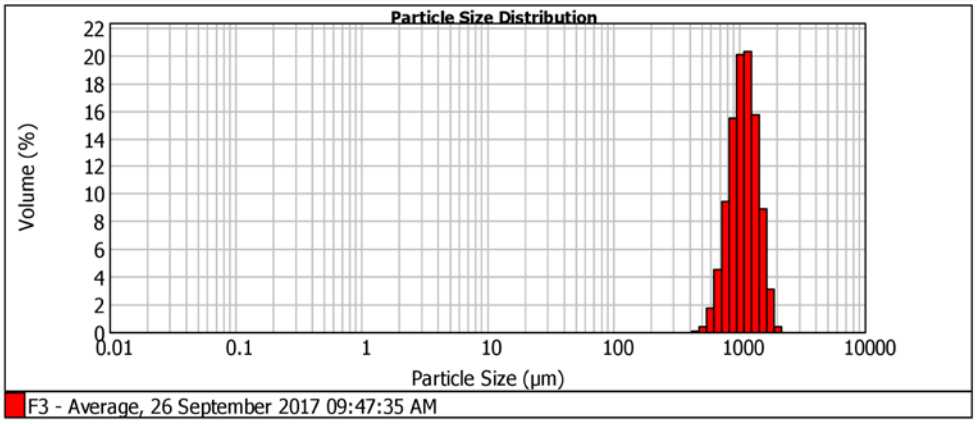
Uniformity:
0.21

Vol. Weighted Mean D[4,3]:
1108.290 um

Result units:
Volume

---

d(0.1): 767.634 um **d(0.5):** 1083.727 um **d(0.9):** 1483.990 um



Size (µm)	Volume In %
0.010	0.00
0.011	0.00
0.013	0.00
0.015	0.00
0.017	0.00
0.020	0.00
0.023	0.00
0.026	0.00
0.030	0.00
0.035	0.00
0.040	0.00
0.046	0.00
0.052	0.00
0.060	0.00
0.069	0.00
0.079	0.00
0.091	0.00
0.105	0.00

Size (µm)	Volume In %
0.105	0.00
0.120	0.00
0.138	0.00
0.158	0.00
0.182	0.00
0.209	0.00
0.240	0.00
0.275	0.00
0.316	0.00
0.363	0.00
0.417	0.00
0.479	0.00
0.550	0.00
0.631	0.00
0.724	0.00
0.832	0.00
0.955	0.00
1.096	0.00

Size (µm)	Volume In %
1.096	0.00
1.259	0.00
1.445	0.00
1.660	0.00
1.905	0.00
2.188	0.00
2.512	0.00
2.884	0.00
3.311	0.00
3.802	0.00
4.365	0.00
5.012	0.00
5.754	0.00
6.607	0.00
7.586	0.00
8.710	0.00
10.000	0.00
11.482	0.00

Size (µm)	Volume In %
11.482	0.00
13.183	0.00
15.136	0.00
17.378	0.00
19.953	0.00
22.909	0.00
26.303	0.00
30.200	0.00
34.674	0.00
39.811	0.00
45.709	0.00
52.481	0.00
60.256	0.00
69.183	0.00
79.433	0.00
91.201	0.00
104.713	0.00
120.226	0.00

Size (µm)	Volume In %
120.226	0.00
138.038	0.00
158.489	0.00
181.970	0.00
208.930	0.00
239.883	0.00
275.423	0.00
316.228	0.00
363.078	0.00
416.869	0.08
478.630	0.42
549.541	1.74
630.957	4.53
724.436	9.44
831.764	15.50
954.993	20.07
1096.478	20.29
1258.925	20.29

Size (µm)	Volume In %
1258.925	15.70
1445.440	8.86
1659.587	3.02
1905.461	0.35
2187.762	0.00
2511.886	0.00
2884.032	0.00
3311.311	0.00
3801.894	0.00
4365.158	0.00
5011.872	0.00
5754.399	0.00
6606.934	0.00
7585.776	0.00
8709.636	0.00
10000.000	0.00

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 12
2017/10/19 03:49:46 PM

7.1.1.3 Formulation 3

In the following Figures, the particle size distribution data for MicroceLac®-containing bead formula 3 (MF3) is given.

MASTERSIZER 2000

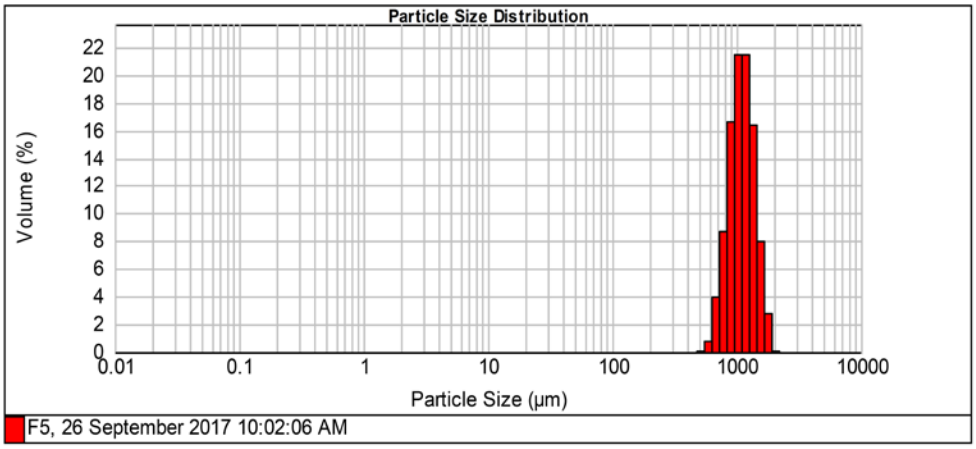
Result Analysis Report

Sample Name: F5	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:02:06 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:02:07 AM
Sample bulk lot ref: F5 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 11.53 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.623 %	**Result Emulation:** Off

Concentration: 1.8311 %Vol	**Span :** 0.613	**Uniformity:** 0.195	**Result units:** Volume
Specific Surface Area: 0.0057 m²/g	**Surface Weighted Mean D[3,2]:** 1053.052 um	**Vol. Weighted Mean D[4,3]:** 1112.568 um	

d(0.1): 795.166 um **d(0.5):** 1087.325 um **d(0.9):** 1461.472 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	16.34
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.97
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.81
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.05
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.07	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.72	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	3.91	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	8.64	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	16.56	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	21.45	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.49		
0.105		1.096		11.482		120.226		1258.925			

Operator notes:

MASTERSIZER 2000

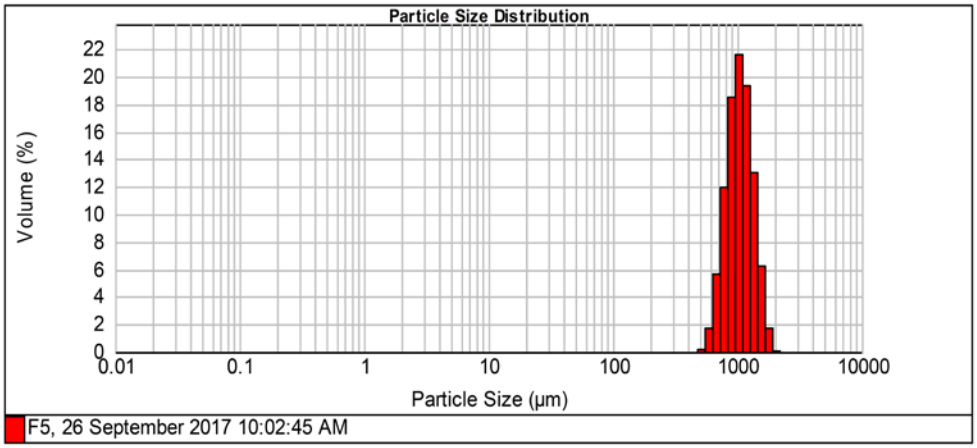
Result Analysis Report

Sample Name: F5	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:02:45 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:02:47 AM
Sample bulk lot ref: F5 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 10.35 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.635 %	**Result Emulation:** Off

Concentration: 1.5509 %Vol	**Span :** 0.635	**Uniformity:** 0.197	**Result units:** Volume
Specific Surface Area: 0.006 m²/g	**Surface Weighted Mean D[3,2]:** 999.364 um	**Vol. Weighted Mean D[4,3]:** 1059.594 um	

d(0.1): 751.466 um **d(0.5): 1031.269 um** **d(0.9): 1406.823 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	13.03
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	6.23
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.68
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.10
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.22	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.70	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	5.60	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	11.97	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	18.52	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.64		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	19.31		

Operator notes:

MASTERSIZER 2000

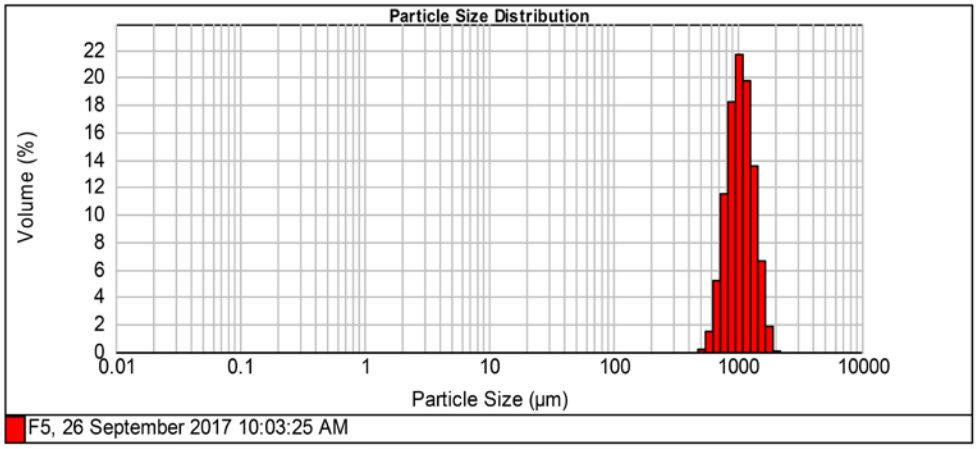
Result Analysis Report

Sample Name: F5	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:03:25 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:03:26 AM
Sample bulk lot ref: F5 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.42 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 5.301 %	**Result Emulation:** Off

Concentration: 2.0650 %Vol	**Span :** 0.632	**Uniformity:** 0.197	**Result units:** Volume
Specific Surface Area: 0.00594 m²/g	**Surface Weighted Mean D[3,2]:** 1009.384 um	**Vol. Weighted Mean D[4,3]:** 1069.343 um	

d(0.1): 760.102 um **d(0.5): 1041.266 um** **d(0.9): 1417.759 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	13.57
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	6.61
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.80
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.11
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.16	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.47	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	5.18	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	11.48	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	18.20	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.69		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	19.73		

Operator notes:

MASTERSIZER 2000

Result Analysis Report

Sample Name:
F5 - Average

SOP Name:
Consolate

Measured:
26 September 2017 10:02:06 AM

Sample Source & type:
CN

Measured by:
Neil Barnard

Analysed:
26 September 2017 10:02:07 AM

Sample bulk lot ref:
F5 (Sample 1)

Result Source:
Averaged

Particle Name:
Titanium Dioxide

Accessory Name:
Hydro 2000SM (A)

Analysis model:
General purpose

Sensitivity:
Enhanced

Particle RI:
2.741

Absorption:
0.1

Size range:
0.020 to 2000.000 um

Obscuration:
11.77 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
5.519 %

Result Emulation:
Off

Concentration:
1.8157 %Vol

Span :
0.629

Uniformity:
0.198

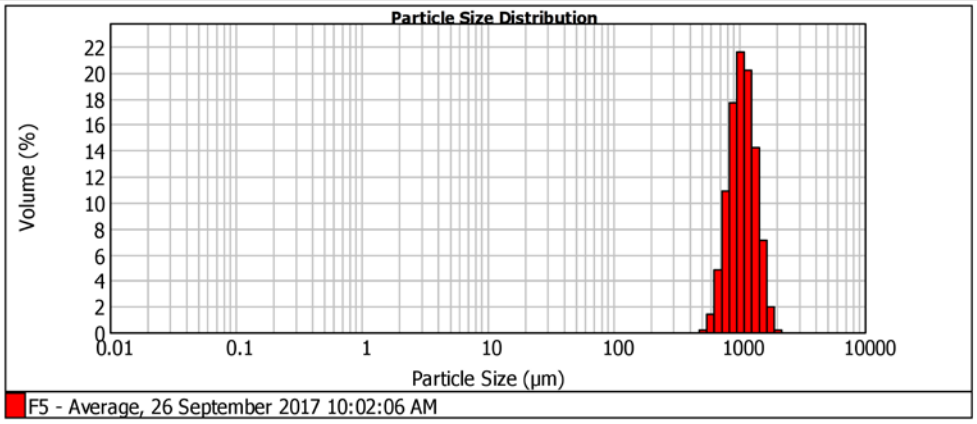
Result units:
Volume

Specific Surface Area:
0.00588 m²/g

Surface Weighted Mean D[3,2]:
1020.073 um

Vol. Weighted Mean D[4,3]:
1080.501 um

d(0.1): 768.253 um **d(0.5):** 1053.255 um **d(0.9):** 1430.947 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	14.23
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.09
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.97
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.13
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.14	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.33	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	4.78	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	10.86	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	17.66	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.61		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	20.18		

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 20
2017/10/19 03:52:04 PM

7.1.2 PHARMACEL®-CONTAINING FORMULATIONS

7.1.2.1 Formulation 1

In the following Figures, the particle size distribution data for Pharmacel®-containing bead formula 1 (PF1) is given.

MASTERSIZER 2000

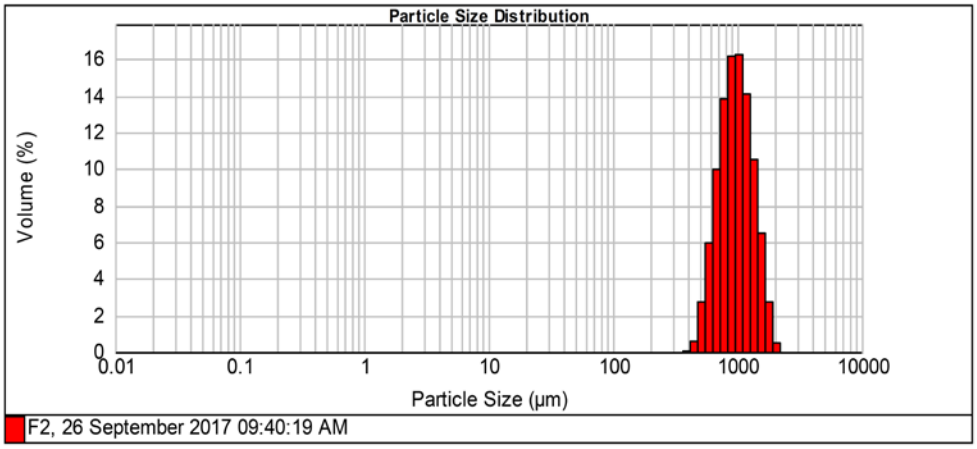
Result Analysis Report

Sample Name: F2	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:40:19 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:40:20 AM
Sample bulk lot ref: F2 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 3.51 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 8.254 %	**Result Emulation:** Off

Concentration: 0.4637 %Vol	**Span :** 0.834	**Uniformity:** 0.26	**Result units:** Volume
Specific Surface Area: 0.00656 m²/g	**Surface Weighted Mean D[3,2]:** 914.136 um	**Vol. Weighted Mean D[4,3]:** 1004.642 um	

d(0.1): 638.149 um **d(0.5): 960.283 um** **d(0.9): 1439.060 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	10.51
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	6.48
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.77
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.48
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.62	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	2.73	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	5.95	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	10.02	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.81	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	16.17	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	16.29	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	14.14		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	14.14		

Operator notes:

MASTERSIZER 2000

Result Analysis Report

Sample Name: F2
SOP Name: Consolate
Measured: 26 September 2017 09:40:58 AM

Sample Source & type: CN
Measured by: Neil Barnard
Analysed: 26 September 2017 09:40:59 AM

Sample bulk lot ref: F2 (Sample 1)
Result Source: Measurement

Particle Name: Titanium Dioxide
Accessory Name: Hydro 2000SM (A)
Analysis model: General purpose
Sensitivity: Enhanced

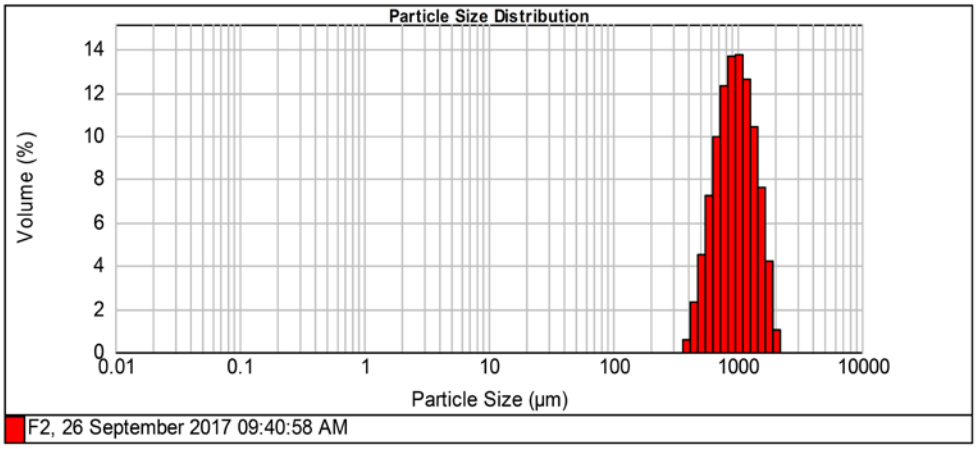
Particle RI: 2.741
Absorption: 0.1
Size range: 0.020 to 2000.000 um
Obscuration: 3.22 %

Dispersant Name: Cyclohexane
Dispersant RI: 1.426
Weighted Residual: 7.673 %
Result Emulation: Off

Concentration: 0.4107 %Vol
Span : 0.977
Uniformity: 0.302
Result units: Volume

Specific Surface Area: 0.00678 m²/g
Surface Weighted Mean D[3,2]: 884.530 um
Vol. Weighted Mean D[4,3]: 1003.610 um

d(0.1): 582.397 um **d(0.5):** 951.156 um **d(0.9):** 1512.107 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	10.40
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.60
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	4.23
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.99
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.54	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	2.30	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.48	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	7.21	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	9.96	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	12.27	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	13.64	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	13.77	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	12.60		
0.105		1.096		11.482		120.226		1258.925			

Operator notes:

MASTERSIZER 2000

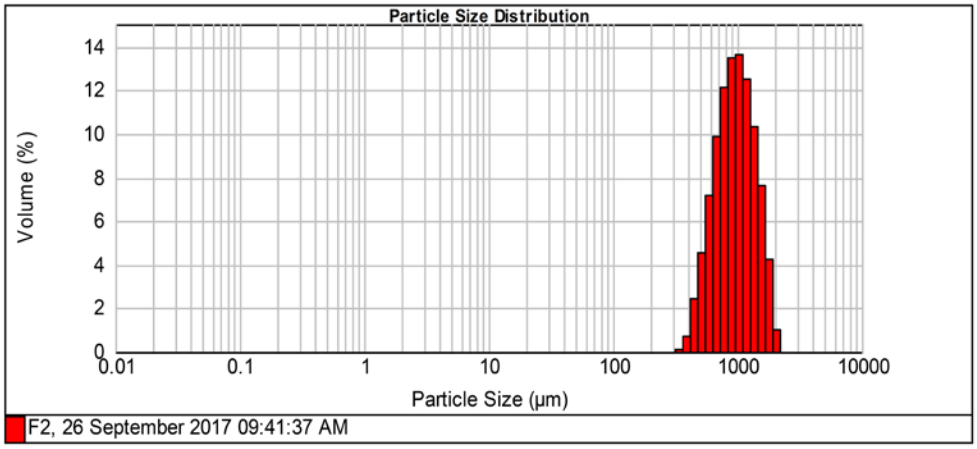
Result Analysis Report

Sample Name: F2	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:41:37 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:41:38 AM
Sample bulk lot ref: F2 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 3.82 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 7.941 %	**Result Emulation:** Off

Concentration: 0.4859 %Vol	**Span :** 0.986	**Uniformity:** 0.305	**Result units:** Volume
Specific Surface Area: 0.00682 m²/g	**Surface Weighted Mean D[3,2]:** 879.382 um	**Vol. Weighted Mean D[4,3]:** 1001.020 um	

d(0.1): 576.402 um **d(0.5):** 949.228 um **d(0.9):** 1512.006 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	10.37
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.60
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	4.23
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.99
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.08	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.74	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	2.43	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.56	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	7.21	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	9.89	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	12.16	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	13.52	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	13.67	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	12.54		
0.105		1.096		11.482		120.226		1258.925			

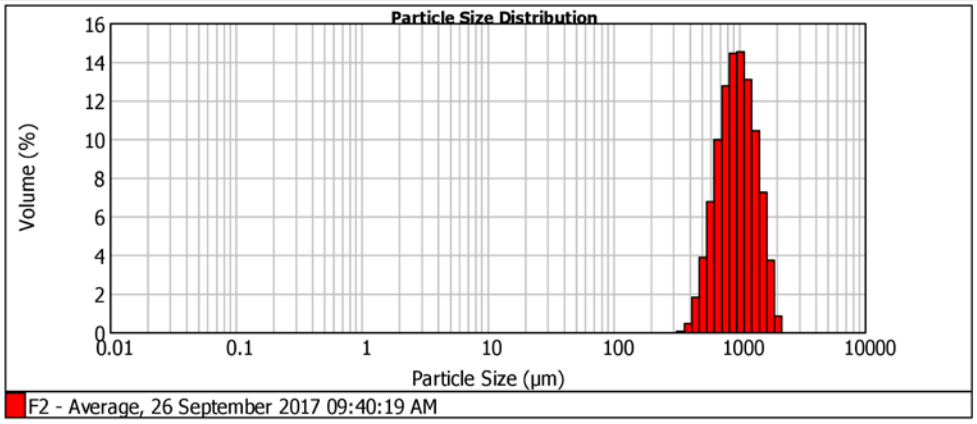
Operator notes:

MASTERSIZER 2000

Result Analysis Report

Sample Name: F2 - Average	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:40:19 AM	
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:40:20 AM	
Sample bulk lot ref: F2 (Sample 1)	**Result Source:** Averaged		
Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 3.51 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 7.956 %	**Result Emulation:** Off
Concentration: 0.4534 %Vol	**Span :** 0.932	**Uniformity:** 0.289	**Result units:** Volume
Specific Surface Area: 0.00672 m²/g	**Surface Weighted Mean D[3,2]:** 892.423 um	**Vol. Weighted Mean D[4,3]:** 1003.091 um	

d(0.1): 598.575 um **d(0.5):** 953.965 um **d(0.9):** 1487.919 um



Size (µm)	Volume In %
0.010	0.00
0.011	0.00
0.013	0.00
0.015	0.00
0.017	0.00
0.020	0.00
0.023	0.00
0.026	0.00
0.030	0.00
0.035	0.00
0.040	0.00
0.046	0.00
0.052	0.00
0.060	0.00
0.069	0.00
0.079	0.00
0.091	0.00
0.105	0.00

Size (µm)	Volume In %
0.105	0.00
0.120	0.00
0.138	0.00
0.158	0.00
0.182	0.00
0.209	0.00
0.240	0.00
0.275	0.00
0.316	0.00
0.363	0.00
0.417	0.00
0.479	0.00
0.550	0.00
0.631	0.00
0.724	0.00
0.832	0.00
0.955	0.00
1.096	0.00

Size (µm)	Volume In %
1.096	0.00
1.259	0.00
1.445	0.00
1.660	0.00
1.905	0.00
2.188	0.00
2.512	0.00
2.884	0.00
3.311	0.00
3.802	0.00
4.365	0.00
5.012	0.00
5.754	0.00
6.607	0.00
7.586	0.00
8.710	0.00
10.000	0.00
11.482	0.00

Size (µm)	Volume In %
11.482	0.00
13.183	0.00
15.136	0.00
17.378	0.00
19.953	0.00
22.909	0.00
26.303	0.00
30.200	0.00
34.674	0.00
39.811	0.00
45.709	0.00
52.481	0.00
60.256	0.00
69.183	0.00
79.433	0.00
91.201	0.00
104.713	0.00
120.226	0.00

Size (µm)	Volume In %
120.226	0.00
138.038	0.00
158.489	0.00
181.970	0.00
208.930	0.00
239.883	0.00
275.423	0.00
316.228	0.02
363.078	0.44
416.869	1.80
478.630	3.91
549.541	6.80
630.957	9.96
724.436	12.75
831.764	14.45
954.993	14.57
1096.478	13.09
1258.925	10.43

Size (µm)	Volume In %
1258.925	10.43
1445.440	7.23
1659.587	3.74
1905.461	0.82
2187.762	0.00
2511.886	0.00
2884.032	0.00
3311.311	0.00
3801.894	0.00
4365.158	0.00
5011.872	0.00
5754.399	0.00
6606.934	0.00
7585.776	0.00
8709.636	0.00
10000.000	0.00

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 8
2017/10/19 03:48:39 PM

7.1.2.2 Formulation 2

In the following Figures, the particle size distribution data for Pharmacel®-containing bead formula 2 (PF2) is given.

MASTERSIZER 2000

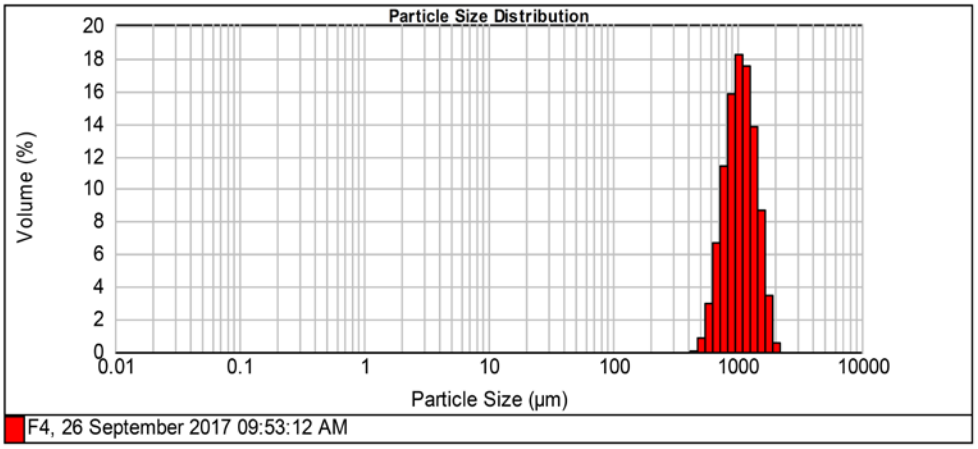
Result Analysis Report

Sample Name: F4	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:53:12 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:53:13 AM
Sample bulk lot ref: F4 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 2.52 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 7.244 %	**Result Emulation:** Off

Concentration: 0.3621 %Vol	**Span :** 0.741	**Uniformity:** 0.231	**Result units:** Volume
Specific Surface Area: 0.00599 m²/g	**Surface Weighted Mean D[3,2]:** 1001.032 um	**Vol. Weighted Mean D[4,3]:** 1081.918 um	

d(0.1): 719.089 um **d(0.5):** 1048.318 um **d(0.9):** 1495.591 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	13.84
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.65
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	3.46
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.53
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.07	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.83	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	2.94	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	6.64	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	11.41	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.87	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	18.27		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	17.51		

Operator notes:

MASTERSIZER 2000

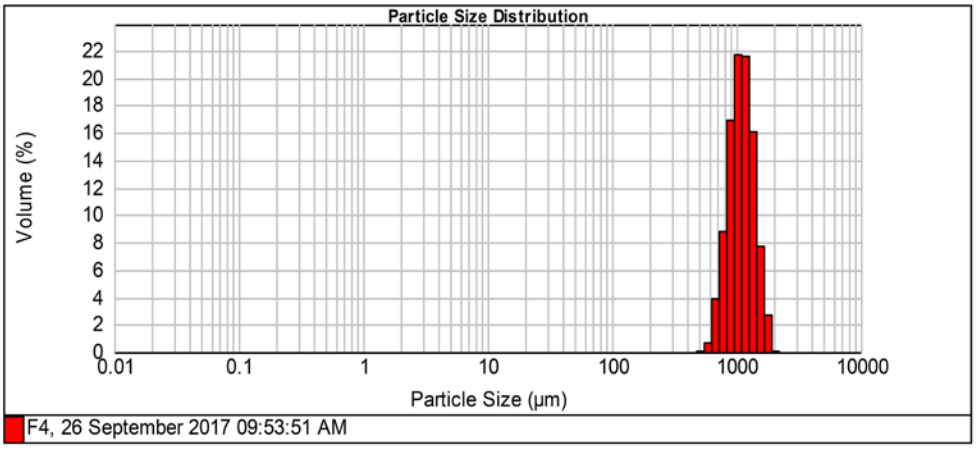
Result Analysis Report

Sample Name: F4	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:53:51 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:53:52 AM
Sample bulk lot ref: F4 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 10.68 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 9.728 %	**Result Emulation:** Off

Concentration: 1.6838 %Vol	**Span :** 0.608	**Uniformity:** 0.194	**Result units:** Volume
Specific Surface Area: 0.00572 m²/g	**Surface Weighted Mean D[3,2]:** 1049.832 um	**Vol. Weighted Mean D[4,3]:** 1108.325 um	

d(0.1): 794.428 um **d(0.5):** 1082.766 um **d(0.9):** 1452.657 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	16.08
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.66
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.67
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.04
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.06	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.69	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	3.93	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	8.76	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	16.86	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	21.74	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.52		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	21.52		

Operator notes:

MASTERSIZER 2000

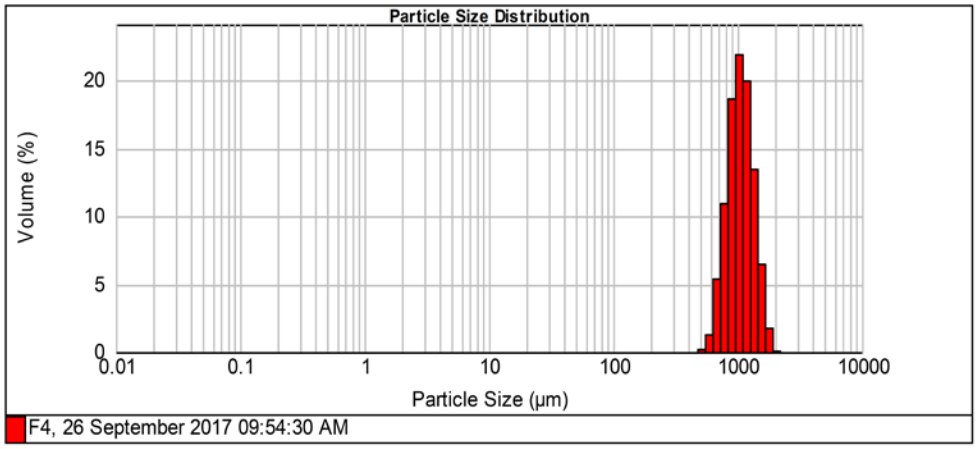
Result Analysis Report

Sample Name: F4	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:54:30 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:54:31 AM
Sample bulk lot ref: F4 (Sample 1)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.02 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 9.993 %	**Result Emulation:** Off

Concentration: 0.8906 %Vol	**Span :** 0.628	**Uniformity:** 0.195	**Result units:** Volume
Specific Surface Area: 0.00594 m²/g	**Surface Weighted Mean D[3,2]:** 1009.447 um	**Vol. Weighted Mean D[4,3]:** 1068.136 um	

d(0.1): 758.154 um **d(0.5): 1040.260 um** **d(0.9): 1411.569 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	13.48
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	6.40
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.70
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.10
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.16	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.29	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	5.41	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	10.93	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	18.65	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.94		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	19.91		

Operator notes:

MASTERSIZER 2000

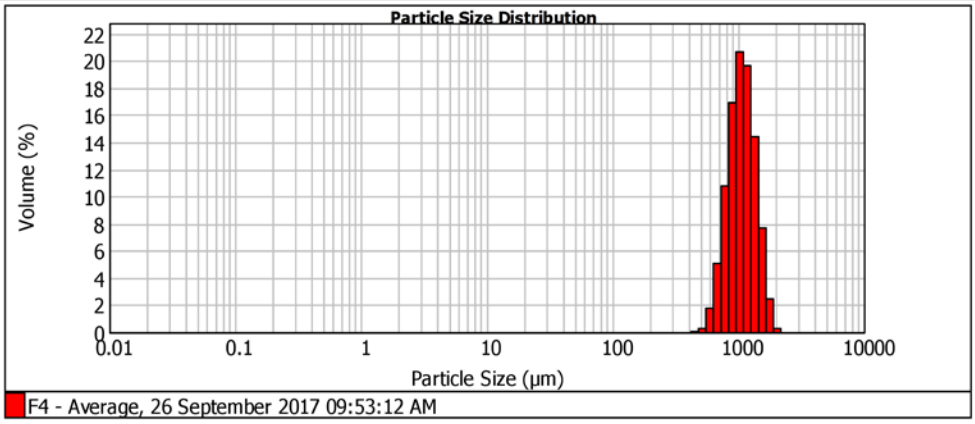
Result Analysis Report

Sample Name: F4 - Average	**SOP Name:** Consolate	**Measured:** 26 September 2017 09:53:12 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 09:53:13 AM
Sample bulk lot ref: F4 (Sample 1)	**Result Source:** Averaged	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.41 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 8.988 %	**Result Emulation:** Off

Concentration: 0.9789 %Vol	**Span :** 0.658	**Uniformity:** 0.207	**Result units:** Volume
Specific Surface Area: 0.00588 m²/g	**Surface Weighted Mean D[3,2]:** 1019.664 um	**Vol. Weighted Mean D[4,3]:** 1086.126 um	

d(0.1): 758.219 um **d(0.5):** 1057.760 um **d(0.9):** 1454.512 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	14.38
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	7.72
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.49
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.26
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.04	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.31	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	1.73	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	5.09	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	10.71	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	16.93	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	20.68		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	19.65		

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 16
2017/10/19 03:50:48 PM

7.1.2.3 Formulation 3

In the following Figures, the particle size distribution data for Pharmacel®-containing bead formula 3 (PF3) is given.

MASTERSIZER 2000

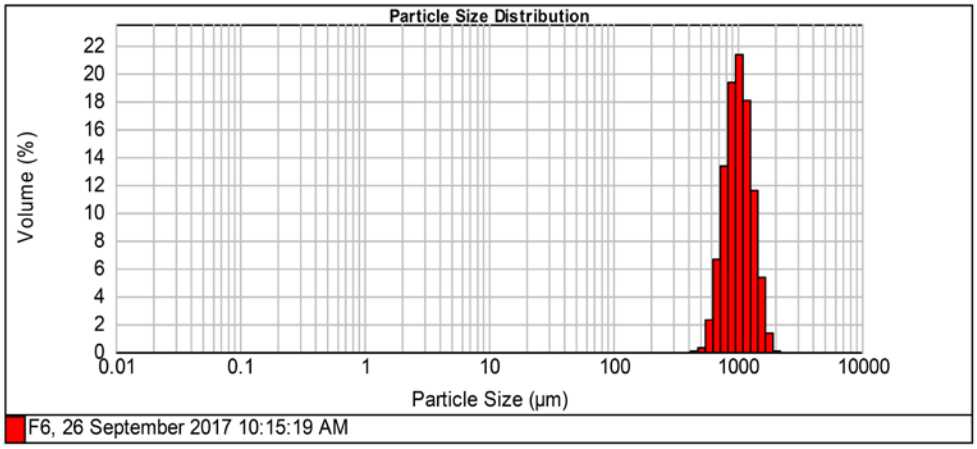
Result Analysis Report

Sample Name: F6	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:15:19 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:15:21 AM
Sample bulk lot ref: F6 (Sample 2)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.38 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 6.935 %	**Result Emulation:** Off

Concentration: 1.0613 %Vol	**Span :** 0.644	**Uniformity:** 0.198	**Result units:** Volume
Specific Surface Area: 0.00616 m²/g	**Surface Weighted Mean D[3,2]:** 974.732 um	**Vol. Weighted Mean D[4,3]:** 1034.805 um	

d(0.1): 731.751 um **d(0.5): 1004.959 um** **d(0.9): 1379.325 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	11.63
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.34
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.40
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.08
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.02	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.33	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	2.24	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	6.68	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	13.34	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	19.42	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.42		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	18.10		

Operator notes:

MASTERSIZER 2000

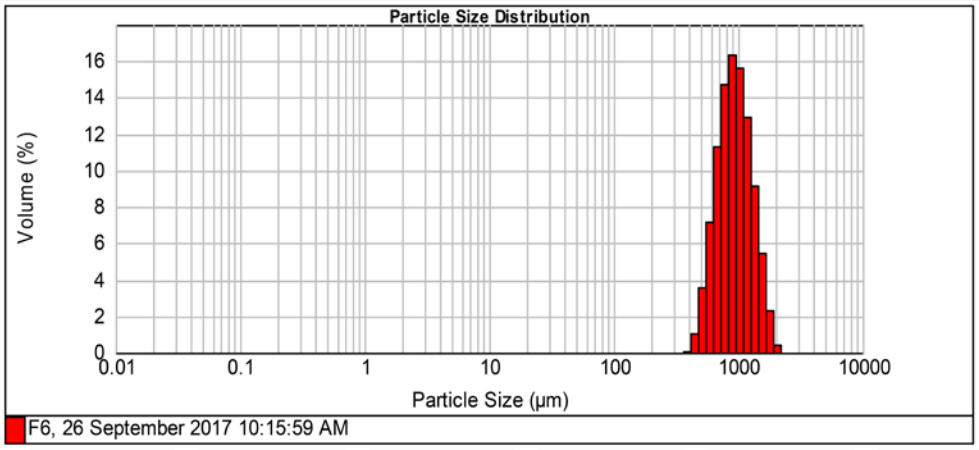
Result Analysis Report

Sample Name: F6	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:15:59 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:16:00 AM
Sample bulk lot ref: F6 (Sample 2)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 3.37 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 7.161 %	**Result Emulation:** Off

Concentration: 0.4283 %Vol	**Span :** 0.850	**Uniformity:** 0.265	**Result units:** Volume
Specific Surface Area: 0.00682 m²/g	**Surface Weighted Mean D[3,2]:** 879.694 um	**Vol. Weighted Mean D[4,3]:** 969.255 um	

d(0.1): 613.305 um **d(0.5):** 921.786 um **d(0.9):** 1397.280 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	9.16
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.45
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.27
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.39
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.06	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	1.07	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	3.52	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	7.17	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	11.30	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	14.74	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	16.35	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.63	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	12.90		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	12.90		

Operator notes:

MASTERSIZER 2000

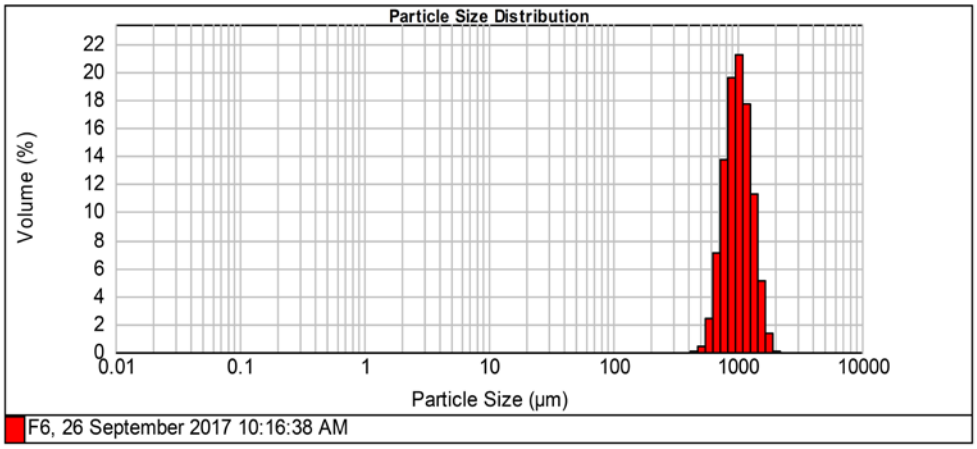
Result Analysis Report

Sample Name: F6	**SOP Name:** Consolate	**Measured:** 26 September 2017 10:16:38 AM
Sample Source & type: CN	**Measured by:** Neil Barnard	**Analysed:** 26 September 2017 10:16:39 AM
Sample bulk lot ref: F6 (Sample 2)	**Result Source:** Measurement	

Particle Name: Titanium Dioxide	**Accessory Name:** Hydro 2000SM (A)	**Analysis model:** General purpose	**Sensitivity:** Enhanced
Particle RI: 2.741	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 12.68 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 6.910 %	**Result Emulation:** Off

Concentration: 1.8619 %Vol	**Span :** 0.648	**Uniformity:** 0.2	**Result units:** Volume
Specific Surface Area: 0.0062 m²/g	**Surface Weighted Mean D[3,2]:** 967.277 um	**Vol. Weighted Mean D[4,3]:** 1027.564 um	

d(0.1): 725.232 um **d(0.5): 997.220 um** **d(0.9): 1371.738 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	11.25
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.13
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.33
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.08
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.03	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	0.38	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	2.45	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	7.06	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	13.75	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	19.60	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	21.24		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	17.70		

Operator notes:

MASTERSIZER 2000

Result Analysis Report

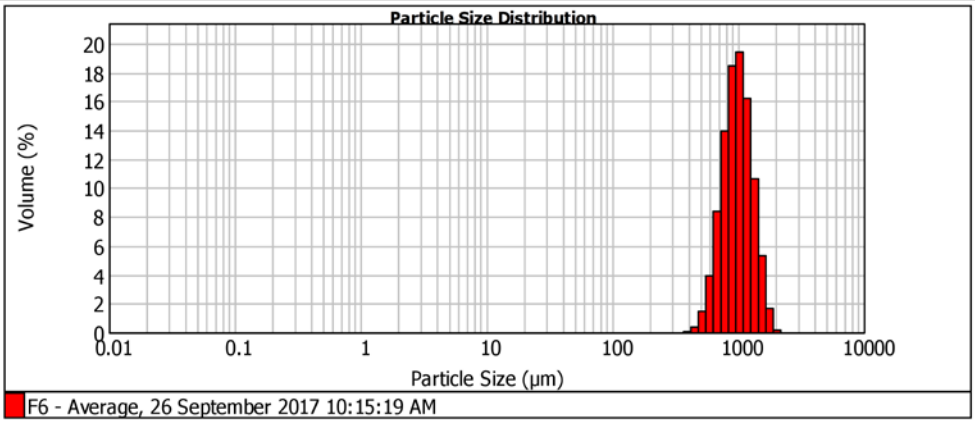
Sample Name: F6 - Average
SOP Name: Consolate
Measured: 26 September 2017 10:15:19 AM
Sample Source & type: CN
Measured by: Neil Barnard
Analysed: 26 September 2017 10:15:21 AM
Sample bulk lot ref: F6 (Sample 2)
Result Source: Averaged

Particle Name: Titanium Dioxide
Accessory Name: Hydro 2000SM (A)
Analysis model: General purpose
Sensitivity: Enhanced
Particle RI: 2.741
Absorption: 0.1
Size range: 0.020 to 2000.000 um
Obscuration: 7.81 %
Dispersant Name: Cyclohexane
Dispersant RI: 1.426
Weighted Residual: 7.002 %
Result Emulation: Off

Concentration: 1.1172 %Vol
Span : 0.713
Uniformity: 0.223
Result units: Volume

Specific Surface Area: 0.00639 m²/g
Surface Weighted Mean D[3,2]: 938.523 um
Vol. Weighted Mean D[4,3]: 1010.542 um

d(0.1): 684.204 um **d(0.5):** 978.648 um **d(0.9):** 1381.944 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	10.68
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.30
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.67
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.19
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.32	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	1.45	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	3.94	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	8.35	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.94	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	18.46	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	19.43	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	16.23		
0.105	0.00	1.096		11.482	0.00	120.226	0.00	1258.925			

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 26 Sept 2017.mea
Record Number: 28
2017/10/19 03:53:14 PM

7.2 ANNEXURE B: FLOWABILITY DATA

7.2.1 MICROCELAC®-CONTAINING BEAD FORMULATIONS

7.2.1.1 Formulation 1

In Tables 7.2.1.1. A – F, flowability data and results are given regarding MicroceLac®-containing bead formulation 1 (MF1) for metformin (MMF1) and gliclazide (MGF1).

A: Flow rate (g/s)

	Flow rate (g/s)	
	MMF1	**MGF1**
1	29.4	29.4
2	29.4	29.4
3	29.4	27.8
AVE	**29.40**	**28.87**
SD	**0.000**	**0.924**

B: COD (Critical orifice diameter)

	COD (mm)	
	MMF1	**MGF1**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	MMF1		MGF1	
	V_o (cm^3)	V_{tap} (cm^3)	V_o (cm^3)	V_{tap} (cm^3)
1	76	70	78	75
2	74	70	81	76
3	75	70	78	76

D: Bulk and tapped densities

	Densities			
	MMF1		MGF1	
	Bulk ρ	Tapped ρ	Bulk ρ	Tapped ρ
1	0.66	0.71	0.64	0.67
2	0.68	0.71	0.62	0.66
3	0.68	0.71	0.64	0.66
AVE	**0.67**	**0.71**	**0.63**	**0.66**
SD	**0.010**	**0.000**	**0.014**	**0.005**

E: Hausner ratio's

	Hausner ratio	
	MMF1	MGF1
1	1.09	1.04
2	1.06	1.07
3	1.06	1.03
AVE	**1.07**	**1.04**
SD	**0.02**	**0.02**

F: Carr's indices

	Carr's index (%)	
	MMF1	MGF1
1	8%	4%
2	5%	6%
3	5%	3%
AVE	**6%**	**4%**
SD	**0.014**	**0.018**

7.2.1.2 Formulation 2

In tables 7.2.1.2. A – F, flowability data and results are given regarding MicroceLac®-containing bead formulation 2 (MF2) for metformin (MMF2) and gliclazide (MGF2).

A: Flow rate (g/s)

	Flow rate (g/s)	
	MMF2	**MGF2**
1	29.4	27.8
2	29.4	27.8
3	29.4	27.8
AVE	**29.40**	**27.80**
SD	**0.000**	**0.000**

B: COD (Critical orifice diameter)

	COD (mm)	
	MMF2	**MGF2**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	MMF2		MGF2	
	V_o (cm^3)	V_{tap} (cm^3)	V_o (cm^3)	V_{tap} (cm^3)
1	77	68	82	74
2	77	66	81	74
3	77	67	83	74

D: Bulk and tapped densities

	Densities			
	MMF2		MGF2	
	Bulk ρ	Tapped ρ	Bulk ρ	Tapped ρ
1	0.65	0.74	0.61	0.68
2	0.65	0.76	0.62	0.68
3	0.65	0.75	0.60	0.68
AVE	**0.65**	**0.75**	**0.61**	**0.68**
SD	**0.000**	**0.011**	**0.007**	**0.000**

E: Hausner ratio's

	Hausner ratio	
	MMF2	MGF2
1	1.13	1.11
2	1.17	1.09
3	1.15	1.12
AVE	**1.15**	**1.11**
SD	**0.017**	**0.014**

F: Carr’s indices

	Car's index	
	MMF2	**MGF2**
1	12%	10%
2	14%	9%
3	13%	11%
AVE	**13%**	**10%**
SD	**0.013**	**0.011**

7.2.1.3 Formulation 3

In Tables 7.2.1.3. A – F, flowability data and results are given regarding MicroceLac®-containing bead formulation 3 (MF3) for metformin (MMF3) and gliclazide (MGF3).

A: Flow rate (g/s)

	Flow rate (g/s)	
	MMF3	**MGF3**
1	29.4	26.3
2	31.3	27.8
3	29.4	27.8
AVE	**30.03**	**27.30**
SD	**1.097**	**0.866**

B: COD (Critical orifice diameter)

	COD (mm)	
	MMF3	**MGF3**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	MMF3		MGF3	
	V_o (cm^3)	V_{tap} (cm^3)	V_o (cm^3)	V_{tap} (cm^3)
1	73	66	77	74
2	75	66	78	73
3	75	66	79	73

D: Bulk and tapped densities

	Densities			
	MMF3		MGF3	
	Bulk ρ	Tapped ρ	Bulk ρ	Tapped ρ
1	0.68	0.76	0.65	0.68
2	0.67	0.76	0.64	0.68
3	0.67	0.76	0.63	0.68
AVE	**0.67**	**0.76**	**0.64**	**0.68**
SD	**0.011**	**0.000**	**0.008**	**0.005**

E: Hausner ratio's

	Hausner ratio	
	MMF3	MGF3
1	1.11	1.04
2	1.14	1.07
3	1.14	1.08
AVE	**1.13**	**1.06**
SD	**0.017**	**0.021**

F: Carr's indices

	Carr's index	
	MMF3	**MGF3**
1	10%	4%
2	12%	6%
3	12%	8%
AVE	**11%**	**6%**
SD	**0.014**	**0.019**

7.2.2 PHARMACEL®-CONTAINING FORMULATIONS

7.2.2.1 Formulation 1

In Tables 7.2.2.1. A – F, flowability data and results are given regarding Pharmacel®-containing bead formulation 1 (PF1) for metformin (PMF1) and gliclazide (PGF1).

A: Flow rate (g/s)

	Flow rate (g/s)	
	PMF1	**PGF1**
1	22.7	20.8
2	22.7	20.8
3	22.7	21.7
Ave	**22.70**	**21.10**
SD	**0.000**	**0.520**

B: COD (Critical orifice diameter)

	COD (mm)	
	PMF1	**PGF1**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	PMF1		**PGF1**	
	V_o (cm^3)	**V_{tap} (cm^3)**	**V_o (cm^3)**	**V_{tap} (cm^3)**
1	105	98	107	97
2	104	98	107	96
3	103	96	105	96

D: Bulk and tapped densities

	Densities			
	PMF1		**PGF1**	
	Bulk ρ	**Tapped ρ**	**Bulk ρ**	**Tapped ρ**
1	0.48	0.51	0.47	0.52
2	0.48	0.51	0.47	0.52
3	0.49	0.52	0.48	0.52
AVE	**0.48**	**0.51**	**0.47**	**0.52**
SD	**0.005**	**0.006**	**0.005**	**0.003**

E: Hausner ratio's

	Hausner ratio	
	PMF1	**PGF1**
1	1.07	1.10
2	1.06	1.11
3	1.07	1.09
AVE	**1.07**	**1.10**
SD	**0.006**	**0.010**

F: Carr's indices

	Car's index	
	PMF1	**PGF1**
1	7%	9%
2	6%	10%
3	7%	9%
AVE	**6%**	**9%**
SD	**0.006**	**0.009**

7.2.2.2 Formulation 2

In Tables 7.2.2.2 A – F, flowability data and results are given regarding Pharmacel®-containing bead formulation 2 (PF2) for metformin (PMF2) and gliclazide (PGF2).

A: Flow rate (g/s)

	Flow rate (g/s)	
	PMF2	**PGF1**
1	21.7	19.2
2	21.7	19.2
3	21.7	19.2
AVE	**21.70**	**19.20**
SD	**0.000**	**0.000**

B: COD (Critical orifice diameter)

	COD (mm)	
	PMF2	**PGF2**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	PMF2		PGF2	
	V_o (cm^3)	V_{tap} (cm^3)	V_o (cm^3)	V_{tap} (cm^3)
1	107	96	118	109
2	104	98	118	110
3	105	98	117	110

D: Bulk and tapped densities

	DENSITIES			
	PMF2		PGF2	
	Bulk ρ	Tapped ρ	Bulk ρ	Tapped ρ
1	0.47	0.52	0.42	0.46
2	0.48	0.51	0.42	0.45
3	0.48	0.51	0.43	0.45
AVE	**0.47**	**0.51**	**0.42**	**0.46**
SD	**0.007**	**0.006**	**0.002**	**0.002**

E: Hausner ratio's

	Hausner ratio	
	PMF2	PGF2
1	1.11	1.08
2	1.06	1.07
3	1.07	1.06
AVE	**1.08**	**1.07**
SD	**0.028**	**0.009**

F: Carr's indices

	Car's index	
	PMF2	PGF2
1	10%	8%
2	6%	7%
3	7%	6%
AVE	**8%**	**7%**
SD	**0.024**	**0.008**

7.2.2.3 Formulation 3

In the Tables 7.2.3. A – F, flowability data and results are given regarding Pharmacel®-containing beads formulation 3 (PF3) for metformin (PMF3) and gliclazide (PGF3).

A: Flow rate (g/s)

	Flow rate (g/s)	
	PMF3	**PGF3**
1	23.8	20.8
2	22.7	20.8
3	22.7	20.8
AVE	**23.07**	**20.80**
SD	**0.635**	**0.000**

B: COD (Critical orifice diameter)

	COD (mm)	
	PMF2	**PGF2**
1	7.0	7.0
2	7.0	7.0
3	7.0	7.0
AVE	**7.0**	**7.0**
SD	**0.000**	**0.000**

C: Bulk and tapped volume

	Volumes			
	PMF3		PGF3	
	V_o (cm^3)	V_{tap} (cm^3)	V_o (cm^3)	V_{tap} (cm^3)
1	98	95	112	103
2	103	93	107	103
3	103	96	107	103

D: Bulk and tapped densities

	Densities			
	PMF3		PGF3	
	Bulk ρ	Tapped ρ	Bulk ρ	Tapped ρ
1	0.51	0.53	0.45	0.49
2	0.49	0.54	0.47	0.49
3	0.49	0.52	0.47	0.49
AVE	**0.49**	**0.53**	**0.46**	**0.49**
SD	**0.014**	**0.009**	**0.012**	**0.000**

E: Hausner ratio's

	Hausner ratio	
	PMF3	**PGF3**
1	1.03	1.09
2	1.11	1.04
3	1.07	1.04
AVE	**1.07**	**1.06**
SD	**0.038**	**0.028**

F: Carr's indices

	Car's index	
	PMF3	**PGF3**
1	3%	8%
2	10%	4%
3	7%	4%
AVE	**7%**	**5%**
SD	**0.033**	**0.025**

7.3. ANNEXURE C: CAPSULE EVALUATION DATA

7.3.1 MASS VARIATION

In Table 7.3.1, the mass variation data and results are given regarding the capsule filled with both MicroceLac®- and Pharmacel®-containing bead formulations.

Table 7.3.1: The mass variation data and results regarding the capsule filled with both MicroceLac®- and Pharmacel®-containing beads formulations

Capsule nr.	MF1	PF1	MF2	PF2	MF3	PF3
1	0.66	0.57	0.61	0.57	0.64	0.6
2	0.65	0.59	0.63	0.56	0.64	0.58
3	0.65	0.57	0.64	0.57	0.62	0.57
4	0.65	0.58	0.62	0.57	0.64	0.57
5	0.65	0.58	0.62	0.57	0.64	0.58
6	0.66	0.58	0.63	0.58	0.64	0.58
7	0.65	0.58	0.63	0.56	0.63	0.59
8	0.65	0.59	0.60	0.56	0.65	0.58
9	0.65	0.56	0.64	0.57	0.65	0.58
10	0.65	0.58	0.62	0.58	0.64	0.63
11	0.65	0.58	0.64	0.58	0.64	0.63
12	0.62	0.57	0.65	0.58	0.64	0.6
13	0.65	0.59	0.61	0.57	0.62	0.59
14	0.64	0.57	0.61	0.58	0.62	0.59
15	0.65	0.57	0.61	0.57	0.62	0.6
16	0.65	0.58	0.62	0.58	0.63	0.58
17	0.66	0.57	0.61	0.58	0.64	0.6
18	0.65	0.60	0.61	0.54	0.64	0.6
19	0.65	0.58	0.62	0.57	0.64	0.6
20	0.65	0.58	0.62	0.57	0.64	0.61
Ave	**0.65**	**0.58**	**0.62**	**0.57**	**0.64**	**0.59**
SD	**0.008**	**0.009**	**0.013**	**0.010**	**0.009**	**0.017**

7.3.2 DISINTEGRATION TIME

In the following Table 7.3.2, the disintegration time data and results are given regarding the capsule filled with both MicroceLac®- and Pharmacel® -containing beads formulations.

Table 7.3.2: Disintegration time data and results regarding the capsule filled with both MicroceLac®- and Pharmacel®-containing bead formulations.

Capsule nr.	MF1	PF1	MF2	PF2	MF3	PF3
1	208	302	247.2	371	192	436.2
2	208	302	395.4	371	309.6	436.2
3	271	335	483	371	383.4	570.6
4	271	482	483	437	383.4	624
5	327	482	483	502	483	624
6	371	678	483	502	483	624
AVE	**276.10**	**430.20**	**429.10**	**425.40**	**372.40**	**552.50**
SD	**64.541**	**147.307**	**95.754**	**64.322**	**110.630**	**92.429**

7.4 ANNEXURE D : DISSOLUTION DATA

7.4.1 MICROCELAC®-CONTAINING FORMULATIONS

7.4.1.1 Formulation 1

In Tables 7.4.1.1. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for MicroceLac® – bead formulated capsules formula 1.

Table 7.4.1.1 A: The metformin % dissolution values recorded at different withdrawal times for formula 1

% Dissolution of metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	4.36	6.00	13.12	12.28
5	43.49	55.55	58.82	53.19
10	81.61	89.31	87.00	84.97
15	90.48	96.72	95.95	90.16
30	96.11	96.93	103.54	92.75
60	93.21	95.75	99.93	92.05
90	92.58	95.62	102.30	88.74
120	95.00	97.31	100.09	95.10
150	96.83	95.79	102.96	96.05
180	97.57	99.35	102.87	99.91
240	99.52	104.02	108.25	94.50
360	96.97	102.22	111.03	94.27
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.1 B: The gliclazide % dissolution values recorded at different withdrawal times for formula 1

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	-13.49	-12.24	-10.62	-11.04
5	-13.49	-12.24	-10.62	-11.04
10	-13.49	-12.24	-10.62	-11.04
15	-13.49	-12.24	-10.62	-11.04
30	-13.49	-12.24	-10.62	-11.04
60	39.08	32.72	31.53	30.53
90	56.77	45.51	44.06	47.48
120	74.71	66.38	58.83	51.36
150	95.39	67.90	72.73	65.53
180	82.08	71.93	70.47	64.91
240	82.58	75.36	73.83	66.54
360	108.68	92.31	92.81	96.91
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.1 C: The metformin and gliclazide $AUC_{(0-360)}$ (%.min) value for formula 1

	$AUC_{(0-360)}$ (%.min)	
	Metformin	**Gliclazide**
Vessel 1	34143.87	25035.75
Vessel 2	35318.20	21398.02
Vessel 3	37169.27	21133.87
Vessel 4	33459.55	20088.62

7.4.1.2 Formulation 2

In Tables 7.4.1.2. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for MicroceLac® – bead formulated capsules formula 2.

Table 7.4.1.2A: The metformin % dissolution values recorded at different withdrawal times for formula 2

% Dissolution of metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	26.73	26.30	25.25	27.85
5	62.72	60.47	59.79	65.89
10	86.29	86.90	94.10	73.31
15	95.55	96.93	92.03	94.84
30	97.61	97.15	97.03	98.14
60	98.06	98.83	98.65	98.80
90	98.62	99.35	99.16	98.92
120	98.38	99.17	98.59	99.11
150	98.54	99.48	99.18	99.40
180	100.06	99.91	99.35	100.59
240	99.96	99.26	99.52	99.80
360	99.66	100.67	100.17	100.36
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.2B: The gliclazide % dissolution values recorded at different withdrawal times for formula 2

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	-2.24	-2.21	-2.78	-2.37
5	-2.24	-2.21	-2.78	-2.37
10	-2.24	-2.21	-2.78	-2.37
15	-2.24	-2.21	-2.78	-2.37
30	28.21	45.25	27.33	23.32
60	45.45	47.57	42.48	47.63
90	55.78	64.12	51.51	60.55
120	66.10	69.20	67.43	63.71
150	69.30	72.07	74.82	65.95
180	73.49	73.13	83.87	72.74
240	83.61	87.37	93.18	94.56
360	93.31	100.04	96.93	99.92
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.2C: The metformin and gliclazide $AUC_{(0\text{-}360)}$ (%.min) value for formula 2

	$AUC_{(0\text{-}360)}$ (%.min)	
	Metformin	**gliclazide**
Vessel 1	35171.73	24116.60
Vessel 2	35256.56	25716.57
Vessel 3	35166.41	25618.47
Vessel 4	35257.24	25388.49

7.4.1.3 Formulation 3

In Tables 7.4.1.3. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for MicroceLac® – bead formulated capsules formula 3.

Table 7.4.1.3A: The metformin % dissolution values recorded at different withdrawal times for formula 3

% Dissolution of metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	7.83	0.97	7.28	3.16
5	61.54	52.28	49.99	54.36
10	90.55	83.82	86.41	85.57
15	98.44	95.41	97.06	95.49
30	98.95	98.55	99.01	98.44
60	99.87	99.52	99.11	98.67
90	100.81	99.70	99.14	99.18
120	99.96	99.52	99.24	99.38
150	100.24	99.57	99.08	99.48
180	100.81	99.33	99.01	100.53
240	101.24	99.67	99.96	99.88
360	100.84	100.18	99.52	100.26
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.3B: The gliclazide % dissolution values recorded at different withdrawal times for formula 3

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	10.71	11.80	9.80	10.72
5	10.71	11.80	9.80	10.72
10	10.71	11.80	9.80	10.72
15	10.71	11.80	9.80	10.72
30	43.65	50.99	40.01	40.26
60	48.51	52.82	42.98	43.10
90	62.96	61.43	48.91	52.22
120	58.20	60.51	51.42	57.32
150	78.39	79.18	65.20	71.27
180	76.10	81.19	66.53	74.80
240	96.22	96.25	85.69	75.98
360	94.33	98.90	94.42	83.42
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.1.3C: The metformin and gliclazide $AUC_{(0-360)}$ (%.min) value for formula 3

	$AUC_{(0-360)}$ (%.min)	
	Metformin	**gliclazide**
Vessel 1	35638.59	26396.13
Vessel 2	35188.68	27266.52
Vessel 3	35155.70	23734.28
Vessel 4	35239.01	23060.06

7.4.2 PHARMACEL®- CONTAINING FORMULATIONS

7.4.2.1 Formulation 1

In Tables 7.4.2.1. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for Pharmacel® – bead formulated capsules formula 1.

Table 7.4.2.1A: The metformin % dissolution values recorded at different withdrawal times for formula 1

% Dissolution of metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	5.85	7.50	7.36	39.13
5	44.62	61.94	63.43	74.41
10	77.47	88.04	89.08	93.76
15	83.60	93.41	95.16	94.65
30	84.75	93.78	94.46	94.92
60	85.70	93.15	94.11	94.87
90	84.96	93.78	94.33	94.85
120	84.94	93.90	94.57	95.69
150	84.45	93.54	95.42	95.60
180	85.31	93.74	94.85	95.03
240	84.98	93.81	94.87	95.37
360	85.26	94.63	94.24	95.60
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.1B: The gliclazide % dissolution values recorded at different withdrawal times for formula 1

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	-2.04	-2.03	-1.78	-2.09
5	-2.04	-2.03	-1.78	-2.09
10	-2.04	-2.03	-1.78	-2.09
15	-2.04	-2.03	-1.78	-2.09
30	-2.04	-2.03	-1.78	-2.09
60	25.92	29.25	30.70	31.67
90	27.50	39.49	41.58	42.03
120	34.13	52.67	58.32	57.73
150	48.82	56.38	68.08	74.77
180	84.01	85.45	103.15	65.81
240	69.21	83.07	62.65	60.81
360	85.71	85.40	89.30	88.30
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.1C: The metformin and gliclazide $AUC_{(0\text{-}360)}$ (%.min) value for formula 1

	$AUC_{(0\text{-}360)}$ (%.min) value	
	Metformin	**Gliclazide**
Vessel 1	30116.13	19154.15
Vessel 2	33305.72	21690.18
Vessel 3	33592.21	21520.77
Vessel 4	33953.86	19827.30

7.4.2.2 Formulation 2

In Tables 7.4.2.2. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for Pharmacel® – bead formulated capsules formula 2.

Table 7.4.2.2A: The metformin % dissolution values recorded at different withdrawal times for formula 2

% Dissolution metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	2.58	2.65	2.36	2.38
5	53.37	63.71	62.82	56.80
10	88.11	92.09	90.38	88.47
15	94.52	97.61	94.49	93.90
30	96.76	96.48	96.13	96.43
60	96.80	97.98	97.47	96.17
90	98.21	96.42	97.12	97.54
120	97.15	96.54	95.22	97.61
150	99.36	97.75	97.78	98.62
180	98.70	98.66	98.30	100.58
240	99.08	99.54	99.00	99.74
360	99.72	101.22	100.50	100.27
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.2B: The gliclazide % dissolution values recorded at different withdrawal times for formula 2

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	-5.57	-6.06	-6.15	-5.29
5	-5.57	-6.06	-6.15	-5.29
10	-5.57	-6.06	-6.15	-5.29
15	-5.57	-6.06	-6.15	-5.29
30	-5.57	-6.06	-6.15	-5.29
60	42.16	39.79	42.37	32.61
90	48.03	44.62	45.28	41.88
120	59.07	75.72	49.63	51.32
150	65.69	66.86	62.01	67.20
180	64.67	70.94	72.71	59.68
240	68.35	70.99	71.00	71.16
360	87.10	89.61	97.78	94.67
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.2C: The metformin and gliclazide $AUC_{(0\text{-}360)}$ (%.min) value for formula 2

	$AUC_{(0\text{-}360)}$ (%.min)	
	Metformin	**gliclazide**
Vessel 1	34856.84	20492.51
Vessel 2	34984.89	21502.94
Vessel 3	34792.30	21238.84
Vessel 4	34986.83	20329.07

7.4.2.3 Formulation 3

In Tables 7.4.2.3. A, B and C, the % dissolution and $AUC_{(0-360)}$ values for metformin and gliclazide recorded at different withdrawal times for Pharmacel® – bead formulated capsules formula 3.

Table 7.4.2.3A: The metformin % dissolution values recorded at different withdrawal times for formula 3

% Dissolution of metformin				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	6.72	7.12	6.05	6.59
5	57.86	61.57	60.12	57.31
10	91.29	94.18	91.47	91.94
15	99.83	98.98	97.36	97.48
30	98.11	98.41	97.76	99.04
60	98.71	98.89	98.75	99.56
90	98.88	98.54	98.65	100.12
120	102.13	98.60	98.88	99.49
150	99.41	98.96	99.43	100.30
180	99.43	99.44	99.09	99.95
240	99.47	100.30	99.50	99.83
360	99.75	100.74	100.19	100.20
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.2B: The gliclazide % dissolution values recorded at different withdrawal times for formula 3

% Dissolution of gliclazide				
Time	**Vessel 1**	**Vessel 2**	**Vessel 3**	**Vessel 4**
0	0.00	0.00	0.00	0.00
2.5	15.15	14.97	14.57	14.86
5	15.15	14.97	14.57	14.86
10	15.15	14.97	14.57	14.86
15	15.15	14.97	14.57	14.86
30	15.15	14.97	14.57	14.86
60	15.15	14.97	14.57	14.86
90	50.05	48.43	47.73	48.18
120	55.17	66.00	63.73	63.99
150	70.08	66.13	61.56	61.66
180	68.89	73.35	75.75	75.53
240	83.48	81.64	79.75	79.39
360	103.87	100.76	95.17	91.85
Final	**100.00**	**100.00**	**100.00**	**100.00**

Table 7.4.2.2C: The metformin and gliclazide AUC value (%.min) for formula 3

	$AUC_{(0\text{-}360)}$ (%.min)	
	Metformin	**gliclazide**
Vessel 1	35281.42	23222.10
Vessel 2	35319.94	23214.97
Vessel 3	35167.20	22561.57
Vessel 4	35373.41	22366.00