Development of a multiple-unit sustained release dosage form containing gliclazide

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Abstract

Multiple-unit drug delivery systems (MUDS) are oral dosage forms consisting of beads or pellets (either coated or uncoated) that may be compressed into tablets or encapsulated. Tablets consisting of beads have been well-defined in scientific literature as exhibiting the ability to deliver a dosage form capable of depicting a modified drug release profile. The purpose of this study was to ascertain whether such a tablet formulation (comprising beads) is capable of producing a dosage from displaying a sustained drug release profile.

The selected fillers (CombiLac®, MicroceLac®, RetaLac®, Pharmacel® 101 and a 80:20 mixture of Cassava starch and Hydroxypropyl Methylcellulose) tested either as a powder or as a bead formulation (as well as with and without 10% w/w gliclazide), were subjected to analysis utilising the SeDeM Diagram Expert System to determine their suitability for direct compression. This investigation included a review of the powder's physical properties, dimensions, compressibility and lubricity. Through this model it can easily be observed which properties of the excipient are suitable for direct compression and where improvement may be recommended.

Bead formulations were subsequently manufactured by means of extrusion-spheronisation utilising selected fillers and 10% w/w gliclazide. These combinations were studied using a full factorial design to identify the optimal concentration of lubricant (magnesium stearate) and binder (Kollidon® 90F) to be included in the final tablet formulations. Powder mixtures and beads were directly compressed into 9 mm concave tablets with a Korsch® single tablet press. The physical properties of the beads, powder tablets as well as bead tablets were studied and compared. Each tablet was formulated to weigh approximately 300 mg and contain 30 mg gliclazide.

Results showed that certain combinations of the binder and lubricant concentrations amounted to formulations displaying more appropriate physical properties to not only obtain acceptable tablets, but that may probably be able to aid in modified drug release. Generally, it could be concluded that the inclusion of magnesium stearate is necessary. Although the concentration was deemed less important through evaluation of most of the tablet properties, according to the disintegration analysis, a 1% w/w concentration will suffice. According to the full factorial design, the inclusion of a binder did not play a significant role, but the inclusion of Kollidon® 90F rendered diverse results where the exclusion of the binder favourably improved mass variation results; the 2% w/w concentration produced tablet formulations that exhibited harder and more resilient tablets; and formulations comprising 5% w/w Kollidon® 90F delivered tablets which depicted delayed disintegration properties. Furthermore, the type of filler included exerted some effect on tablet properties, though the method of production was of more importance. Powder formulations generally displayed more favourable tablet properties, except for the disintegration characteristic where the bead formulations were considered more ideal. Permitting these results obtained, formulations comprising 1% w/w magnesium stearate and 2% w/w Kollidon® 90F were selected for additional investigations.

Following evaluation of the physical properties of the various tablet formulations; the formulations that were deemed optimal, through analysis by means of the full factorial design, were tested with regards to swelling, erosion and drug release properties. Drug release profiles were consequently compiled of the formulations (powder tablets, beads and bead tablets) that contained the different selected fillers. Overall, the various methods of manufacture each presented formulations that did not perform optimally. The powder tablet formulations generally exhibited faster drug release profiles where more gliclazide was obtained in solution (i.e. 100% released). Bead and bead tablet formulations, mostly depicted modified release profiles (either delayed release or slow release), but none of the formulations demonstrated a distinct sustained release profile. None of these formulations were able to release gliclazide completely, however, the RetaLac® bead tablet formulation depicted the most appropriate modified release profile.

Key Words: Modified drug release; SeDeM Diagram Expert System; Spherical Beads; Extrusion-spheronisation; Gliclazide

Chapter 1:

INTRODUCTION, PROBLEM STATEMENT, AIM AND OBJECTIVES

1.1 Introduction

1.1.1 Gliclazide and Its Role in Diabetes

Gliclazide is a second generation sulfonylurea, an oral hypoglycaemic drug, which is used in the treatment of non-insulin-dependent diabetes mellitus. The effects of the drug include enhanced insulin secretion, a decrease in insulin resistance as well as the lowering of glucose levels (Palmer & Brogden, 1993).

Absorption of gliclazide is limited due to its high lipophilicity as well as its limited release from immediate release solid oral dosage forms. However, amongst others, the hydrophilicity of gliclazide can be increased by adding co-solvents (e.g. ethanol) to the formulation. Additionally, modified release drug delivery systems that included gliclazide, have shown improved drug release profiles (Reddy & Navaneetha, 2017, Qazi *et al.*, 2017). Nonetheless, current products on the market illustrate weak absorption, with a leading brand, Diamicron® MR 30 mg, displaying a peak bioavailability of only 22% on average and a typical pharmacological action of 14 hours (Servier, 2012). A limiting factor of gliclazide is its dissolution rate, which is largely due to its weak hydrophilicity (aqueous solubility of gliclazide at 25°C is 138.4 mg/l). As stated, methods for correcting this problem are possible, and include for example, the formation of more water-soluble salts or micronisation. These techniques are effective, but will increase the costs associated with the product. The cost of gliclazide products is already quite expensive, retailing between R 9.00ï R 15.00 per tablet. Micronisation of the gliclazide powder will furthermore weaken the productõs powder flow characteristics and therefore create additional production problems (Rojanasthien *et al.,* 2012; Barzegar *et al.*, 2010; Wang *et al.,* 2010).

Due to economic struggles of the average citizen, the fact that South Africa is a third world economy, and diabetes in the country is the second highest ailment with regards to prevalence in Africa; a more affordable solution to healthcare must be created. According to Dr. Larry Distiller of the Centre for Diabetes and Endocrinology, there are more than 4 million people in South Africa with diabetes, half of whom are undiagnosed or unaware that they indeed have diabetes (Belseck, 2016).

1.1.2 Modified Release Drug Delivery

Modified release dosage forms are capable of producing drug release at a specified desired rate and/or at pre-determined time points or specific target sites in the gastrointestinal tract. Various drug release modification mechanisms can be utilised in different kinds of dosage forms. For example, with delayed release dosage forms a lag time occurs amid the point of administration and the point when the drug is pharmaceutically available for absorption. Modified release drug delivery systems are characterised by the type of formulation used (e.g. granules, beads and/or mini-tablets) or the manufacturing process (e.g. tableting, film coating, extrusion-spheronisation and/or encapsulation). The most regularly utilised mechanisms among these are however film coating and production of matrix systems (McConnell & Basit, 2013; Porter, 2013a; Rajabi-Siahboomi *et al.*, 2013).

Matrix systems are monolithic drug delivery systems consisting of a drug dispersed throughout a solid medium of polymeric excipients. Matrix-type tablet drug delivery systems on the other hand can easily be manufactured through direct compression of the drug that was mixed with polymeric excipients. Drug release rates from these types of tablets depend on the number of pores which form in the matrix, the size of these pores, as well as the tortuosity of the matrix during the dissolution stage of the dosage form. These dosage form types can furthermore be coated with a film through which the drug must first slowly diffuse; however, film coating is an extremely technical and relatively expensive technique (McConnell & Basit, 2013; Porter, 2013b; Rajabi-Siahboomi *et al.*, 2013).

Single-unit and multiple-unit solid oral drug delivery systems, such as film-coated tablets (e.g. Diamicron® MR 30 mg) and film-coated granules (e.g. Rinex® Diffucaps) are both effective at obtaining modified release profiles. Single-unit dosage forms comprise one full dose of the drug in every unit intended to be administered once-off (Gandhi *et al.*, 1999). These systems result in a higher bioavailability as opposed to multiple-unit delivery systems that are defined as oral dosage forms consisting of multiple small discrete sub-units, each containing a fraction of the complete drug dose, that are combined into one dosage form (Abdul *et al.*, 2010, Kan *et al.*, 2014). Moreover, Multiple-unit pellet (or bead) Systems or MUPS is a term used by the pharmaceutical industry and research community to describe tablets or capsules prepared by compaction of spherical beads. MUPS consist of several hundred coated, or uncoated compressed beads, each containing a portion of the drug(s), which release the drug at a modified rate to provide a constant blood/drug concentration. These tablets are administered with ease, just as a single-unit oral dosage form would be, but will disperse into their sub-units post administration; and distribute into the stomach and small intestine (Panda *et al.*, 2013; Pathikkumar *et al.*, 2013). All these units contribute to the overall desired controlled release of the drug dose. It is well known that multiple-unit controlled release dosage forms such as MUPS depict numerous biopharmaceutical advantages over its larger single-unit equivalents, predominantly regarding the duration (release the drug over a longer period of time) and the reproducibility of the gastric emptying time, i.e. single-unit delivery systems show more variation between patients with regards to bioavailability (Hamdani *et al.,* 2002; Varum *et al.* 2010). It furthermore increase drug stability by protecting it from hydrolysis or other degradative changes in the gastrointestinal tract (Abdul *et al.,* 2010; Ishida *et al.,* 2008; Pathikkumar *et al.*, 2013; Ramu *et al.*, 2013; Sachdeva *et al.*, 2013).

By formulating MUPS containing for example, gliclazide, and that was tableted into a single dose in order to produce modified drug delivery, a reduction of the dosage frequency is observed. Moreover, if modified release was obtained, symptoms that occur due to drug concentration plummeting below the minimum effective concentration will less likely appear; and side-effects that appear due to high peak drug concentration (thus peaking above the minimum toxic concentration) will be reduced (Aulton, 2012, Gandhi *et al.*, 1999). Therefore, it will only be necessary for the drug to be administered once daily, which may probably improve patient compliance with their drug regime and possibly improve patient lifestyle due to improved quality of life.

1.1.3 Formulation Methods

Formulation methods (i.e. extrusion-spheronisation and direct compression into a single oral dosage form, enteric coating of tablets, creation of capsules and formulation of dosage forms containing matrixes) focused on modified release will improve compliance with patients. Due to the release profile generated by a modified-release dosage form, compliance should improve due to a decrease in side-effects caused by a controlled release of the drug, thus not reaching systemic drug levels so high that a minimum toxic concentration is obtained (Aulton, 2012, Gandhi *et al.*, 1999).

1.1.3.1 Extrusion-spheronisation

Extrusion-spheronisation produces beads that are capable of creating a multiparticulate dosage form (Muley *et al.*, 2016). In this study, beads or pellets were created using extrusion-spheronisation. This process can be described as extrusion of a wetted powder mass through a 1 mm sieve in order to produce rod-shaped cylinders, after the powder was wetted to an ideal level, normally using a mixture of water and ethanol. Post extrusion, the rods are transferred to a spheroniser, which rotates rapidly with external air that flows into the apparatus to create beads from the rods. Beads used in the production of pharmaceutical products are preferred at sizes between 0.5 mm ï 1.5 mm (Torrado & Augsburger, 2008).

Beads offer many advantages over fine powders and even granules, for example, increased flow rate and less attractive forces between the powder and the surface area of the hopper shoe can be achieved with this production method. The system of extrusion-spheronisation offers advantages over other techniques of preparing beads such as the ability to regulate bead size and more accurately; produce higher density beads with lower friability; the ability to have high levels of drug included without producing beads that are too large; as well as improve physical characteristics such as flow rate and inter-particular attraction of the beads that are decreased through this method (Agrawal & Naveen, 2011, Gandhi *et al.*, 1999, Muley *et al.*, 2016).

1.1.3.2 Direct Compression versus Wet Granulation

Wet granulation is widely used to increase flowability of powder mixtures intended for tableting. In short, agglomerated powder particles or granules are created through wet granulation and can be described as an agglomerated particle created by wetting of a powder mix and forcing it through for example, a 1 mm sieve (Muley *et al.*, 2016, Gandhi *et al.*, 1999). Granules normally exhibit increased flowability when compared to powders due to the increased size and weight; and the decreased inter-particle forces of attraction. As stated, weak flow properties of powders can easily be masked through wet granulation. However, this process is extremely time-consuming (Jivraj *et al.*, 2000).

Direct compression, on the other hand, has become the preferred method for manufacturing tablets due to its efficiency pertaining to time and cost (Haware *et al.*, 2015). According to Shangraw (1989) the costs associated with direct compression are considerably lower compared to wet granulation. Direct compression also has a more significant effect in maintaining stability of the drug as it excludes the heat and moisture factors, thus maintaining stability of thermo labile and moisture sensitive drugs (Gohel & Jogani, 2005). Moreover, in this study, beads were prepared by means of extrusion-spheronisation prior to utilising direct compression as production method, which improved powder flowability due to the larger and more uniform size of the beads compared to normal granules.

1.1.4 SeDeM Diagram Expert System

The SeDeM Diagram Expert System (Khan *et al.*, 2014; Sauri *et al.*, 2014; Suñé-Negre *et al.*, 2011a; Aguilar-Diaz *et al.*, 2009) is a system for applied pre-formulation methodology for the development of solid dosage forms by means of direct compression. This system analyses various aspects of powder flow properties. It is based on the concept of Quality by Design (ICH Q8) as described by Defloor *et al.* (2009) and focuses on 12 key parameters of powder flow which influence the final quality of the product (Aguilar-Diaz *et al.*, 2009). The SeDeM Diagram Expert System is capable of offering suggestions as to what properties to improve and how to achieve the said improvement. Overall, the system is extremely valuable as it is reproducible and offers a standard process through which to assess a powdersô suitability for direct compression (Khan *et al.*, 2014).

From the results generated during pre-formulation testing, the SeDeM Diagram expert system is able to provide a profile of the excipients and the active ingredients in an uncompressed powder form. This profile, in the form of a diagram or polygon, can designate whether a powder mixture is suitable for direct compression and/or how it needs to be adjusted to become a more optimal powder for direct compression (Suñé-Negre *et al.*, 2011a).

The SeDeM Diagram Expert System utilises powder flow tests as prescribed by the United States Pharmacopoeia (Suñé-Negre *et al.*, 2011a) and converts the results to a radial value (r = 1-10), which is plotted on a diagram (Figure 1.1). These 12 parameters are grouped into five factors based on the physical characteristics of the powder, namely, the dimensional parameter, compressibility parameter, flowability/powder flow parameter, lubricity/stability parameter and the lubricity/dosage parameter (Suñé-Negre *et al.*, 2011a; Khan *et al.*, 2014; Aguilar-Diaz *et al.*, 2009). Following, the radial values of the parameters are used to calculate the total acceptability of the powder for direct compression, where 5 is the minimum acceptable value for a parameter and further calculations are applied to receive suggestions on improvement of the powder (Pèrez *et al.*, 2006).

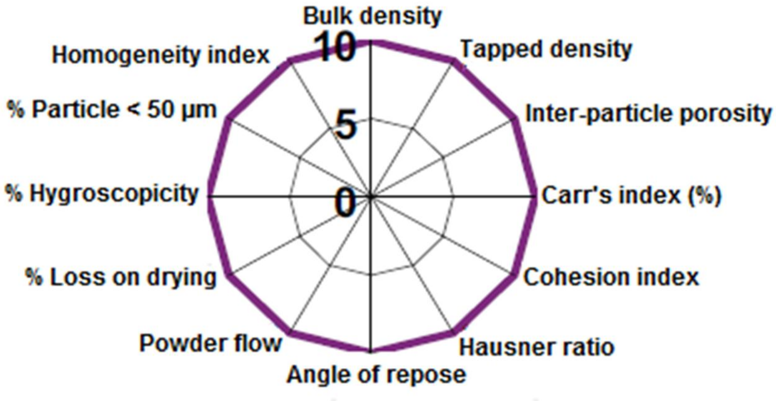


Figure 1.1: *The SeDeM Diagram with 12 parameters (Suñé-Negre et al., 2011a)*

In this study, the SeDeM Diagram Expert System was utilised to evaluate the flowability and compressibility of the selected fillers and bead formulations in order to establish if it was at all possible to predict the strengths and weaknesses of the formulation(s) for the production of a modified release oral dosage form containing gliclazide (Suñé-Negre *et al.*, 2011a). This system was utilised in the study as it identified the different powdersôweaknesses with regards to their acceptability for direct compression, which allow improvements to be made to specific areas; and thus less experimentation was needed to create the most optimum powder mixture for direct compression from the excipients that were tested.

1.2 Research Problem

Despite research being focused on various other delivery routes for providing effective treatment of numerous complications or disease states such as diabetes mellitus, the oral route still remains the most preferred route of drug administration. Diabetes mellitus is still one of many complications that have impacted on the world economy, medical expenses, reduced health status of the third world population, as well as productivity of many patients. Gliclazide, which is currently prescribed for non-insulin-dependent diabetes mellitus, appeals to a smaller margin of diabetics compared to other regimens due to the cost of this drug. Patient compliance along with effective treatment regimens of diabetes mellitus are essential to ensure a successful outcome and management of the condition.

Immediate release dosage forms have a higher dosing frequency compared to modified release formulations, however, modified release dosage forms of gliclazide are expensive and therefore not readily available to the general diabetes populous, especially in South Africa. A multiple-unit solid oral dosage form containing gliclazide, utilising frequently used excipients that were not specifically modified, will probably contribute to improving patient compliance by providing a modified release profile without the use of additional specialised excipients or film coatings of the tablets. This dosage form may further potentially decrease side-effects, which can lead to an enhanced therapeutic outcome.

1.3 Aims and Objectives

The aim of this study is to formulate a modified release solid oral dosage form containing gliclazide, utilising a minimal amount of excipients. With this delivery system we ascertained whether it was possible to obtain an extended release profile through the use of basic excipients, extrusion-spheronisation and direct compression only; without additional film coating.

The objectives for the study were to:

- Characterise the different selected fillers (CombiLac®, MicroceLac®, RetaLac®, Pharmacel® 101 and a mixture of Cassava starch and hydroxypropyl methylcellulose (or HPMC) with regards to physical properties and morphology.
- Formulate beads by means of extrusion-spheronisation containing one of the selected fillers (CombiLac®; MicroceLac®, RetaLac®, Pharmacel® 101, and Cassava starch/HPMC) and gliclazide (a weak acidic active ingredient with a pKa of 5.6) which is poorly water soluble, using a full factorial design of experiments.
- Evaluate the flowability and compressibility of the selected fillers and bead formulations by means of the SeDeM expert system to predict the shortcomings and strengths of the formulation(s) for the production of a modified release oral dosage form containing gliclazide.
- Evaluate the efficacy of the SeDeM expert system to ascertain whether it is applicable to beads.
- Assess the bead formulations in terms of physical properties, surface morphology, as well as drug content.
- Prepare concave tablets (9 mm) by means of direct compression of the powder and bead formulations; and evaluate their physical properties, including surface morphology, hardness, diameter, thickness, tensile strength, friability, disintegration, and mass variation.
- Evaluate and compare tablets produced from the different powder and bead formulations in terms of drug release time and amount over an extended period.

Chapter 2:

LITERATURE STUDY

2.1 Gliclazide and its role in diabetes

Gliclazide is a second generation sulfonylurea, and oral hypoglycaemic drug, which is used in the treatment of non-insulin-dependent diabetes mellitus. It also displays significant inhibition of ATP-dependant potassium channels. The effects of the drug include enhancement of defective insulin secretion, a decrease in insulin resistance as well as the lowering of glucose levels over long and short term therapy. Due to the haemobiological action of gliclazide, it may be useful in combination with insulin to patients with diabetic retinopathy. Gliclazide may furthermore assist in slowing the progression of diabetic retinopathy and aid in the treatment of metabolic effects of non-insulin dependent diabetes mellitus (Palmer & Brogden, 1993).

Oral hypoglycaemic drugs show the greatest efficacy when rapid gastrointestinal tract (GIT) absorption is observed, however, absorption from the GIT may be influenced by many factors, such as gastric motility, gastric content as well as the varying pH levels of the GIT, to name but a few. Gliclazide displays a decreased rate of absorption, which may be due to the abovementioned factors; or it may even be due to reduced dissolution rates from different formulations, towing to poor drug permeability and/or the hydrophobic nature of gliclazide (Hong *et al.*, 1998). By incorporating gliclazide into a modified drug release dosage form, many of these problems may be circumvented (Al-Kassas *et al.*, 2007).

The physical properties of gliclazide are not ideal for the purposes of formulating an aqueous liquid dosage form as it is practically insoluble in water (0.19 mg/mL) and only slightly soluble in alcohol (Martindale, 2017). It has a pK_a value of 5.8 and an oral bioavailability of only 59% (More *et al.*, 2015). Absorption of the drug is limited as it is highly plasma protein bound (94%) and it furthermore undergoes extensive hepatic metabolism (through CYP2C9) where the formed metabolite does not portray any significant hypoglycaemic activity (Pubchem, 2017).

2.2 Modified drug release

2.2.1 Introduction

As of late, there has been an increased interest in the formulation of modified release preparations. Due to advances in technology and an increased understanding of the mechanisms by which formulations achieve a delayed drug release profile, it is now possible to manufacture a dosage form that exhibits the desired dissolution profile through various techniques. Dosage form design and development focus on two main features, namely, that drug delivery must occur either site specific and/or at a predetermined time points; and secondly, that the drug release profile must exhibit a predetermined rate of drug release (McConnell & Basit, 2013; Rajabi-Siahboomi *et al.*, 2013).

Modified release dosage forms are defined by the British Pharmacopoeia (2016) as a preparation where the rate and/or site of release of the selected drug is different from a conventional tablet administered via the same route. Modified release dosage forms may be divided into different classes such as delayed release, targeted release and sustained drug release tablets. Delayed drug release dosage forms initially exhibit no release of the drug and form a lag time from the point of administration until the drug is released at a certain time point and at a normal rate. Targeted drug release displays a similar release profile as delayed drug release, however release is initiated in a specific area of the GIT. This may be accomplished through enteric coating of the tablet which dissolves when the surrounding pH reaches the target level. Sustained drug release tablets, on the other hand, exhibit a slow, constant release rate depicting release over several hours (Rades & Perrie, 2009).

Multiple-unit drug systems (or MUDS) may be more effective when compared to conventional release tablets or dosage forms. The profile obtained by immediate release dosage forms depicts a rapid rise in blood concentration followed by a decline as the drug is metabolised. Due to this profile, an extended duration of action is not possible, and therefore a controlled rate of drug release may extend the duration of action (Nokhodchi *et al.*, 2012). By delivering a slower release profile, dosage frequency and drug level fluctuations are reduced (Abdul *et al.*, 2010).

2.2.2 Types of modified drug release preparations

Modified release drug delivery systems are characterised by the type of formulation used (e.g. granules, beads and/or mini-tablets) or manufacturing process (e.g. tableting, film coating, encapsulation and/or extrusion-spheronisation). However, film coating and matrix system production are the most regularly utilised of these mechanisms. Numerous modifications may be implemented to achieve modified release (Figure 2.1). These modifications all deliver a different type of release profile (McConnell & Basit, 2013; Porter 2013a; Rajabi-Siahboomi *et al.*, 2013).

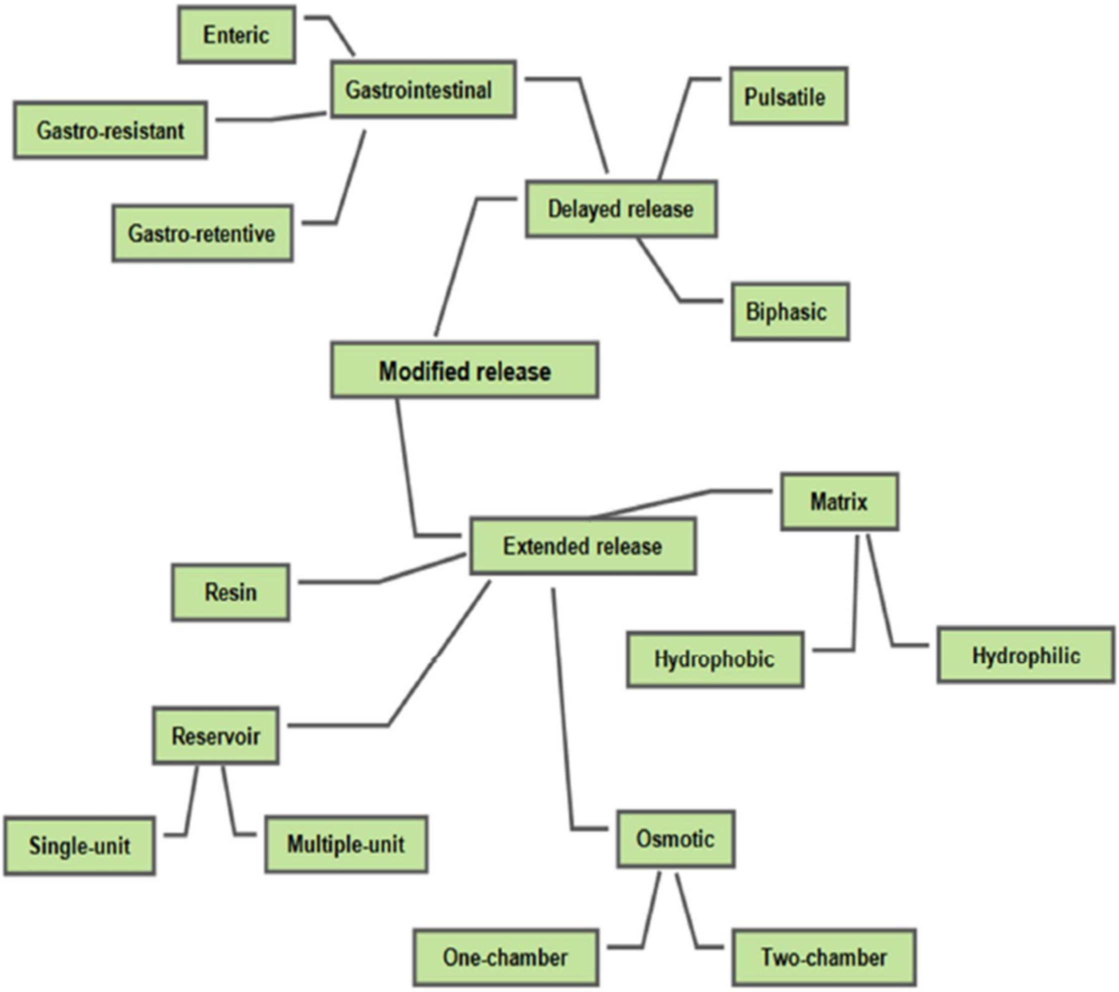


Figure 2.1: *Modified drug release exposition (Esterhuizen-Rudolph, 2015 as adapted from McConnell & Basit, 2013; Rajabi-Siahboomi et al., 2013; Qiu, 2009)*

Matrix systems are monolithic drug delivery systems consisting of a drug dispersed throughout a solid medium of polymeric excipients (Alderblom, 2013). Matrix-type tablet drug delivery systems can easily be manufactured by direct compression of a selected drug mixed with polymeric excipients (such as hydroxypropyl methylcellulose - HPMC). Drug release rates from these tablets depend on the porosity of the matrix, the size of these pores, as well the tortuosity of the matrix (Figure 2.2). These dosage form types may also be coated with a polymeric film through which the drug must first slowly diffuse. This, however, is an extremely technical step which requires experienced formulators and is relatively expensive when compared to uncoated tablets (McConnell & Basit, 2013; Porter, 2013b; Rajabi-Siahboomi *et al.*, 2013).

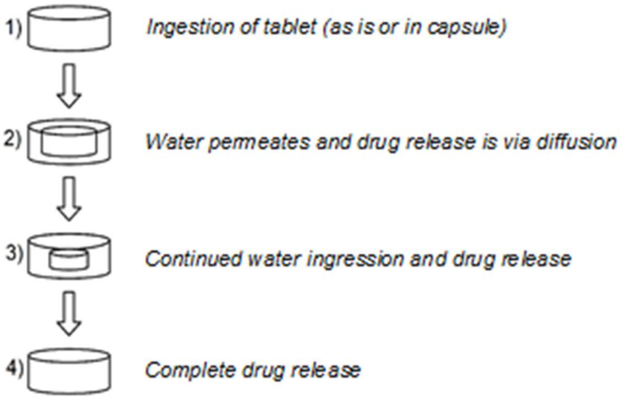


Figure 2.2: *Drug release from hydrophilic matrix systems (adapted from Qiu, 2009)*

The advantages to utilising matrix systems as the preferred system for achieving a modified drug release profile are that if a drug is soluble in the chosen media, high dosages thereof may be included into the system, drug release kinetics may be modified to suit the desired drug release profile, and multiple-unit delivery systems are possible to formulate (Qiu, 2009).

Single-unit and multiple-unit solid oral delivery systems, such as film-coated tablets (e.g. Diamicron® MR 30 mg) and film-coated granules (e.g. Rinex® Diffucaps) are both effective at obtaining modified release profiles. Single-unit dosage forms comprise one full dose of the drug in every unit intended to be administered once-off (Gandhi *et al.*, 1999). These systems will result in a higher bioavailability as opposed to multiple-unit delivery systems that are defined as oral dosage forms consisting of multiple small discrete sub-units, each containing a fraction of the complete drug dose that are combined into one dosage form (Abdul *et al.*, 2010). Moreover, multiple-unit pellet (or bead) systems or MUPS is a term used by the pharmaceutical industry and research community to describe tablets or capsules prepared by compaction of spherical beads. MUPS consist of several hundred coated or uncoated compressed beads, each containing a portion of the drug(s), which release the drug at a modified rate to provide a constant blood/drug concentration. These tablets are administered with ease, just as a single-unit oral dosage form would be, but will disperse into their sub-units post administration; and will distribute into the stomach and small intestine (Panda *et al.*, 2013; Pathikkumar *et al.*, 2013). All these units contribute to the overall desired controlled release of the drug dose. It is well known that multiple-unit controlled release dosage forms such as MUPS depict numerous biopharmaceutical advantages over its larger single-unit equivalents, predominantly regarding the duration (release the drug over a longer period of time) and the reproducibility of the gastric emptying time, i.e. single-unit delivery systems show more variation between patients with regards to bioavailability (Hamdani *et al.*, 2002; Varum *et al.,* 2010). It furthermore increases drug stability by protecting it from hydrolysis or other degradative changes in the GIT (Abdul *et al.*, 2010; Ishida *et al.*, 2008; Pathikkumar *et al.*, 2013; Ramu *et al.*, 2013; Sachdeva *et al.*, 2013).

By formulating MUPS containing gliclazide and tableting it into a single dose, where these tablets need to first disintegrate into beads and from beads into particles that may enter into solution (Figure 2.3), modified drug release is achieved. The drug release profile generated by modified release formulations may decrease the amount of side-effects observed due to the drug levels rarely peaking above the minimum toxic concentration (Allen & Cullis, 2004; Capuzzi *et al.*, 1998).

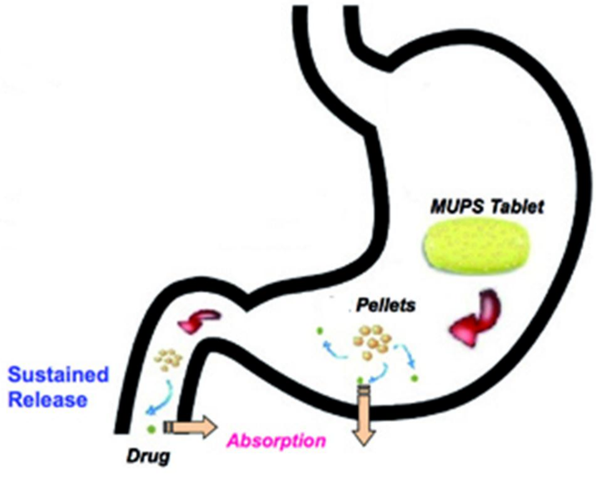


Figure 2.3: *Disintegration steps of a MUPS tablet (Martinez-Marcos & Lanao, 2012)*

Conventional release dosage forms are formulated to be unrestricted with regards to the rate of release, whereas modified release tablets and capsules have rate-limiting components, such as time-specific coatings or an enteric coating to delay immediate release of the drug.

According to McConnell & Basit (2013), modified release dosage forms have the following advantages:

- Therapeutic drug levels are sustained for a longer period of time;
- Therapeutic levels are sustained sufficiently to decrease the frequency of dosage;
- A decrease in concentration-related side effects may be observed;
- Patient compliance may be enhanced; and
- Site-specific release may be achieved.

Currently, there is a greater need for modified release dosage forms (Snyman, 2015). As discussed, delayed drug release is described as a dosage form that does not exhibit drug release directly after administration, but rather displays a lag-time before drug release is observed (Qiu & Zhou, 2011). Delayed release may be obtained through a variety of methods. Film coating is the most popular way of achieving delayed release (Bashaiwoldu *et al.*, 2011) due to the coating being able to completely coat the dosage form and it remains intact throughout production up until administration. Film coating is a versatile method of obtaining modified release, as it can be applied to a variety of dosage forms such as tablets, beads, granules and capsules (Torrado & Augsburger, 2008). Film coating may be divided into different categories, such as time-dependant, enzymatically-degradable, pressure-sensitive and pH-sensitive coating (Maroni, 2013). These different types of coating can be achieved utilising a variety of polymers to coat the dosage forms that each exhibit different characteristics, which support the desired drug release profile.

Advantages to coating dosage forms vary, and include (Porter, 2013; Mahato, 2007):

- Protection from environmental factors (such as light and moisture);
- Manipulation of organoleptic properties (e.g. an unpleasant taste);
- Aiding in identification of a tablet;
- Improved handling; and
- Improved drug release kinetics.

Apart from film coating, modified release profiles may be obtained through different mechanisms. Several dosage forms combine different forms of drug release to create a unique dissolution profile. For example, a conventional (or immediate) drug release preparation may be combined with a prolonged drug release formulation (such as pulsatile or phasic release dosage forms). These combination systems achieve a longer duration of action due to an incorporated system of higher frequency drug release (Long & Chen, 2009). Systems such as these therefore exhibit the advantages of both immediate and modified release dosage forms:

- An increase in patient compliance due to a decreased dosing regimen (with regards to dosage frequency);
- The ability to modify the drug release profile to suit the desired illness and to optimise treatment; and
- Earlier onset of action may be observed when compared to other modified release dosage forms (Rathod *et al.*, 2014).

Modified release dosage forms may furthermore exhibit an extended release profile. In literature, extended is often used interchangeably with other terms, for example sustained, prolonged or controlled. This system aims to maintain drug levels in the blood over an extended period of time, thus reducing the need for frequent dosages when compared to conventional release dosage forms (Alderblom *et al.*, 2013; Ding *et al.*, 2009). Although many researchers differ on the precise definition of extended release, the general consensus may be described as a constant rate of drug delivery at a predetermined time and/or rate of drug release (Rajabi-Siahboomi, 2013; Ratnaparkhi & Gupta-Jyoti, 2013; Mahato, 2007; Ding *et al.*, 2005; Lund, 1994). Multiple mechanisms of drug release have been proven to deliver extended drug release, and include:

- Passive diffusion across a gel layer or through pores or channels;
- Erosion and/or diffusion; and
- Osmotic pressure initiated drug release (Porter, 2013b).

In order to successfully formulate an extended release dosage form, the physical-chemical properties (molecular size and weight, solubility, pK_a and stability) need to be considered above and beyond the normal level; and special attention needs to be given to the biological properties (plasma concentration, dosage size, drug half-life and therapeutic index) of the drug (Ratnaparkhi & Gupta-Jyoti, 2013).

2.2.2 Method of formulation

Extrusion-spheronisation is often utilised in the manufacture of beads or pellets (Figure 2.4). This process may be described as the extrusion of a wetted powder through a sieve (1 mm for the purpose of this study) to produce rod-shaped cylinders, after a powder mass was wetted to an experimentally determined level using a mixture of water and ethanol (or a suitable wetting agent). Post extrusion, the rods are transferred into a spheroniser, which rotates at a high speed with an external air supply that flows into the apparatus to create beads (or ideally spheroids) from the rods. Beads utilised in the production of pharmaceutical preparations are preferred at sizes between 0.5ï 1.5 mm (Torrado & Augsburger, 2008).

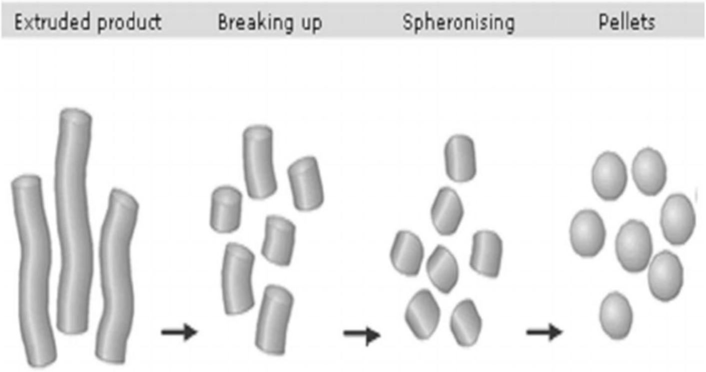


Figure 2.4: *Process of particle form change through extrusion-spheronisation (Shinde et al., 2014)*

The formation of beads offer many advantages over fine powders or even granules by offering, for example, an increased flow rate and less attraction forces between particles due to the decreased surface area of the particle. This may also result in lower attraction forces between the particles and the hopper shoe of the tablet press. The system of extrusion-spheronisation moreover offers advantages over other techniques of preparing beads, for instance, the ability to more accurately regulate bead size, produce high density beads with low friability, the ability to include higher levels of drug without producing overly large beads, and improved physical characteristics, such as an increased flow rate (Agrawal & Naveen, 2011).

The process of wet granulation is similarly widely used to increase the flowability of powder mixtures intended for tableting. In principle, this process shares similarity with extrusion-spheronisation, but the spheronisation step is omitted and replaced by the regranulation step. These methods of bead formulation are largely implemented to mask the weaker flowability of a powder or powder mixture. The disadvantages of these methods are that they are time consuming and require a higher amount of apparatus when compared to direct compression (Jivraj *et al.*, 2000).

Direct compression has become the preferred method of tablet manufacturing due to its efficiency pertaining to time and cost (Haware *et al.*, 2015). As described by Shangraw (1989) the costs associated with direct compression are considerably lower when compared to wet granulation, although direct compression calls for more specialised excipients, which may increase the associated costs. A combination of the abovementioned methods could result in tablets that exhibit good flowability associated with beads, but may benefit from the use of specialised excipients normally used in direct compression.

2.2.3 Use of specialised excipients

As mentioned, the use of specialised excipients may aid in the establishment of a modified drug release profile. Polyvinylpyrrolidone (Kollidon® 90F) is primarily a binder, but may aid in construction of a modified release profile (Biswal *et al.*, 2009). The release profile is influenced by the viscosity of the gel layer, which forms once fluid is introduced, and contains the drug within the tablet while regulating the rate of drug release by blocking the pores of the tablet. Thus, the rate of drug release is dependent on erosion of the tablet as well as passive diffusion. Although the rate of drug regulation is not as high as seen with binders, including HPMC; PVP exhibits enhanced complimentary properties with regards to tableting, such as increased hardness and decreased friability. When Kollidon® 90F is compared with Kollidon® 25 and Kollidon® 30, an increased disintegration time may be noted, which is beneficial as Kollidon® 90F increases tablet hardness (Bühler, 2004). The combination of PVP K90 and microcrystalline cellulose may also result in harder, more rigid tablets (BASF, 2008).

HPMC (or hypromellose) may contribute to a modified release profile due to the formation of a matrix system (with or without granulation and non-dependence on pH) which controls drug release by passive diffusion and swelling (Figure 2.5). Once the dosage form containing HPMC takes up fluid and swells, it forms a gelatinous polymer layer which extends erosion time (Colombo, 2008; Davis *et al.*, 2008; Salsa *et al.*, 1997). According to Andreopoulos and Tarantili (2001) diffusion of the selected drug proceeds via Fickian diffusion and is moreover dependant on the water solubility of the drug. Although HPMC is generally accepted as an excipient capable of aiding in modified release, the drug release rate may be influenced by gastric transit time and content, which could affect dose-to-dose variation (Nokhodchi *et al.*, 2012).

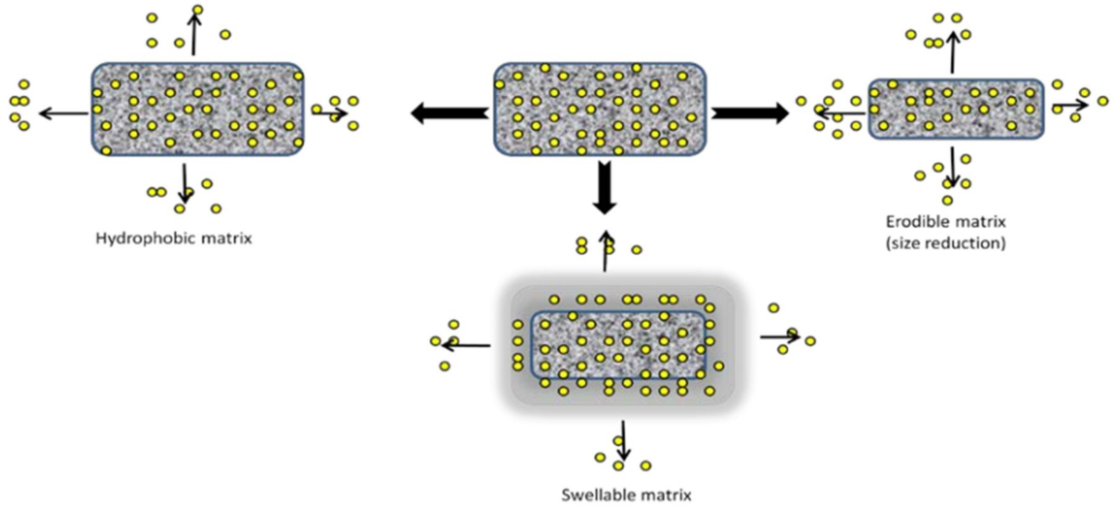


Figure 2.5: *Drug release from matrix tablets (Nokhodchi et al., 2012)*

Another way of optimising a dosage form is through co-processing of excipients. These excipients deliver the optimal physical-chemical properties from each of the selected fillers in the mixture. Co-processing modifies the components on a physical level, yet no change is observed on a chemical level. A homogeneous distribution of the excipients is delivered and avoids disadvantages of powder mixtures such as segregation and adhesion to the mixing vesicle (such as a glass container). Excipients may be co-processed as a way to compensate for poor flow, e.g. ő-lactose monohydrate, which exhibits excellent flowability, yet it does not possess ideal binding properties. Therefore, it may be beneficial to co-process it with MCC (as observed in MicroceLac® 100), thus increasing the binding properties of the mixture as well as depicting an increased flow; it may even exhibit synergistic effects on disintegration (Gohel & Jogani, 2005). Advantages of co-processed excipients include improved flowability, compressibility and consistency in tablet mass (Chowdary & Ramya, 2013).

2.4 SeDeM Diagram Expert System

2.4.1 Introduction

The SeDeM Diagram Expert System (Khan *et al*., 2014; Sauri *et al*., 2014; Suñé-Negre *et al*., 2011a; Aguilar-Diaz *et al*., 2009), or ñSediment Delivery Modelò is a system for applied pre-formulation methodology for the development of solid dosage forms by means of direct compression, through analysing various aspects of the powder flow properties. This System is based on the concept of Quality by Design (ICH Q8) as described by Defloor *et al*. (2009). It focuses on 12 key parameters of powder flowability which influence the final quality of the product (Aguilar-Diaz *et al*., 2009); and is capable of offering suggestions as what properties to improve and how to achieve the said improvement. Overall, the system is extremely valuable as it is reproducible and offers a standard process through which to assess a powderôs suitability for direct compression (Khan *et al*., 2014).

The System analyses 12 parameters by means of experimentation and from the results generated during pre-formulation testing, the SeDeM Diagram Expert System provides a profile of the excipients and the active ingredients in an uncompressed powder form. This profile in the form of a polygon can designate whether a powder mixture is suitable for direct compression and/or how it needs to be adjusted to become a more optimal powder for direct compression (Suñé-Negre *et al*., 2011a).

The SeDeM Diagram Expert System utilises powder flow tests as prescribed by the United States Pharmacopoeia (Suñé-Negre *et al*., 2011a) and converts the results to a radial value (r = 0ï 10), which is plotted on a diagram or polygon (Figure 2.6). These 12 parameters are grouped into five factors based on the physical characteristics of the powder, namely, the dimensional factor, compressibility factor, flowability/powder flow factor, lubricity/stability factor, and the lubricity/dosage factor (Suñé-Negre *et al*., 2011b; Khan *et al*., 2014; Aguilar-Diaz *et al*., 2009). The radial values of each parameter are then used to calculate the total acceptability of the powder for direct compression, where 5 is the minimum acceptable value for a parameter and further calculations are applied to receive suggestions on improvement of the powder. The System also provides 3 equations to calculate the Parameter Index (PI), Parameter Profile Index (PPI) and the Good Compressibility Index (GCI). These index values then indicate whether or not the powder or powder mixture is suitable for direct compression (Suñé-Negre *et al*., 2011a).

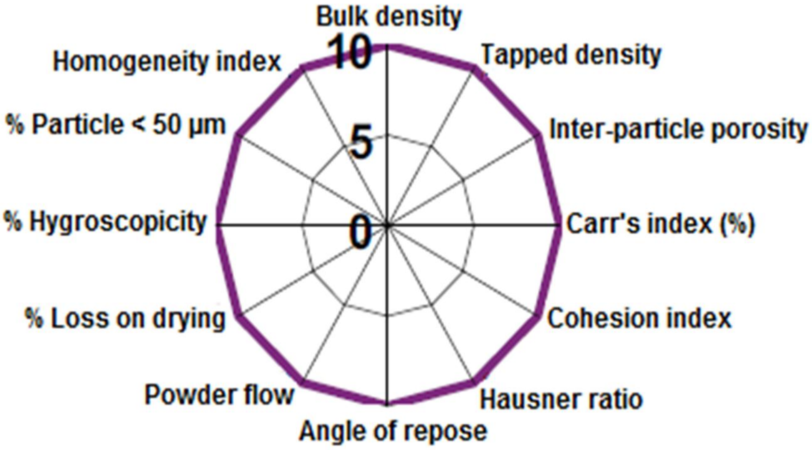


Figure 2.6: *The SeDeM Diagram with 12 parameters (Suñé-Negre et al., 2011a)*

In this study, the SeDeM Diagram Expert System was utilised to evaluate the flowability and compressibility of the selected fillers and bead formulations in order to establish if it is at all possible to predict the strengths and weaknesses of the formulation(s) for the production of a modified release oral dosage form containing gliclazide (Suñé-Negre *et al.*, 2011a). This System was also utilised in the study to identify the powdersôweaknesses with regard to thier acceptability for direct compression, which will allow improvements to be made to specific properties (such as flowability or compressibility) and thus less experimentation is needed to formulate the best possible powder mixture for direct compression, utilising excipients that may influence the physical properties of a powder (for example, a lubricant and a binder).

The SeDeM Diagram Expert System may be applied to:

- Analyse a drugôs suitability for direct compression and also examine the suitability of an excipient to correct for the weaknesses displayed by the drug or to compliment the strengths thereof. The SeDeM Diagram Expert System subjects the powder to testing in order to establish values for the 12 parameters. Thereafter, a SeDeM Diagram is constructed to visually display the properties of the selected powder. These values are interpreted and converted to radius values (r) and implemented in equations to characterise the powder as acceptable or not acceptable for direct compression.
- Control uniformity with regards to substances which are chemically similar. This application serves to indicate whether a property of the tested powder is unique to the powder or whether the trait is shared among all substances in the related chemical family.

- Distinguish between excipients which share a common functional group or serve the same pharmaceutical purpose, such as a binder or a lubricant (Bhavsar *et al.*, 2015).

2.4.2 Parameters analysed by the SeDeM Diagram Expert System

The SeDeM Diagram Expert System utilises various tests to determine whether or not the powder is suitable for direct compression (Khan *et al.*, 2014). These tests serve to indicate the many properties of a powder or powder mixture, and the results thereof are converted to rate the suitability of the powder (Bhavsar *et al.*, 2015). The SeDeM Diagram Expert System utilises the following tests (Suñé-Negre *et al.*, 2011a):

- Bulk density (ɟ $_b$): The aerated density of a powder before tapping. The value of this parameter is given in g/ml and the density is affected by the shape, size cohesion forces of a powder, or powder mixture.
- Tapped density (ɟ $_t$): The density of a powder after agitation (or tapping). The value, once again, is given as g/ml, and is influenced by the shape of the powder particles and how effectively they pack.
- Interparticle porosity (Ie): An indication of the empty spaces between the particles of a powder. This parameter does not have a unit, but is measured as a ratio.
- Carrôs index (CI): This parameter is an indication of the percentage (%) of the powder that compresses. It is measured in percentage (%) and a higher value is indicative of enhanced powder compressibility, but a lower value is indicative of improved powder flowability.
- Cohesion index (Icd): This parameter refers to the maximum force with which the powder can be compacted. The unit for this parameter is Newton (N).
- Hausner ratio (HR): This value is indicative of the flowability of the powder. It is measured as a ratio and therefore has no unit. A lower value suggests enhanced flowability.
- Angle of repose (d): It is the angle that forms between the powder pileôs surface and the surface upon which it is measured. This parameter is measured in degrees (°) and is indicative of the inter-particular attraction forces of the powder.
- Powder flow (F): This parameter is the rate (g/sec) at which a powder freely flows through an orifice of 10 mm. This serves as an indication to the inter-particular forces between powder particles and whether they can be overcome by gravitational force.

- Loss on drying (LOD): This experiment is used to determine the amount of moisture present in the powder mixture. It is measured in percentage (%) and a lower value demonstrates a more stable powder.
- Hygroscopicity (%H): It is the amount of atmospheric moisture that a powder absorbs whilst subjected to an enclosed space with controlled temperature and humidity (22 ± 2°C and 76 ± 2% humidity) for 24 h. The parameter is measured in percentage (%) and a lower value indicates a more stable powder.
- Particles <50 εm ($\%F_m$): This parameter specifies the percentage of particles which are smaller than 50 εm in size. $\%F_m$ exerts influence on the homogeneity of powder mixtures.
- Homogeneity index (Id): This parameter is a mathematical equation which it utilised to determine the uniformity of the powderôs particle size distribution. It is measured in a ratio and a larger value denotes a more homogeneous powder.

The above described parameters are grouped into 5 factors that indicate the suitability of a powder for direct compression. These factors address key aspects of a powderôs suitability and include the following:

- Dimensional factor: This factor consists of the Bulk and Tapped density parameters. The factor reveals how effectively a powder may pack whilst the dye is filling and the values of these two experiments are used in the calculation of other parameters as well (for example, Carrôs index).
- Compressibility factor: This factor is made up of the interparticle porosity, Carrôs index and the cohesion index parameters. The factor value predicts the suitability of a powder with regards to its compressibility.
- Flowability factor: The factor includes the Hausner ratio, angle of repose and the powder flow parameters. It indicates the appropriateness of a powder to freely flow and may influence the consistency at which tablets are produced due to effective and constant dye filling.
- Lubricity/stability factor: This factor comprises the loss on drying and hygroscopicity parameters. It serves as an indication of the stability of the powder as well as the lubricity the powder may exhibit.
- Lubricity/dosage factor: This factor consists of the particles <50 εm and homogeneity index parameters. The lubricity/dosage factor portrays the consistency observed in the powder with regards to the particle size and distribution (Suñé-Negre *et al.*, 2013).

Upon completion of the abovementioned experiments, the experimental results are converted into SeDeM Diagram values, utilising the equations observed in Table 2.1.

Table 2.1: *List of symbols, units, limits and radius value conversion equations of the different parameters in each factor (adapted from Suñé-Negre et al., 2013)*

Factor	**Parameter**	**Symbol**	**Acceptable ranges**	**Equation for conversion to radius values**
Dimension	Bulk density Tapped density	ɟ b ɟ t	0-1 g/ mL 0-1 g/ mL	10(ɟ b) 10(ɟ t)
Compressibility	Interparticle porosity Carr's index Cohesion index	Ie CI Icd	0-1.2 0-50 (%) 0-200 (N)	(10Ie) / 1.2 CI / 5 Icd / 20
Flowability	Hausner ratio Angle of repose Powder flow	HR ɗ F	3-1 50-0 (°) 20-0 (s)	(30-10 HR) / 2 10-(ɗ / 5) 10-(F / 2)
Lubricity/Stability	Loss on drying Hygroscopicity	LOD %H	10-0 (%) 20-0 (%)	10- LOD 10-(%H / 2)
Lubricity/Dosage	Particles < 50 µm Homogeneity index	$\%F_m$ Iɗ	50-0 (%) 0-(2x10^{-2})	10-($\%F_m$ /5) 500(Iɗ)

The SeDeM Diagram Expert System indicates the strengths and weaknesses of the powder and accordingly it may be adjusted to be more suitable for direct compression (Suñé-Negre *et al.*, 2011b). The obtained radius values are utilised to calculate the suitability of the powder for direct compression by deeming it acceptable or not acceptable through the use of the PI, PPI and GCI equations.

2.4.3 Acceptability of a powder for direct compression

As previously stated, the SeDeM Diagram Expert System considers a powder acceptable or not acceptable for direct compression. Utilising the radius values from the 12 tested parameters, the following equations are implemented (Suñé-Negre *et al.*, 2011a):

Parameter Index (PI):

$$\text{Parameter Index (PI)} = \frac{\text{No.P} \geq 5}{\text{No.Pt}} \qquad \textbf{[2.1]}$$

Where No.PÓ5 is the number of parameters with a value equal to or greater than 5; and No.Pt is the number of parameters utilised.

Parameter Profile Index (PPI):

$$\text{Parameter Profile Index (PPI)} = \text{mean r} \geq 5 \text{ for all parameters} \qquad \textbf{[2.2]}$$

Where mean r is the mean value of all the parameters subjected to testing; and

Good Compressibility Index (GCI):

$$\text{Good Compressib ility Index (GCI)} = \text{PPI} \times \text{f} \qquad \textbf{[2.3]}$$

Where f is the reliability factor and is 0.952 when 12 parameters are tested.

A powder is considered acceptable for direct compression when the PI value is Ó0.5 and the PPI and GCI values are Ó5 (Bhavsar *et al.*, 2015).

Recently, there has been a renewed interest in the SeDeM Diagram Expert System and the applications thereof with beads (or pellets) rather than powders. It was found by Hamman *et al.* (2017) that the SeDeM Diagram Expert System may be successfully applied to beads, however there is a shortcoming in the SeDeM Expert Diagram System regarding the compressibility factor and may need correction to better accommodate the use of beads. It was furthermore indicated that the homogeneity index of the beads may be a challenge, as blending homogeneously with such large particle size differences may be more of a challenge.

In the light of the literature study, it was decided that a sustained drug release profile would be manufactured utilising the SeDeM Diagram Expert System to characterise the selected fillers (in both powder and bead form) before and after the addition of 10% w/w gliclazide. The fillers include excipients which are co-processed and excipients physically blended with HPMC to benefit from the modified release properties HPMC possesses. The flowability of the powder and bead preparations were subjected to the testing criteria as described in the BP (2016). Upon characterisation of the powders and beads, the beads were tableted and tested by means of a full factorial design to ascertain the correct concentration of both lubricant and binder to be included. After analysis utilising the full factorial design, the optimal combination of binder and lubricant was incorporated into the powder and bead formulations and subjected to swelling and erosion tests, as well as drug release profile analysis (by dissolution studies).

* * *

Chapter 3:

MATERIALS AND METHODS

3.1 Introduction

As clearly stated before, diabetes mellitus remains one of the many complications that have, and are still impacting on not only the African economy, but also world economy. Gliclazide, which is presently recommended for treatment of non-insulin-dependent diabetes mellitus, appeals to a significantly smaller margin of diabetics due to cost implications. Patient compliance along with effective treatment regimens are indispensable in warranting successful management of this condition. Furthermore, although research is focussing on various other delivery routes for providing effective treatment of diabetes mellitus amongst other complications; the oral delivery route remains the most preferred route of drug administration and tablets the most favoured dosage form. Unfortunately immediate release dosage forms have a higher dosing frequency compared to modified release formulations which contributes to poor patient compliance. Likewise, modified release dosage forms comprising gliclazide are relatively more expensive and therefore not readily available, thus further increasing this problem. Development of a multiple-unit solid oral dosage form containing gliclazide and employing excipients normally utilised in direct compression is thus essential to contribute in improving patient compliance by providing a modified release profile without the use of additional specialised excipients or film coatings of the tablets. This chapter deals with the motivation for the choice of the excipients utilised in all of the formulations prepared as well as the method of production of the modified release tablets manufactured in this study in order to develop a solid multiple-unit oral delivery system. The compounds used in this study were selected specifically for their specialised properties identified in literature. The methods carried out to evaluate the effect of the selected excipients on the physical properties of the different formulations are described in detail.

First, a full factorial design was employed to be able to evaluate formulation variables and to identify the optimum ratios for each excipient that was included in the different formulations. In order to characterise flowability and compressibility of the different fillers, powder mixtures and bead formulations as well as to better understand their shortcomings and to improve upon them during formulation of the various bead and tablet formulations, the SeDeM Expert Diagram System was utilised. After some adjustments to the different formulations, they were subsequently tableted by means of direct compression and their physical properties and dissolution behaviour consequently evaluated in order to determine if it was indeed possible to formulate a solid multiple-unit oral delivery system containing gliclazide that displays modified drug release properties.

3.2 Materials

The materials used in this study were all of analytical grade and are listed in Table 3.1.

Table 3.1: *List of materials*

Material	Manufacturer	Lot Number
Gliclazide	D B Fine Chemicals (Pty) Ltd, Johannesburg, South Africa	20161025
Cassava Starch	Meelunie, BV. Amsterdam, Netherlands	169A-27-11-12
CombiLac	Meggle Group, Wasserburg, BG Excipients & Technology	L1433
RetaLac	Meggle Group, Wasserburg, BG Excipients & Technology	L416300
MicroceLac® 100	Meggle Group, Wasserburg, BG Excipients & Technology	L91928
Pharmacel 101	Warren Chem Specialties, Johannesburg, South Africa	100043
Hydroxypropyl Methylcellulose (HPMC)	Shin-Etsu Chemical, Ltd. Tokyo, Japan	110404
Ethanol	Associated Chemical Enterprises Ltd, Johannesburg, South Africa	30468
Cyclohexane	Associated Chemical Enterprises Ltd, Johannesburg, South Africa	7338
Hydrochloric Acid (32%)	Associated Chemical Enterprises Ltd, Johannesburg, South Africa	33080
Kollidon 90 F	BASF The Chemical Company, Ludwigshafen, Germany	39801647GO
Tri-Sodium Orthophosphate Anhydrous	Associated Chemical Enterprises Ltd, Johannesburg, South Africa	31841
Magnesium Stearate	Warren Chem Specialties, Cape Town, South Africa	21203

3.3 Formulation of powder batches and beads

3.3.1 Preparation of Powder Batches for analysis using SeDeM Expert Diagram System

Initially, gliclazide and all the fillers were individually weighed and analysed using the SeDeM Expert Diagram System, to be discussed in Section 3.4. Individually, the selected fillers together with 10% w/w gliclazide were weighed into 250 cm^3 glass containers, sealed with Parafilm® (Pechiney Plastic Packaging, Menasha, Chicago, IL) and fitted with a screw cap. The powder batches were mixed for 5 min in a Turbula® mixer (model T2C, W.A., Basle, Switzerland) at 69 rpm. The glass containers were again sealed with Parafilm® and stored in a cool, dark area until use.

3.3.2 Bead Manufacture by means of extrusion-spheronisation

In order to prepare the bead formulations, 150 g of a selected filler was blended with 10% w/w gliclazide for 5 min utilising a Turbula® mixer (model T2C, W.A., Basle, Switzerland) at 69 rpm, to produce 100 g of beads for testing. The subsequent mixture was transferred to a Kenwood® mixer (model FP731 Multi-Pro, Kenwood®, South Africa) and wetted with a wetting liquid (an experimentally determined mixture of ethanol and distilled water). Next, the wetted mass was mixed for 10 min, conveyed into the Extruder 20 (Caleva®, England), and extruded through a 1 mm sieve, followed by spheronisation in a multi-bowl spheroniser (Caleva®, England) at times and speeds portrayed Table 3.2 (Bashaiwoldu *et al.,* 2011). The spheronised beads were air dried in an EcoTherm Labotec oven at 50ºC and weighed every 90 min until no variation in the bead mass occurred.

Afterwards, the dried beads were sieved using an orifice size of 1.5 mm to establish a more uniform particle size distribution. During the course of the extrusion-spheronisation process it was impossible to produce the different bead formulations under exactly the same conditions, therefore small variations were made for each formulation to assure effective bead preparation.

Table 3.2: *Preparation and settings for bead production via extrusion-spheronisation*

Filler	**CombiLac®**			**MicroceLac® 100**			**RetaLac®**			**Pharmacel® 101**			**Cassava Starch/ HPMC**		
Binder in Liquid (% w/w)	0	2	5	0	2	5	0	2	5	0	2	5	0	2	5
Filler/Drug Ratio	90/10	88/10	85/10	90/10	88/10	85/10	90/10	88/10	85/10	90/10	88/10	85/10	90/10	88/10	85/10
Binder Liquid (H_2O_{Dist}/EtOH)	80/20			80/20			15/85			80/20			75/25		
Liquid/ Powder Ratio	1:2			1:2			2:1			1:1			2:5		
Extrusion Speed (rpm)	35			35			35			35			35		
Spheronisation Speed (rpm)	1680			1860			2050			1800			1500		
Spheronisation Time (min)	5			5			10			10			6.5		

3.4 Powder and Bead Characterisation as per SeDeM Expert System

The gliclazide powder; selected fillers; mixtures of gliclazide with each selected filler; beads produced from each of the selected fillers; and beads containing gliclazide and one of the selected fillers (samples), were analysed according to the parameter tests of the SeDeM Expert Diagram System. These parameters include the bulk density (ρ_b), tapped density (ρ_t), interparticle porosity (Ie), Carr's index (CI), cohesion index (Icd), Hausner ratio (HR), angle of repose (α), powder flow (F), loss on drying (LOD), hygroscopicity (%H), particle size (%F_m), and the homogeneity index (Iθ). Results obtained from the parameters were processed utilising the different equations (Suñé-Negre *et al.,* 2014) shown in Table 3.3 in order to formulate the different SeDeM factors discussed in the following sections.

Table 3.3: *List of abbreviations, units, limits and radius value conversion equations of the different parameters in each factor*

Factor	Parameter	Symbol	Acceptable ranges	Equation for conversion to radius values
Dimension	Bulk density Tapped density	ρ_b ρ_t	0-2 g/ mL 0-1 g/ mL	10(ρ_b) 10(ρ_t)
Compressibility	Interparticle porosity Carr's index Cohesion index	Ie CI Icd	0-1.2 0-50 (%) 0-200 (N)	(10Ie) / 1.2 CI / 5 Icd / 20
Flowability	Hausner ratio Angle of repose Powder flow	HR α F	3-1 50-0 (°) 20-0 (s)	(30-10 HR) / 2 10-(α / 5) 10-(F / 2)
Lubricity/Stability	Loss on drying Hygroscopicity	LOD %H	0-10 (%) 20-0 (%)	10- LOD 10-(%H / 2)
Lubricity/Dosage	Particles < 50 µm Homogeneity index	%F_m Iθ	50-0 (%) 0-($2x10^{-2}$)	10-(%F_m /5) 500(Iθ)

The SeDeM parameter values for each sample are converted into radius values with which an asymmetrically shaped polygon with a maximum radius of 10 is constructed. This polygon serves as a graphical illustration of the benefits and drawbacks of each of the respective pharmaceutical samples. These polygons may then be superimposed to emphasise the shared characteristics of the individual samples. The SeDeM Expert Diagram System is furthermore able to suggest whether or not a specific sample will be appropriate for direct compression. In the instance that a radius value of 5 or lower is attained for a specific parameter, it is an indication that the sample displays limited qualities for that specific parameter. Additionally, the system is also able to predict the amount of excipient required to compensate for inadequate drug characteristics. In this way, preformulation trials as well as time taken to conduct these experiments are restricted (Pérez-Lozano *et al.,* 2006; Suñé-Negre *et al.,* 2005; Suñé-Negre *et al.,* 2008).

3.4.1 Dimensional Factor

The dimensional factor affects many features, including tablet size and the powder's ability to flow into a tablet press, thus providing crucial information regarding dosage possibilities per tablet (Suñé-Negre *et al.,* 2011a). It consists of two parameters, namely the bulk (ρ_b) and tapped (ρ_t) densities that were measured according to method 1 in the British Pharmacopoeia (BP) as described in Appendix XVII S (BP, 2016). A 100 g (m) sample was weighed and transferred into a clean, dry 250 ml graduated cylinder. The bulk volume (V_b) was noted where after the cylinder was connected onto the Tap Density Tester (Erweka® SVM 121/221, Germany). The machine was operated for 3 min at 200 taps/min and the tapped volume (V_t) subsequently noted. Using Equations 3.1 and 3.2, the ρ_b and ρ_t (g.ml^{-1}) were calculated.

$$\rho_b = \frac{m}{V_b} \qquad \textbf{[3.1]}$$

$$\rho_t = \frac{m}{V_t} \qquad \textbf{[3.2]}$$

3.4.2 Compressibility Factor

The compressibility factor is represented by the interparticle porosity, Carr's index and the cohesion index. Both the bulk (ρ_b) and tapped (ρ_t) densities were utilised to calculate the interparticle porosity and Carr's index. Equation 3.3 was used to calculate the interparticle porosity (Ie); whereas Carr's index (CI) was determined using Equation 3.4 (Suñé-Negre *et al.* 2011a):

$$\mathrm{Ie} = \frac{\rho_t - \rho_b}{\rho_t \times \rho_b} \qquad \textbf{[3.3]}$$

$$\mathrm{CI} = \left(\frac{V_b - V_t}{V_b} \right) \times 100 \qquad \textbf{[3.4]}$$

The cohesion index (Icd) for a specific sample was experimentally determined through the compression of that sample on a Korsch® XP1 single station tablet press (Korsch®, Germany) using the maximum possible force to compress it into tablets. The selected powders; powder mixtures and bead formulations were compressed and the tablet hardness (N) of 10 randomly selected tablets from each formulation was noted. The mean values were subsequently calculated and compared (Suñé-Negre *et al.* 2011a).

The SeDeM Expert Diagram System suggests that if a powder mixture cannot be tableted, a lubricant powder mixture comprising 2.36% w/w talc, 0.14% w/w Aerosil® 200, and 1.00% w/w magnesium stearate, to improve the compressibility, should be added (Suñé-Negre *et al.,* 2011a). First, the crude powders, powder mixtures, or bead formulations were tested; and since these samples could be compressed effortlessly, it was not required to add any other excipients.

3.4.3 Flowability/Powder Flow Factor

The flowability/powder flow factor includes the Hausner ratio (HR), angle of repose (θ) and powder flowability (F) parameters (Suñé-Negre *et al.,* 2011a). The HR was measured and characterised according to the standards set in Appendix XVII N of the BP (BP, 2016). Equation 3.5 was used to calculate the HR:

$$\mathrm{HR} = \frac{V_b}{V_t} \qquad \textbf{[3.5]}$$

The angle of repose (d) was measured according to the customary criteria of the BP in Appendix XVII N, where a 100 g sample of a selected powder or bead formulation was placed in a stainless steel funnel with a 10 mm diameter orifice, which was then placed 100 mm above the surface, thus utilising both the fixed-diameter and fixed-height methods (BP, 2016). The sample was allowed to flow through the funnel by removing the shutter so that a heap was formed on a solid horizontal surface. Equation 3.6 was consequently used to calculate the angle of repose.

$$\tan(\theta) = \frac{h}{r} \qquad \textbf{[3.6]}$$

Where both the height (h) of the funnel and base or radius (r) of the powder or bead heap was measured in millimetres.

Flow (F) or flow rate through an orifice was measured according to the criteria obtained from the BP (2016) in Appendix XVII N, where a 100 g of a selected powder or bead formulation was weighed and placed in a stainless steel funnel with an orifice of 10 mm. The funnel was set up at a fixed height of 100 mm above the horizontal surface. The shutter was opened and the time it took the powder or bead sample to flow through the orifice was noted. The mean flow rate was calculated according to the weight of the powder utilising Equation 3.7.

$$F = \frac{m}{t} \qquad \textbf{[3.7]}$$

Where, F, is the flow rate ($g.s^{-1}$); m, is the powder or bead mass (g); and, t, is the time measured in seconds.

3.4.4 Lubricity/Stability Factor

Loss on drying and hygroscopicity are parameters measured to determine the lubricity/stability factor. According to Suñé-Negre *et al.* (2011a), loss on drying (LOD) can be calculated in order to measure the amount of water and volatile substances in a sample when it is dried under specified conditions. A selected powder or bead sample (1 g) was therefore placed in a drying oven set to 105°C ± 2°C until a constant weight was obtained that was noted for three consecutive measurements. The LOD was calculated using Equation 3.8.

$$LOD = \left(\frac{m_u - m_d}{m_u}\right) \times 100 \qquad \textbf{[3.8]}$$

Where, m_u, is the mass (g) of powder or bead sample noted pre-exposure to the set conditions; and, m_d, is the dried mass (g) post-exposure.

For determination of the hygroscopicity (%H), a 1 g sample of a selected powder or bead formulation was stored in a Binder® KBF 240 Climate Chamber (Binder®, Germany), set at a relative humidity of 76% (± 2%) and a temperature of 22°C (± 2°C) for 24 h (Suñé-Negre *et al.*, 2011a). Equation 3.9 was subsequently employed to calculate %H.

$$\%H = \left(\frac{m_e - m_0}{m_e} \right) \times 100 \qquad \textbf{[3.9]}$$

Where, m_0, is the mass (g) of powder or beads noted pre-exposure to the set conditions and, m_e, is the dried mass (g) post-exposure.

3.4.5 Lubricity/Dosage Factor

Particle size analyses of the different samples was conducted via laser diffraction utilising a Malvern® Mastersizer-2000 (Malvern Instruments Ltd®, UK) equipped with a Hydro 2000 SM dispersion unit. A suitable dispersion medium was selected for each filler based on the compatibility of the dispersion medium with the selected filler. For the lactose-containing fillers (CombiLac®, MicroceLac® and RetaLac®), cyclohexane was found to be a suitable dispersion medium (Peña *et al.*, 2000). Pharmacel® 101, which consists of microcrystalline cellulose, is insoluble in ethanol (Yamamoto *et al.*, 1976) which was subsequently utilised as dispersion medium; and Cassava starch/HPMC was dispersed in ethanol.

The selected sample was dispersed in the designated dispersion medium and analysed with regards to its particle size and distribution via laser diffraction. The percentage particles ($\%F_m$) measuring smaller than 50 εm in size was determined. The homogeneity index (Iɗ), on the other hand, was calculated from the data obtained from the particle size analysis. These results were fractioned into the following ranges: > 0.335 mm; 0.212 ï 0.335 mm; 0.100 ï 0.212 mm; 0.05 ï 0.100 mm; and < 0.05 mm. The percentage (%) particles in each size range were calculated. Equation 3.10 was applied to the obtained data (Suñé-Negre *et al.*, 2011a).

$$\mathrm{Iɗ} = \frac{F_m}{100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + (d_m - d_{m-2})F_{m-2} + \ldots \atop \ldots. + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}} \qquad \textbf{[3.10]}$$

Where (Iɗ) is the relative homogeneity index; F_m = %particles in the majority range; F_{m-1} = %particles in the range immediately below the majority range; F_{m+1} = %particles in the range immediately above the majority range; n = order number of the fraction studied under a series, with respect to the major faction; d_m, = mean diameter of the particles in the major fraction;d_{m-1}, = mean diameter of the particles in the fraction of the range immediately below the majority range; d_{m+1} = mean diameter of the particles in the fraction of the range immediately above the majority range.

3.4.6 *Determination of Suitable Limit Values for Each Parameter*

According to Suñé-Negre *et al.* (2011a) the numerical values of the tests are to be converted into radial- or r-values (1ï 10, where 5 is the mean average value) based on the limit values suggested or specified. These values indicate the suitability of the aspect measured relative to direct compression. To determine whether these values lead to a powder or bead formulation with acceptable powder flow properties for direct compression in numerical form, the subsequent indexes (Equations 3.11ï 3.15) were calculated based on the SeDeM analysis (Khan *et al*., 2014; Sauri *et al*., 2014; Suñé-Negre *et al*., 2011a).

$$\text{Parameter Index (PI)} = \frac{\text{No.P} \geq 5}{\text{No.Pt}} \qquad \textbf{[3.11]}$$

Where No. P Ó5 is the number of parameters with values equal to, or more than 5; and No.°Pt is the total number of parameters applied. The acceptability limit corresponds to a value of 5 or higher.

$$\text{Parameter Profile Index (PPI)} = \text{mean r} \geq 5 \text{ for all parameters} \qquad \textbf{[3.12]}$$

Where mean r is the mean value of the parameters calculated. The acceptable limit corresponds to a score of 5 or higher.

$$\text{Good Compressibility Index (GCI)} = \text{PPI} \times \text{f} \qquad \textbf{[3.13]}$$

Where f is the reliability factor and was calculated as follows:

$$\text{f} = {}^{\text{Polygon area}}\!\big/_{\text{Circle area}} \qquad \textbf{[3.14]}$$

The acceptability limit was calculated by:

$$\text{GCI} = \text{PPI} \times \text{f} > 5 \qquad \textbf{[3.15]}$$

3.5 Additional Powder or Bead Characterisation

3.5.1 *Critical Orifice Diameter*

The Critical Orifice Diameter (COD) is defined as the smallest possible diameter that a powder can continuously and freely flow through. The method and apparatus utilised to determine the COD of each powder and bead formula was developed by Buys (2006). Copper discs with different sized openings through their centres were placed on top of one another to form a smooth funnel. The assembly was placed on top of a tripod and was consequently raised approximately 10 cm above the horizontal surface. A disc containing a shutter was opened and closed, with the disc containing the smallest opening being removed after each round of testing. Once the powder flowed freely through an opening, that opening was considered the COD.

3.5.2 Morphology

The morphological features of the model compound and the various fillers were evaluated using a scanning electron microscope (SEM). Samples of each powder was mounted onto a metal disc with a silicon adhesive and the samples were coated with a thin layer of a gold and palladium (66:34) mixture under a vacuum of 1.5 torr in an Eiko® ion coater (model IB-2, Eiko Engineering, Japan). The sample surfaces were inspected by means of a scanning electron microscope using a FEI Quanta® 250 Environmental Scanning Electron Microscope with a Field Emission Gun (FEI, Quanta® 250, Netherlands). Micrographs of the surfaces of the samples were taken at 75X - 1000X magnification to inspect the morphological features (Ibrahim, 2012).

3.6 Direct Compression into Tablets

In order to ensure scientific accuracy and to ensure that the optimum ratio of binder and lubricant was used, a full factorial design was employed to test a variety of concentrations of both the binder and lubricant that needed to be incorporated.

3.6.1 Factorial Design

Conventionally, trial-and-error experiments were intended to define the effect of ONE variable on ONE response. However, to be able to research the various effects that different formulation factors have on the physical and dissolution properties of a multiple-unit sustained release dosage form containing gliclazide, a full factorial design was employed in this study as little information is still known concerning the performance of the selected fillers when utilised to manufacture bead formulations. Factorial design is a significant statistical method able to define substantial interactions and effects of numerous variables or factors, as well as different levels thereof, on a response. Many advantages exist in combining a study of multiple variables in the same factorial experiment as it can reduce the number of tests that has to be conducted by studying multiple factors simultaneously. In addition, it can be exploited in achieving both key effects (from each independent factor) and interaction effects (when both factors must be used to explain the outcome). A factorial design is able to provide an impartial, systematic guide to evaluate several excipients and their concentrations on dosage form performance, ensuing optimisation of these formulations. Thus, the speculation from experimentation is evaded (de Kock, 2005).

A full factorial design was therefore used to evaluate three formulation variables, i.e. filler type, binder concentration, and lubricant concentration. The fillers studied were; CombiLac®; MicroceLac®100; RetaLac®; Pharmacel® 101 and a physical blend of cassava starch and hydroxypropyl methylcellulose (HPMC). Kollidon® 90F and magnesium stearate were included in various concentrations as the binder and lubricant, respectively. Abbreviations were assigned to the factors measured; and are presented in Table 3.4. The factors were assessed at different levels, namely five filler types, three binder concentrations (0, 2 and 5% w/w); and two lubricant concentrations (0.5 and 1% w/w), respectively. Inclusion of a binder was necessary due to complications experienced during the spheronisation step when the different bead formulations were manufactured from powder mixtures via extrusion-spheronisation. The addition of magnesium stearate was deemed compulsory as powder mixtures and beads stuck to the equipment during powder flowability tests as well as during direct compression.

Table 3.4: *Formulation factors, variables and levels during investigation in the study.*

Factor	Variable	Level
Filler type	Pharmacel® 101 (PC)	**5**
	CombiLac® (CL)	
	MicroceLac®100 (ML)	
	RetaLac® (RL)	
	Cassava starch & HPMC (CSH)	
Binder concentration (Kollidon® 90F)	0%	**3**
	2%	
	5%	
Lubricant concentration (Magnesium Stearate)	0.5%	**2**
	1%	

Table 3.5 illustrates the factorial design with the different formulations for direct compression of both powder mixtures and bead formulations prepared from the different powder mixtures. In the interest of uncomplicated referencing, acronyms were assigned to each formulation indicating the filler type and concentrations of the binder and lubricant incorporated. For example, 0.5CL5 signifies 0.5% w/w magnesium stearate (lubricant) with CombiLac® as filler

and 5% w/w Kollidon® 90F (binder). Likewise, 1CS2 indicates 1% w/w magnesium stearate that was combined with Cassava starch/HPMC and 2% w/w Kollidon® 90F in order to produce both a physical mixture and a bead formulation.

Table 3.5: *Factorial design illustrating the powder mixtures.*

				Filler type:				
				CombiLac®	**MicroceLac® 100**	**RetaLac®**	**Pharmacel® 101**	**Cassava starch / HPMC**
Magnesium stearate (% w/w)	**0.5**	**Kollidon® 90F (% w/w)**	**0**	0.5CL0	0.5ML0	0.5RL0	0.5PC0	0.5CS0
			2	0.5CL2	0.5ML2	0.5RL2	0.5PC2	0.5CS2
			5	0.5CL5	0.5ML5	0.5RL5	0.5PC5	0.5CS5
	1.0		**0**	1CL0	1ML0	1RL0	1PC0	1CS0
			2	1CL2	1ML2	1RL2	1PC2	1CS2
			5	1CL5	1ML5	1RL5	1PC5	1CS5

3.6.2 Preparation of powder mixtures and beads for direct compression

As discussed in the factorial design, powder mixtures were prepared containing one filler and also a predetermined concentration of both the lubricant and the binder in order to determine the optimum formula for further testing. Powder mixtures and beads prepared from abovementioned mixtures, were prepared according to Table 3.5. The powder mixtures were prepared using the same steps and techniques as described in section 3.3.1. The beads that were used to produce tablets were formed using the same steps and techniques as described in section 3.3.2, with the only difference being that the binder was dissolved in the binder liquid.

3.6.3 Direct compression into tablets

These mixtures were compressed into 9 mm concave tablets, with a weight of approximately 300 mg, using a Korsch® XP1 single station tablet press (Korsch®, Germany). The compression force was adjusted for each formula to the point that the tablets could be handled and tested with ease.

3.7 Evaluation of Tablets

To ensure that an objective scale for evaluation was used throughout the process, all the tablets were evaluated using the criteria set for conventional tablets found in the BP (2016).

The tablets were then compared objectively and the optimum formulation was chosen with regards to the concentration of the binder and the lubricant.

3.7.1 Tablet Weight Uniformity

Tablet weight variation is a fundamental limitation and plays a critical part in influencing the drug content uniformity in tablet formulations. A large variation in tablet weight is a sign of poor or fluctuating flow properties. In this study the objective was to keep the weight of the different tablets constant at approximately 300 mg per tablet. The BP requirement in Appendix XII C for tablets having an average mass of 250 mg or higher, is that not more than 2 tablets may deviate in the set weight with more than 5% from the mean tablet weight (BP, 2016). Therefore, to determine tablet weight variation of the different formulations, 20 randomly selected tablets from each formulation were individually dusted and weighed using a Mettler Toledo® balance (Mettler, Germany, Model MS205DU). The average mass, standard deviation (SD) and percentage standard deviation (%RSD) of the tablets were subsequently calculated and assessed.

3.7.2 Friability

Friability of both the beads and the tablets were tested (BP, 2016). Ten tablets were dusted to remove loose, excess powder and were weighed (M1) and placed in the friabilator (ERWEKA® GmbH, Heusenstamm, Germany). The friabilator was set to rotate at 25 rpm for 4 min (to total 100 revolutions). The tablets were then removed and dusted and weighed (M2) again after completion of the test. Friability testing on the beads was done in accordance with the BP (2016) Appendix XVII G, wherein 10 g of the beads was transferred to a glass container after being sieved to remove fine powder and oscillated for 100 oscillations. After oscillation, the beads were sieved once more using the same sieve and then weighed. The experiment was done in triplicate to determine the mean friability value (%F) using Equation 3.17:

$$\%F = \frac{M_1 - M_2}{M_1} \times 100 \qquad \textbf{[3.17]}$$

3.7.3 Tablet Hardness and Tensile Strength

Crushing strength, otherwise known as tablet hardness, diameter and thickness were assessed using a PharmaTest® tablet test unit (model PTB-311, Switzerland). Samples of 10 randomly selected tablets from each formulation were compressed at a rate of 0.1 cm.min^{-1} to measure the diameter (D), thickness (H) and hardness (F) of the tablets. The average standard deviation (SD) and percentage standard deviation (%RSD) were consequently calculated. To be able to compare tablet hardness of the different formulations, the geometry of the tablets need to be taken into account, therefore, the tensile strength (σ_x) was calculated utilising Equation 3.18:

$$\sigma_x = \left(\frac{10F}{\pi D^2}\right)\left[\left(\frac{2.84H}{D}\right) - \left(\frac{0.126H}{W}\right) + \left(\frac{3.15W}{D}\right) + 0.01\right]^{-1} \qquad \textbf{[3.18]}$$

Where, σ_x, is the tensile strength ($N.mm^{-1}$); F, is the crushing strength/hardness (N); D, is the diameter (mm); H, is the tablet thickness (mm); and, W, is the centre cylinder thickness measured in millimetres (Viljoen *et al.,* 2014).

3.7.4 Disintegration

The BP (Appendix XII A) sets certain standards for disintegration of conventional tablets namely, 6 tablets should fully disintegrate within 15 min in a disintegration bath filled with water and maintained at a temperature of 37 ± 0.5°C (BP, 2016). As this study attempted to manufacture a multiple-unit sustained/modified release dosage form, it was decided that the tablets had to remain intact for at least 15 min in order to possibly accomplish modified/delayed release.

Disintegration of the various tablet formulations was evaluated using a basket-rack assembly disintegration type II apparatus (Erweka® model D-63150, Heusenstamm, Germany). The apparatus contains 6 baskets that are mechanically raised and lowered in a water bath containing distilled water and that is maintained at 37°C (± 2°C). The disintegration time of each of the 6 randomly selected tablets was documented upon complete disintegration, or the test was stopped after 15 min and the mean disintegration time calculated.

3.7.5 Determination of optimum tablet formulations

After initial testing, all the tablets, produced using the factorial design, were compared with regards to the results obtained from the different tests performed as explained in sections 3.7.1 – 3.7.4. From these results, the most optimum formulations were selected in terms of the concentration of both the binder and the lubricant incorporated. Following, these formulations were again mixed, and either directly tableted (powder tablets), or beads were formed and then tableted (bead tablets). The subsequent beads and tablets were subjected to further testing.

3.7.6 Percentage Swelling and Erosion

Swelling and erosion of the final selected beads, powder tablets and bead tablet formulations were conducted according to a method previously published by Singh *et al.* (2009). A sample of a single tablet or 300 mg of beads was weighed and introduced into a type II Erweka Dissolution Bath basket system (ERWEKA® GmbH, Heusenstamm, Germany) under standard BP (2016) conditions (37 ±0.5°C). All swelling and erosion tests were done in triplicate. The baskets containing the individual tablets or beads were again weighed and the initial weight (T) recorded. At predetermined times intervals (2, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150 min), or once the samples were fully disintegrated, the dissolution apparatus was stopped and the basket was blotted with filter paper. It was weighed again and this measurement was noted as the swollen weight (S). Measurements were taken until the tablets completely disintegrated or the weight remained constant for 3 consecutive measurements. After completion, the swollen samples were dried in an EcoTherm Labotec oven at 40°C until no further loss in weight was measured. This weight was noted as the final mass to determine if any erosion occurred (BP, British Pharmacopoeia, 2015). The percentage swelling and percentage erosion of the samples were calculated according to the following equations:

$$\%\text{Swelling} = \frac{S}{T} \times 100 \qquad \textbf{[3.20]}$$

$$\%\text{Erosion} = \frac{T - R}{T} \times 100 \qquad \textbf{[3.21]}$$

Where, T, is the initial mass (g); S, is the swollen weight (g); and, R, is the mass after erosion (g).

3.7.7 Morphology

The morphological features of the various powders, beads and tablets were evaluated using a scanning electron microscope. Different samples were each mounted onto a metal disc with a silicon adhesive and the samples were coated with a thin gold and palladium layer (66:34) mixture under a vacuum of 1.5 torr in an Eiko® ion coater (model IB-2, Eiko engineering, Japan). The sample surfaces and internal structures were inspected by means of scanning electron microscopy using a FEI Quanta® 250 Environmental Scanning Electron Microscope with a Field Emission Gun (FEI, Quanta® 250, Netherlands). Micrographs of the outer surfaces and inner structures of the different samples were taken at 75X - 1000X magnification to inspect the morphological features (Ibrahim, 2012).

3.7.8 Assay to Determine Drug Content

An assay was conducted on the bead, powder tablet and bead tablet formulations according to the BP (2016) criteria. Twenty tablets from each formulation was crushed in a mortar and pestle; 100 mg of the subsequent powder (or beads) was dispersed in 100 ml ethanol and made up to volume (500 ml) using 0.2 M Na_3PO_4. The dispersion was stirred for 4 h and ultra-sonicated in a Labotec EcoBath® (model 103, Labotec, South Africa) for 30 min. Samples were withdrawn and filtered through a 450 nm Millipore® filter that was attached to a syringe. The gliclazide content was determined by measuring the absorbance of the different solutions with a Shimadzu UV spectrophotometer (model UV-1700, Shimadzu Corporation©, Kyoto, Japan). Gliclazide absorbance was measured at 231 nm; followed by calculation of the drug content. This gliclazide concentration calculated was taken as the experimental value which was compared to the theoretical gliclazide amount initially weighed using Equation 3.22.

$$\%\,\text{Content} = \left(\frac{\text{Experimental value of gliclazide content}}{\text{Theoretical value of gliclazide content}} \right) \times 100 \qquad \textbf{[3.22]}$$

3.7.9 Dissolution Studies

Drug release or dissolution studies were performed in six-fold at 37 ± 0.5°C on a type II apparatus Distek® dissolution system (2501049, Distek® Inc., North Brunswick, New Jersey, USA), which was connected to the Distek® Evolution 4300 auto sampler (4301920) together with a Distek syringe pump (SP02716) and set to a paddle speed of 50 rpm. All dissolutions were conducted in 600 ml of 0.1 M HCl (pH 1.2) for the first 2 h, after which 300 ml of Na_3PO_4 was added, and the pH of the solution was adjusted to 6.8 using either 2 M HCl or 2 M NaOH, for the remaining 10 h.

As soon as the desired rotational speed was reached by the motor, the samples were introduced into the medium at time zero (t = 0). A total of 6 tablets were randomly selected from each formulation and tested. Aliquots of 5 ml were periodically withdrawn at 2, 5, 10, 15, 30, 60, 90, 120, 150, 180, 240, 300, 390, 480, 600 and 720 min and immediately replaced with fresh preheated dissolution medium. After withdrawal of the last sample, the paddle speed was increased to 250 rpm for 15 min to ensure maximum drug release, and the final sample, known as the infinity sample, was collected. Samples were filtered through a 0.45 µm Millipore® filter unit attached to a syringe and consequently spectrophotometrically analysed at 321 nm (BP, 2016; Jamadar *et al.,* 2011).

3.8 Ultraviolet Spectrophotometric Analysis of Gliclazide

The gliclazide concentrations in the different samples collected from the assay and dissolution studies were measured in triplicate using an Analytikjena® UV-spectrophotometer (Speccord® 200 Plus, Jena, Germany), fitted with a super sipper and a 1 cm^3 flow-through quartz cell. During the dissolution studies hydrochloric acid (0.1 M, pH 1.2) was used as a blank reference for samples taken in the first 2 h and a 2:1 HCl: Na_3PO_4 (pH 6.8) mixture was utilised as a blank reference for the remaining samples. For the assay, hydrochloric acid (0.1 M, pH 1.2) and a 2:1 HCl: Na_3PO_4 (pH 6.8) was utilised as blank references.

3.8.1 Absorbance Wavelength

The absorbance maxima for gliclazide was determined using the spectral scan feature of the Speccord® 200. According to Jamadar *et al.* (2011) the optimum absorbance for gliclazide is obtained at 229.5 nm, however, through preliminary experiments, it was established that peak absorbance of ultraviolet light for gliclazide occurs at a wavelength of 231 nm in both the acidic as well as the buffered media.

3.8.2 Preparation of stock solutions containing gliclazide

In order to accurately determine the concentrations of gliclazide, stock solutions of known concentrations in both acidic and buffer mediums needed to be prepared and analysed. Approximately 50 mg gliclazide was precisely weighed and accurately transferred to a 500 ml A-grade volumetric flask. To aid in dissolving the gliclazide, 100 ml ethanol was first added to the volumetric flask. The stock solution was made up to volume using either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) to yield an end gliclazide concentration of 100 µg/ml. Thus, two stock solutions were prepared, one containing an acidic medium and the other a buffer medium and therefore two standard curves were plotted prior to each dissolution test. The following dilutions were made from the stock solution using A- grade pipettes:

- 5 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 250 ml A-grade volumetric flask, yielding a gliclazide concentration of 2 µg/ml.

- 5 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 5 µg/ml.
- 10 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 10 µg/ml.
- 15 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 15 µg/ml.
- 20 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 20 µg/ml.
- 25 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 25 µg/ml.
- 15 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 50 ml A-grade volumetric flask, yielding a gliclazide concentration of 30 µg/ml.
- 35 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 100 ml A-grade volumetric flask, yielding a gliclazide concentration of 35 µg/ml.
- 20 ml of the stock solution was withdrawn and filled up to volume with either 0.1 M HCl (pH 1.2) or a 0.1 M HCl: 0.2 M Na_3PO_4 mixture in a 2:3 ratio (pH 6.8) in a 50 ml A-grade volumetric flask, yielding a gliclazide concentration of 40 µg/ml.

3.8.2.1 Construction of standard curve

Standard curves were constructed prior to each assay or dissolution study in both of the dissolution media. The stock solution and dilution samples (2–40 µg/ml) were prepared as described in the previous section. For each dilution sample containing gliclazide, the UV-absorbance was measured in triplicate at 231 nm in the acidic media and buffered media, respectively. The mean UV absorbance values were subsequently plotted against the concentrations in each phase and a linear regression analysis was conducted on each curve. Analysis of this data produced a straight line through the measured values (as coordinates). All of the standard curves obeyed the principles of Beer's law in the concentration range that was applied and outstanding correlation coefficients were attained (R^2 Ó0.999 was considered satisfactory). In order to calculate the gliclazide concentration in solution for each formulation, the y-interception (c) and the slope (m) of the curves were obtained by regression as additional parameters.

3.9 Statistical Data Analysis

From the dissolution data collected, the parameters described below were calculated utilising Microsoft® Excel ™ 2010 for Windows ™ (Microsoft ® Corporation, Seattle, Washington, USA). Where necessary, the collected data was furthermore statistically analysed by means of a one way analysis of variance (ANOVA) at the 5% level of confidence to indicate significant differences ($p < 0.05$).

3.9.1 Mean dissolution time

The mean dissolution time (MDT) is a statistical moment for the cumulative dissolution process and provides an accurate drug release rate. This parameter reveals the drug-release process with higher values indicating higher drug retarding ability of the formulation (Vueba *et al.*, 2004). The MDT-value of each selected formulation was calculated according to Equation 3.23 (Reppas & Nicolaides, 2000; Sousa *et al.*, 2002).

$$MDT = \frac{\sum_{j=1}^{n} t_{mid} \Delta x_d}{\sum_{j=1}^{n} \Delta x_d} \qquad \textbf{[3.23]}$$

Where, j, is the sample number; n, is the total number of sample times; t_{mid}, is the midpoint time between j and (j-1); and, φx_d, is the additional mass of drug dissolved between j and (j-1) (Costa & Lobo, 2001).

3.9.2 Fit Factors

The fit factors also known as the difference and similarity factors, f_1 and f_2, are equational tools respectively used to equate the difference and similarity of dissolution profiles of test formulations with that of a reference formulation. The difference factor, f_1, approximates the percentage error between two curves over all time points where 0 signifies identical curves and the value increases as the dissimilarity between the two profiles increases. Values Ò15 for f_1 specifies that the dissolution profiles are similar. The similarity factor, f_2, is a logarithmic transformation of the sum of squared error. This factor takes the average sums of squares of the difference between the test and reference dissolution profiles and fits the result between 0 and 100. If the test and reference profiles are identical, f_2 has a value of 100; and approaches zero as the dissimilarity increases. Thus, for the dissolution profiles to be relatively similar, a value of f_2 must be Ó50 (Costa & Lobo, 2001). Equations 3.24 and 3.25 represent the fit factors, f_1 and f_2, respectively.

$$f_1 = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} \left(R_j + T_j \right) / 2} \times 100 \qquad \textbf{[3.24]}$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(1/n \right) \sum_{j=1}^{n} \left| R_j - T_j \right|^2 \right]^{-0.5} \times 100 \right\} \qquad \textbf{[3.25]}$$

Where, R_j, is the reference assay at time point, t. T_j, is the test assay at time point, t; and, n, is the number of pull points (Moore & Flanner, 1996).

* * *

Chapter 4:
RESULTS AND DISCUSSION

4.1 Introduction

This chapter is set to provide details regarding obtained results that were processed and interpreted. Concisely, gliclazide, and a variety of fillers (CombiLac®, MicroceLac® 100, RetaLac®, Pharmacel® 101 and Cassava starch/HPMC), were characterised regarding its powder flow by utilising the SeDeM Diagram Expert System to obtain a profile of the physical properties, flow properties, and its suitability for direct compression. The profile also provides a layout of each powder’s strengths and weaknesses, and how to correct for weaknesses using corrective excipients (Aguilar-Diaz *et al.*, 2014; Khan *et al.*, 2013; Suñé-Negre *et al.*, 2011a).

In order to be able to determine the most acceptable formulation(s) for tablets containing gliclazide a full factorial design was implemented to accommodate the recommendations made by the SeDeM Diagram Expert System. A full factorial design was implemented due to the fact that no substantial excipient physicochemical characteristics, when incorporated into sustained release beads, are available yet.

The powder mixtures, containing different concentrations of a binder, lubricant and gliclazide, were tableted and subsequently tested according to the British Pharmacopoeia criteria, in terms of morphology, mass variation, crushing strength and disintegration. Once tablet formulations that adhered to all the standards set were identified, these selected tablet formulations were subjected to additional tablet tests. These formulations were tested for swelling and erosion, after which the drug release profile was characterised for each formulation. The formulation that depicted the most sustained gliclazide release as well as adhered to all the physical criteria, is considered the most optimal formulation.

4.2 Evaluation of powder and bead flow properties

4.2.1 Particle size analysis and morphology

Powder flowability is subjective to various factors including particle size; particle size distribution; and particle shape. As the particle size of a powder increases, gravity and momentum similarly increase, thus surpassing the inter-particular adhesion forces present between the individual particles. Powder flow is then enhanced as a result (Li *et al.*, 2004b). Hence, in order to promote the optimum flowability of a powder, an increase in particle size and reduction in the particle size distribution should be considered (Li *et al.*, 2004b).

Powder samples from gliclazide, each filler (CombiLac$^{®}$, MicroceLac$^{®}$ 100, RetaLac$^{®}$, Pharmacel$^{®}$ 101 and Cassava starch/HPMC), as well as the beads produced from the fillers (as described in section 3.3.2), with and without 10% w/w gliclazide, were analysed in terms of particle size and particle size distribution using a Malvern$^{®}$ Mastersizer-2000 (Malvern Instruments Ltd$^{®}$, UK) as described in section 3.4.5. Results obtained are tabulated in Table 4.1 and raw data on each sample can be found in Annexure B. From Table 4.1, it is clear that gliclazide has an extremely small particle size relative to the other powders, averaging 45.913 εm, which can lend itself to weak powder flow, because of increased inter-particle attraction forces. CombiLac$^{®}$ powder, whether pure or mixed with gliclazide, displayed the most optimum span regarding particle size distribution, i.e. have the most uniform particle size compared to the other fillers tested. The cassava starch/HPMC mixture (with or without gliclazide), on the other hand, has the widest span with a mostly negative skew particle size distribution (relatively more larger particles compared to smaller particles). Though, all of the tested powders could be considered as having a negatively skewed particle size distribution. Overall, the RetaLac$^{®}$ powder depicted the largest particles size, followed by CombiLac$^{®}$, MicroceLac$^{®}$, Pharmacel$^{®}$ 101, and Cassava starch/HPMC. This trend was also observed once gliclazide was added to the different fillers. Interesting to note is that once gliclazide was added to the different fillers, the span of CombiLac$^{®}$ and MicroceLac$^{®}$ decreased, thus implicating that powder flow would probably be improved if only considering particle size. Generally, the particle size distribution of the bead formulations are more uniform than the corresponding powders as indicated by the decrease in span. The Cassava starch/HPMC mixtures (with or without gliclazide) formed the largest beads, whereas the smallest beads were produced by the gliclazide/RetaLac$^{®}$ powder mixture. Thus, hypothetically the flowability of the fillers was improved by the construction of the corresponding bead formulations due to the increase in the mean particle sizes as well as a decrease in the size distribution (i.e. span values). If only considering particle size and size distribution, the Cassava starch/HPMC bead formulations will probably depict the highest flowability, followed by Pharmacel® 101 beads, MicroceLac® beads, CombiLac® beads, and lastly, RetaLac® beads.

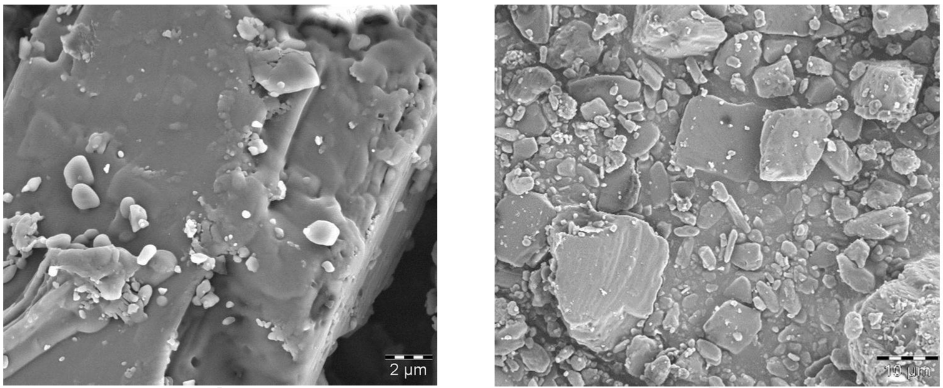
Table 4.1: *Average size, span and the dispersion media of the tested powders and beads*

Powder tested	Form tested	Ave. Size (µm)	Span	Dispersion Media
Gliclazide	Powder	45.913	2.670	Water
CombiLac®	Powder	193.748	1.422	Cyclohexane
	API* Powder	185.825	1.414	
	Beads	858.699	1.113	
	API* Beads	981.811	0.936	
MicroceLac® 100	Powder	174.850	1.655	Cyclohexane
	API* Powder	177.343	1.579	
	Beads	896.752	0.745	
	API* Beads	902.091	1.202	
RetaLac®	Powder	216.485	1.600	Cyclohexane
	API* Powder	230.745	1.625	
	Beads	889.241	0.781	
	API* Beads	875.734	1.035	
Pharmacel® 101	Powder	74.726	1.717	Ethanol
	API* Powder	70.602	1.999	
	Beads	959.567	0.927	
	API* Beads	1024.894	0.643	
Cassava starch/ HPMC	Powder	50.139	2.761	Ethanol
	API* Powder	52.405	2.888	
	Beads	1032.623	0.700	
	API* Beads	1041.870	0.955	

*****API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

However, when studying powder flowability, one cannot disregard particle shape as the shape of a particle directly influences the flowability of a powder (Wong & Pipel, 1990). Therefore, examination of the morphological features of the selected powders and the bead formulations were conducted using a scanning electron microscope. Electron-micrographs were taken at different magnifications that ranged between 130X and 1 000X due to the substantial variation in size of the different formulations studied.

Upon inspection of the morphology of gliclazide, it was clear that gliclazide does not only have small particles, but these particles are furthermore rather flat and geometrically shaped. In Figure 4.1 gliclazide particles depicted, are relatively small, ranging mostly from 10 εm ï 40 εm that allow for maximum inter-particular attraction forces (Nyström *et al.*, 1993), thus indicating that according to shape, gliclazide particles will portray rather poor flowability.



A **B**

Figure 4.1: *SEM micrographs of gliclazide at A) 1000X magnification and at A) 800X magnification*

Figure 4.2 presents SEM micrographs taken from the different selected filler powders. Comparing the different filler powders, it is rather clear that the Cassava starch/HPMC mixture (Figure 4.2E) has significantly smaller particles, followed by Pharmacel® 101 (Figure 4.2D). Cassava starch/HPMC shows elongated HPMC particles as well as smaller clusters of starch particles. The clusters tend to be rounder which generally enhances flowability in comparison to the elongated particle shape of HPMC. Due to the small size of the starch particles, inter-particle attraction forces will be higher, which will probably lead to an overall noteworthy decrease in the quality of flow of this powder mixture (Nyström *et al.*, 2008). Pharmacel® 101 powder, on the other hand, displays a more relatively sharp edged, elongated particle shape that will most likely exhibit poor powder flow (Horio *et al.*, 2014; Chatlapalli & Rohera, 1998; Hickey & Concessio, 1997). This negative property will possibly influence consistent dye filling during tableting (Wu *et al.*, 2003). However, studying Figure 4.2, the flowability of Pharmacel® 101 will probably be more increased compared to the Cassava starch/HPMC mixture.

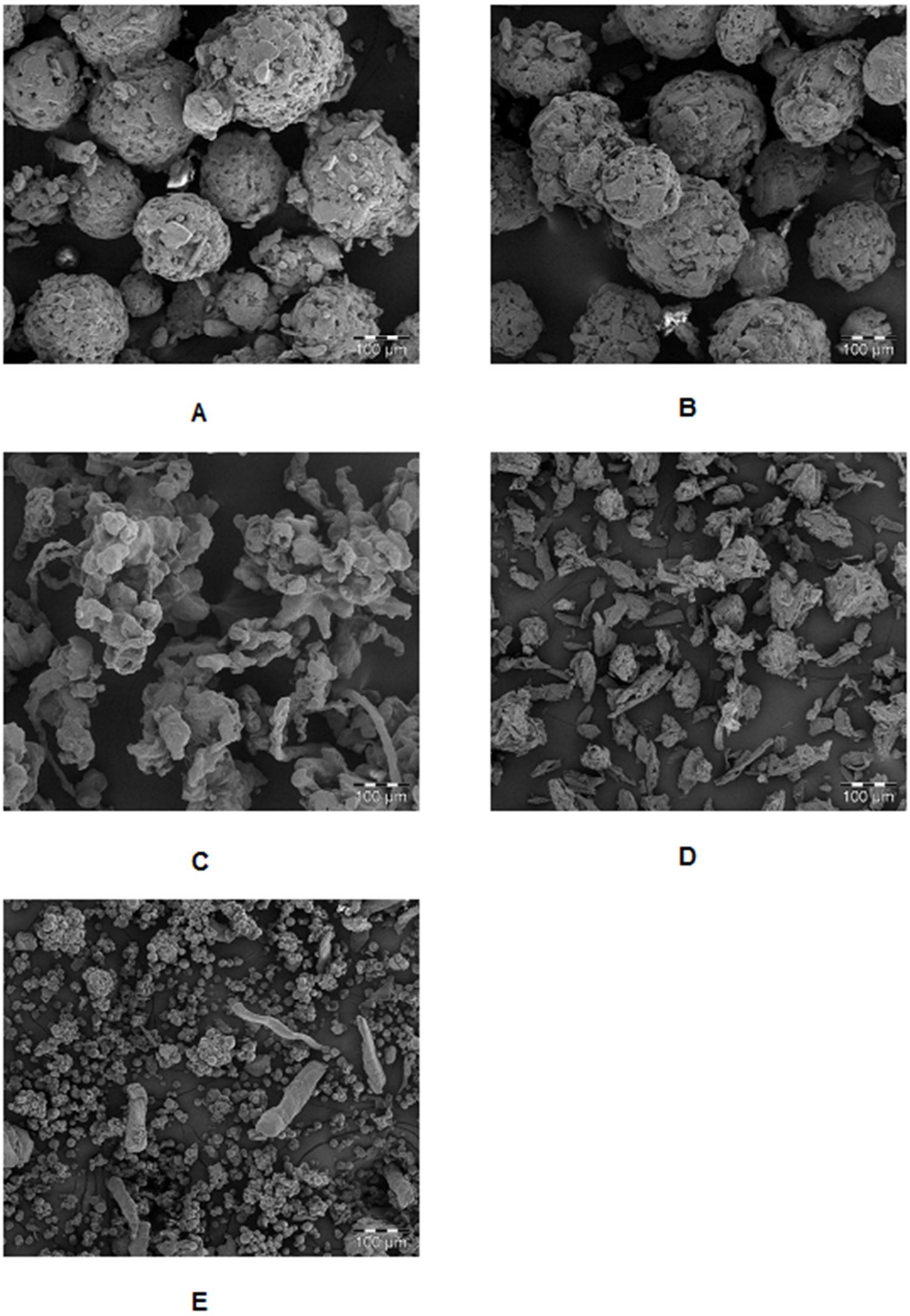


Figure 4.2: *SEM micrographs of powder samples of A) CombiLac®, B) MicroceLac® 100, C) RetaLac®, D) Pharmacel® 101 and E) Cassava Starch/HPMC taken at 700X magnification.*

RetaLac® (Figure 4.2C) illustrates relatively larger particles compared to both Pharmacel® 101 and the Cassava starch/HPMC mixture. These particles are relatively porous, elongated and irregular structured. RetaLac® is a co-processed excipient consisting of equal parts hypromellose and milled Ŭ-lactose monohydrate that are responsible for the particle shape. This filler was designed to exhibit improved flowability and bendability. Meggle (2014c) furthermore stated that enhanced compactibility occurs due to the brittle and plastic fracture deformation properties present, which additionally provide a platform to modify drug release.

CombiLac® (Figure 4.2A) and MicroceLac® (Figure 4.2B) have more similarly shaped particles (relatively spherical agglomerates), however, as confirmed with particles size analysis, the CombiLac® powder comprises relatively larger, more uniform agglomerates compared to the MicroceLac® powder. These two fillers will probably display better flow properties compared to the other fillers due to their shape and size (Horio *et al.*, 2014). CombiLac® is a high-functionality, co-processed ternary admixture consisting of Ŭ-lactose monohydrate (70%), microcrystalline cellulose (20%) and white native corn starch (10%). The three individual components are integrated into a mono-particulate structure that cannot be physically separated. According to Meggle (2014a) this filler was designed to improve flowability in such a way that dosage form weight uniformity and throughput during direct compression are enhanced. The spherical shape of MicroceLac® 100 particles is due to the co-spray-drying production process utilising 75% Ŭ-lactose monohydrate and 25% microcrystalline cellulose. A mono-particulate powder with dual compaction mechanisms (i.e. brittle fracture and plastic deformation) within the powder particles is produced by this means. Increased flowability is obtained, which is desirable, as improved flowability of the powder into the tablet press die not only causes a more homogenous distribution of ingredients throughout the tablets, but also improves compactibility. Tablets produced by means of direct compression that exhibited improved compactibility would generally display improved physical tablet properties (Li *et al.*, 2008).

Figure 4.3 portrays the SEM micrographs (130X) taken from the different bead formulations produced from the selected fillers by means of extrusion-spheronisation, either without gliclazide or with the addition of the drug. Rows Aï E present the different fillers researched whereas the columns display the beads containing no gliclazide (column I and II) and beads where 10% w/w gliclazide was incorporated (column III and IV). Columns I and III shows examples of the whole beads, whereas columns II and IV depict the internal structures of the corresponding beads.

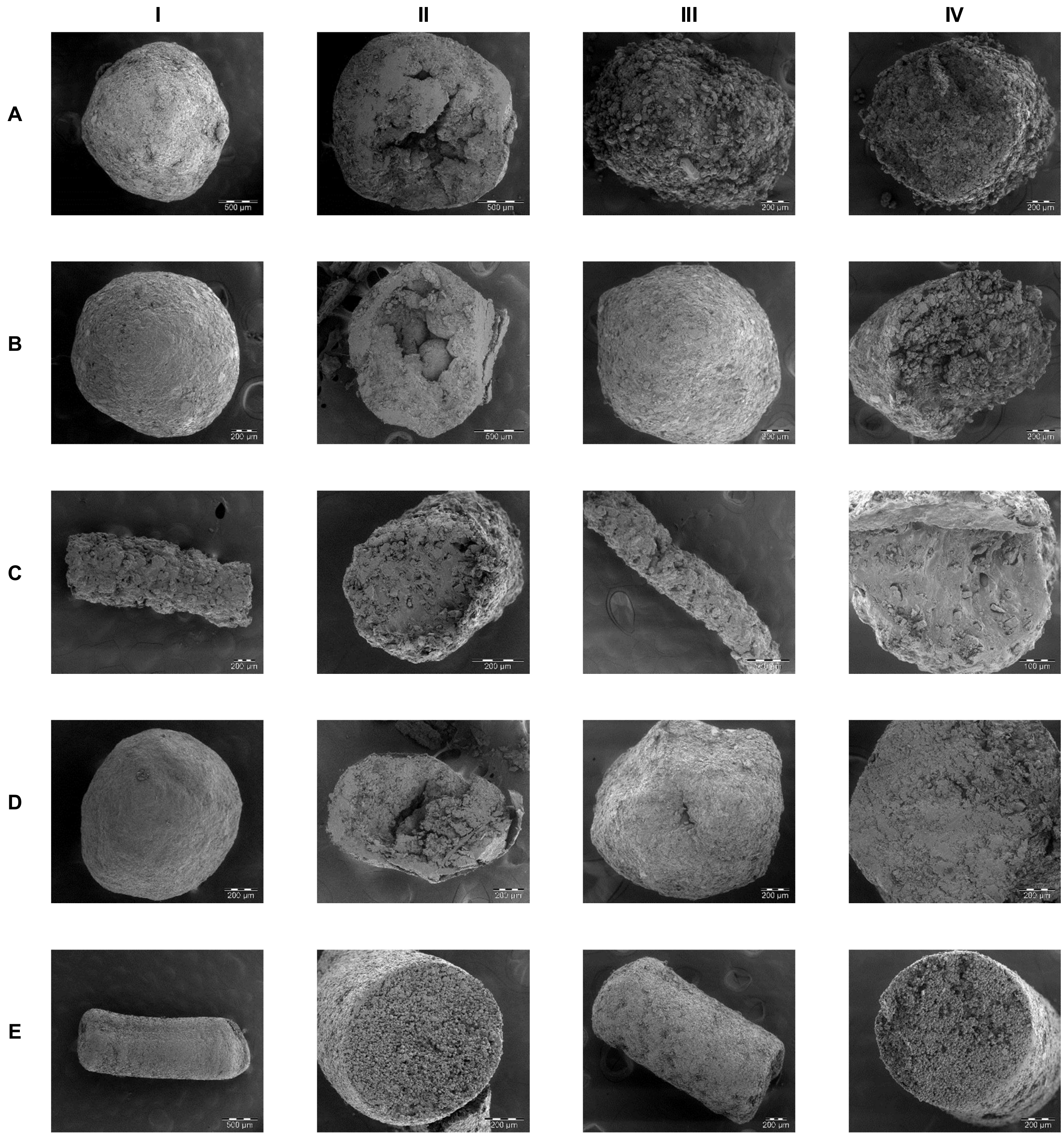


Figure 4.3: *SEM micrographs of A) CombiLac® powder, B) MicroceLac® 100, C) RetaLac®, D) Pharmacel® 101 and E) Cassava Starch/HPMC taken at 130X magnification showing I) whole beads, II) cross section micrographs of the beads, III) whole beads containing 10% w/w gliclazide and IV) cross section micrographs of beads containing 10% w/w gliclazide*

Visible differences could be observed between the various bead formulations. The CombiLac®, MicroceLac®°100 and Pharmacel® 101 bead formulations appeared comparable in spherical shape, but differed somewhat in smoothness. Examining the filler beads (i.e. columns I and III), the Pharmacel® 101 beads display surfaces that are notably smoother compared to the MicroceLac®°100 (semi-smooth) and CombiLac® (relatively more crude) beads. The smoothness of bead surfaces might be directly correlated to the particle size of the starting material (i.e. the filler powder). Particle size would meaningfully affect the critical wetting liquid prerequisite for the specific filler powder; consequently prominently influencing the plasticity of the resulting wet mass, which in turn would have an effect on some physical properties of the beads, e.g. size, sphericity, and morphology (Chatlapalli & Rohera, 1998). The Pharmacel® 101 beads (with or without the inclusion of gliclazide) which were formed from particles with the smallest mean particle size compared to the MicroceLac®°100 and CombiLac® beads, yielded the smoothest beads, whereas the CombiLac® beads that were produced from the larger particles formed more robust and coarse beads.

Inspecting the internal structures of the different beads containing no gliclazide, prominent crevices could definitely be seen in the beads produced by the CombiLac® powder (Figure 4.2 A.II). These cracks may aid in water penetration which in turn will allow the beads to swell and eventually release the incorporated drug. The MicroceLac® 100 beads (Figure 4.3 B.II) also depicted large cavities. However, here bead-like particles can be observed inside the formed beads, which are particles that have not deformed during extrusion-spheronisation. Likewise, water will also be able to penetrate the internal structure of these beads, though, release of the drug might be more delayed due to the bead-like particles observed that tend to decrease the inter-particular spaces. The SEM micrograph of the internal structure of the Pharmacel® 101 bead (Figure 4.3 D.II), conversely depicted a deformed spherical bead (changed to more oval-shaped) with additional crevices and fibrous strands. This deformation occurred upon splitting the bead to view the internal structure, indicating that beads produced from Pharmacel® 101 are more brittle and tend to flake once pressure is exerted. Bashaiwoldu *et al.* (2004) described that the water retentive mechanism of microcrystalline cellulose was due to the fibrous, rubbery nature of this excipient, which physically entraps water within its intricate structure of varying capillaries and inner openings. These systems of fibrous, rubbery constituents form complex structural hindrances at molecular level within the capillaries of microcrystalline cellulose. These obstacles postpone the elimination of water from the beads during the drying stage of the manufacturing process of the beads, which subsequently lead to the formation of the various fissures. Once gliclazide was incorporated into the various bead formulations, it was evident that the CombiLac®, MicroceLac®°100 and Pharmacel® 101 bead formulations (Figure 4.3 A.IV; B.IV; and D.IV) are more densely compacted, still showing various voids and capillaries between the different particles. However, these cavities are significantly smaller in size.

Viewing the RetaLac® and Cassava starch/HPMC bead formulations (Figure 4.3 rows C and E), it is evident that these beads could not be spheronised. These beads, regardless the absence or presence of gliclazide, formed rod-like particles rather than spheres, which will have a negative effect on the flowability of the beads. The Cassava starch/HPMC beads have smoother outer surfaces and are comparatively larger in size. Both the RetaLac® and Cassava starch/HPMC bead formulations have internal openings, though relatively smaller when compared to the other bead formulations. Although the outer surface of RetaLac® seems porous, the internal structure appears more densely packed. It furthermore looks like some of the internal particles fused with one another, which might be the water-soluble hypromellose that formed solid-bridges during the drying process (Mount & Schwartz, 2008; Reynolds *et al.*, 2004; Chatlapalli & Rohera, 1998). Similarly, the internal surface of the Cassava starch/HPMC bead formulations displayed densely packed starch particles engulfed by evenly distributed HPMC that was spread in a web-like manner surrounding the starch particles. Upon addition of gliclazide to the Cassava starch/HPMC bead formulations, it is evident that the newly formed beads are more brittle compared to the beads that did not contain any gliclazide.

4.2.2 Analysis of powder and bead flowability

Flowability of gliclazide, the selected fillers and the different bead formulations, containing either no or 10% w/w gliclazide, were investigated utilising the following methods: Hausner ratio, Carrôs index, flow rate, angle of repose, and critical orifice diameter.

The prerequisites for evaluation of flow properties are presented in Table 4.2, which is adopted from the British Pharmacopeia (2016). Classes describing powder flowability range from extremely poor to excellent; with a value connected to each class to assist in the classification of every powder. For example, for a sample to be considered having excellent flowability, this sample should have a Carrôs Index value of Ó10, a Hausner Ratio of Ó1.11, and an angle of repose Ó30 (BP, 2016).

Table 4.2: *Prerequisite scale for flowability*

	Carr’s Index (%)	Hausner Ratio	Angle of Repose (°)
Excellent	1ï 10	1.00ï 1.11	25ï 30
Good	11ï 15	1.12ï 1.18	31ï 35
Fair	16ï 20	1.19ï 1.25	36ï 40
Passable	21ï 25	1.26ï 1.34	41ï 45
Poor	26ï 31	1.35ï 1.45	46ï 55
Very Poor	32ï 37	1.46ï 1.59	56ï 65
Extremely Poor	> 38	> 1.60	> 66

The average flow properties tested in this study for the various samples are displayed in Tables 4.3ï 4.8. From Table 4.3 it is evident that the gliclazide powder possesses extremely poor flowability due to the fact that the Hausner ratio was calculated as 1.607; the Carrôs index as, 37.774%, and the angle of repose was measured as 36.429°. Additionally, the flow rate of gliclazide could not be measured as the powder stuck to the surface of the apparatus.

Table 4.3: *Flow properties of gliclazide. (Percentage relative standard deviation indicated in parenthesis)*

	Gliclazide
Bulk Density (g/cm3)	0.403 (0.658)
Tapped Density (g/cm3)	0.648 (1.107)
Hausner Ratio	1.607 (1.062)
Carr's Index (%)	37.774 (7.214)
Flow Rate (g/s)	*NF**
Angle of Repose (°)	36.429 (3.343)
Critical Orifice Diameter (mm)	*NF**

NF: *NF (No Flow) indicates that the powder did not flow, and therefore no results could be observed*

Studying Tables 4.4ï 4.8, it can be postulated that generally the selected filler powders displayed poorer flowability compared to the bead formulations. Likewise, the inclusion of gliclazide, either into the powder mixtures or the bead formulations, influenced the flowability negatively. Overall, CombiLac® powder (with or without the addition of 10% w/w gliclazide) seemed to possess enhanced flowability, followed closely by MicroceLac® 100, compared to the other selected fillers. The Cassava starch/HPMC powders, on the other hand, displayed extremely poor flowability, which was confirmed by the fact that various tests could not be performed due to the inability of the powder to flow. The formation of beads rendered interesting results as beads consisting of MicroceLac® 100 depicted the most favourable flowability results; and RetaLac® beads portrayed substantially poorer flowability. A general rank order could be established between the bead formulations: MicroceLac® 100 >> Pharmacel® 101 > CombiLac® > Cassava starch/HPMC >> RetaLac®. These results are an indication that the particle size and shape do play a noteworthy role in the flowability of a sample.

Table 4.4 provides the results of the flow properties of the various CombiLac® formulations. From the results, it can be deduced that pure CombiLac® powder shows fair flow with regards to the obtained Hausner ratio and Carr's index values and falls within the excellent category for the angle of repose value obtained. After the addition of gliclazide, both the Hausner ratio and Carr's index values increased, thus, shifting flowability into the passable category. This is an indication that the presence of gliclazide has a negative influence on the flow properties of the powder mixture. Normally the formation of beads is a method employed to improve powder flow (Hou & Sun, 2008), which could clearly be seen once CombiLac® beads were manufactured from the individual powder formulations. All tests conducted on the different CombiLac® bead formulations indicated excellent powder flow, despite the addition of gliclazide to the beads. However, this addition did decrease the flow rate and increased the Hausner ratio, Carr's index and angle of repose values; though not to such an extent that the flowability of the beads could not be described as excellent.

Table 4.4: *Flow properties of gliclazide, CombiLac®, CombiLac® API powder, CombiLac® beads and CombiLac® API beads (Percentage relative standard deviation indicated in parenthesis)*

	CombiLac® Samples Tested			
	Powder	API* Powder	Beads	API* Beads
Bulk Density (g/cm3)	0.472 (0.770)	0.476 (0.777)	0.929 (1.917)	0.640 (1.093)
Tapped Density (g/cm3)	0.575 (0.938)	0.625 (1.020)	0.981 (2.402)	0.718 (0.679)
Hausner Ratio	1.218 (0.861)	1.313 (0.243)	1.056 (0.544)	1.122 (0.460)
Carrôs Index (%)	17.923 (3.955)	23.811 (0.777)	5.272 (9.819)	10.870 (3.776)
Flow Rate (g/s)	56.648 (5.067)	49.004 (3.642)	87.896 (9.078)	59.660 (1.715)
Angle of Repose (°)	19.307 (1.682)	27.356 (0.762)	19.733 (6.273)	21.481 (4.923)
Critical Orifice Diameter (mm)	1.5-3	1.5-3	8-12	8-12

***API**: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

Viewing results obtained for the MicroceLac® 100 powders and beads (Table 4.5) the same trend was followed as with the CombiLac® samples. All of the powder formulations show fair flow with regards to the Hausner ratio and Carrôs index values. The angle of repose values indicate excellent flow for both MicroceLac® 100 powders and bead formulations, irrespective of the inclusion of gliclazide. The formation of beads significantly improved flowability as the Hausner ratio and Carrôs index values for these beads indicate excellent flowability, with or without the addition of gliclazide. Remarkable to note is that the formation of beads increased the flow rate by approximately 25 g/s, whereas the addition of gliclazide to the MicroceLac® 100 powder decreased the flow rate by approximately 30 g/s. This is an indication that the addition of gliclazide has a more profound effect on flowability compared to the manufacturing of beads.

Table 4.5: *Flow properties of gliclazide, MicroceLac®, MicroceLac® API powder, MicroceLac® beads and MicroceLac® API beads (Percentage relative standard deviation indicated in parenthesis)*

	MicroceLac® 100 Samples Tested			
	Powder	API* Powder	Beads	API* Beads
Bulk Density (g/cm3)	0.510 (1.667)	0.505 (0.824)	0.874 (4.234)	0.763 (0.623)
Tapped Density (g/cm3)	0.625 (2.041)	0.633 (1.033)	0.907 (3.567)	0.804 (0.378)
Hausner Ratio	1.225 (1.909)	1.253 (0.208)	1.039 (1.019)	1.054 (0.730)
Carr's Index (%)	18.358 (8.433)	20.203 (0.824)	3.751 (26.015)	5.085 (13.563)
Flow Rate (g/s)	69.365 (3.436)	39.489 (1.955)	94.624 (5.420)	71.960 (1.539)
Angle of Repose (°)	16.886 (1.835)	27.282 (1.239)	16.733 (2.859)	18.293 (1.243)
Critical Orifice Diameter (mm)	1.5-3	1.5-3	8-12	8-12

*API: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

RetaLac® powder and all formulations thereof were analysed in terms of powder flow. These results are listed in Table 4.6. The Hausner ratio and the Carr's index values for both powder formulations (i.e. with and without gliclazide) are indicative of passable flowability, whereas these values rendered the RetaLac® bead formulations containing no gliclazide as exhibiting excellent flowability and beads containing gliclazide as having good flowability. As previously seen, gliclazide tends to have a negative impact on the flow of the formulations, and a similar trend was followed with RetaLac®/gliclazide beads. The values showed a decrease in flow properties from the RetaLac® beads, yet still improved upon the values of the powder formulations. Contrary to what occurred with the MicroceLac® 100 formulations, the addition of gliclazide did not impact the flowability of the RetaLac® formulations to the same extent.

However, the production of beads depicted a more substantial effect. The inclusion of gliclazide into the bead formulation displayed the most significant change (negative) in flowability. Furthermore, it can be noted that the formation of RetaLac® beads did not increase the flow rate, but rather displayed a negative impact, especially after the inclusion of gliclazide to the bead formulations.

Table 4.6: *Flow properties of gliclazide, RetaLac®, RetaLac® API powder, RetaLac® beads and RetaLac® API beads (Percentage relative standard deviation indicated in parenthesis)*

	RetaLac® Samples Tested			
	Powder	API* Powder	Beads	API* Beads
Bulk Density (g/cm3)	0.341 (1.151)	0.357 (0.583)	0.486 (1.359)	0.411 (1.029)
Tapped Density (g/cm3)	0.436 (0.412)	0.476 (0.777)	0.517 (1.296)	0.473 (0.886)
Hausner Ratio	1.279 (0.920)	1.333 (0.194)	1.066 (0.933)	1.151 (0.685)
Carr's Index (%)	21.810 (3.280)	25.001 (0.583)	6.144 (14.351)	13.148 (4.516)
Flow Rate (g/s)	45.690 (2.462)	38.468 (0.972)	41.113 (2.034)	7.126 (0.617)
Angle of Repose (°)	26.868 (3.191)	28.468 (0.492)	28.300 (0.763)	36.753 (2.252)
Critical Orifice Diameter (mm)	3-8	3-8	8-12	8-12

***API**: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

Table 4.7 summarizes the results obtained from evaluation of Pharmacel® 101 and the various formulations thereof. From this table it is clear that there was no significant change in the flowability after adding gliclazide to either the powder or bead formulations. Again the formation of beads promoted the Pharmacel® 101 formulations from having passable flowability to excellent. This can also be concluded from the flow rate values as the flow rate increase by approximately 59 g/s. On the other hand, the inclusion of gliclazide did not have the same effect on the flow rate (±15 g/s slower).

Table 4.7: *Flow properties of gliclazide, Pharmacel$^{®}$ 101, Pharmacel$^{®}$ 101 API powder, Pharmacel$^{®}$ 101 beads and Pharmacel$^{®}$ 101 API beads (Percentage relative standard deviation indicated in parenthesis)*

	Pharmacel$^{®}$ 101 Samples Tested			
	Powder	API* Powder	Beads	API* Beads
Bulk Density (g/cm3)	0.345 (1.476)	0.364 (1.484)	0.721 (1.373)	0.711 (0.667)
Tapped Density (g/cm3)	0.460 (1.152)	0.476 (1.944)	0.743 (1.414)	0.754 (0.707)
Hausner Ratio	1.335 (2.568)	1.310 (0.459)	1.030 (0.040)	1.060 (1.192)
Carr's Index (%)	25.030 (7.555)	23.642 (1.484)	2.885 (1.373)	5.681 (19.814)
Flow Rate (g/s)	23.640 (3.986)	8.848 (1.969)	82.587 (4.469)	58.274 (1.911)
Angle of Repose (°)	27.144 (3.014)	25.125 (0.788)	16.067 (7.249)	18.385 (2.857)
Critical Orifice Diameter (mm)	8-12 (0)	8-12 (0)	8-12 (0)	8-12 (0)

***API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

As previously stated, Cassava starch/HPMC powder mixture exhibited the most unacceptable powder flow properties of the tested fillers. Overall, the powder formulations (Table 4.8) depicted fair flow and the bead formulations displayed excellent flowability. The addition of gliclazide furthermore showed nearly no significant change in the flowability of the respective formulations. This may be due to the particle size of gliclazide being of similar size to that of the Cassava starch. These inadequate flow properties of the powders may be attributed to two factors. First, the small size of the starch particles may contribute to increased inter-particulate attraction forces due to an increased surface area, and secondly, the shape of the

HPMC particles may donate to interlocking. Both these factors can be visibly seen in Figure 4.2E. After manufacturing beads, flow properties drastically improved to a level where it can be classified as having excellent flow.

Table 4.8: *Flow properties of gliclazide, Cassava Starch/HPMC, Cassava Starch/ HPMC API powder, Cassava Starch/HPMC beads and Cassava Starch/ HPMC API beads (Percentage relative standard deviation indicated in parenthesis)*

	Cassava Starch/HPMC Samples Tested			
	Powder	API* Powder	Beads	API* Beads
Bulk Density (g/cm3)	0.495 (0.808)	0.481 (0.785)	0.667 (0.084)	0.623 (1.543)
Tapped Density (g/cm3)	0.617 (1.008)	0.595 (0.972)	0.711 (0.667)	0.662 (0.930)
Hausner Ratio	1.247 (1.042)	1.238 (0.186)	1.066 (0.667)	1.064 (2.332)
Carr's Index (%)	19.790 (7.362)	19.232 (0.785)	6.222 (10.101)	5.984 (36.786)
Flow Rate (g/s)	*NF**	*NF**	75.233 (2.457)	52.369 (1.552)
Angle of Repose (°)	39.580 (3.081)	41.770 (0.549)	18.667 (2.201)	25.780 (2.014)
Critical Orifice Diameter (mm)	*NF**	*NF**	8-12	8-12

****API***: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

****NF***: *NF (No Flow) indicates that the powder did not flow, and therefore no results could be observed*

4.3 Characterisation of gliclazide and selected fillers as per SeDeM Diagram Expert System

4.3.1 Evaluation of gliclazide powder as per SeDeM Diagram Expert System

The SeDeM Diagram Expert System was employed to analyse a 100 g gliclazide powder sample, which depicted notably small particles with a relatively narrow particle size distribution as established in the previous section (Table 4.1). The powder was subjected to testing with regards to the 12 parameters dictated by the SeDeM Diagram Expert System and the experimental values were converted to radius values (r) portrayed in Table 4.9. Note that values printed in bold signify unacceptable values according to the criteria set by the SeDeM Diagram Expert System. The raw data to obtain the parameter and factor values are shown in Annexure C. These values were consequently utilised to construct a radial graph or SeDeM Diagram (Figure 4.5), which provides an accurate visual representation of the results obtained. To ensure an accurate representation, ñrò values Ó10 were converted to 10 (the maximum radius value) and negative values were altered to zero (the minimum radius value).

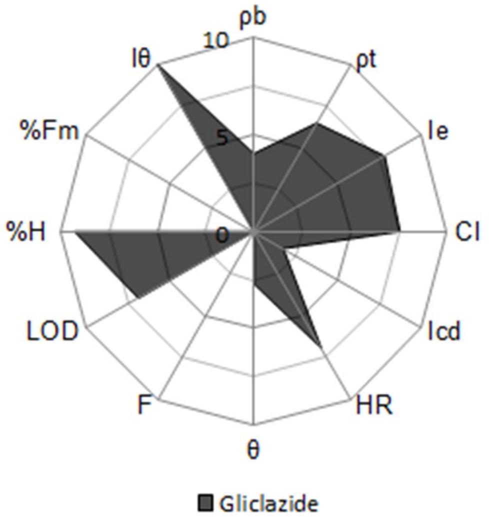


Figure 4.4 *SeDeM Diagram for gliclazide powder.*

From Table 4.9 it is evident that seven of the twelve parameters obtained values higher than the minimum acceptable value of 5, according to the SeDeM Diagram Expert System (Suñé-Negre *et al*., 2011a). The remaining five parameters (bulk density; angle of repose; cohesion index, powder flow and particles <50 µm), however, showed values below 5, and therefore, according to the System, need improving in order for the powder to be suitable for direct compression. Powder flow displayed the least favourable result as no flow for gliclazide could be confirmed. These parameters can only be increased if the crystalline structure of gliclazide is changed in order to increase its particle size, or if gliclazide powder is mixed with a more ideal powder containing larger particles with a higher bulk density.

Table 4.9: *Experimental values (V) and converted experimental values (r) for gliclazide powder as per SeDeM Diagram Expert System.*

Parameter	**Limits (V)**	**Results**		
		Experimental Values (V)	**Radius values (r)**	**Factor and average values**
Bulk Density (ρ_b)	0-1 (g/mL)	0.40	**4.03**	Dimensional 5.26
Tapped Density (ρ_t)	0-1 (g/mL))	0.65	6.48	
Inter-particle Porosity (Ie)	0-1.2	0.94	7.81	Compressibility 5.70
Carr Index (CI)	0-50 (%)	37.77	7.55	
Cohesion Index (Icd)	0-200 (N)	35.00	**1.75**	
Hausner Index (HR)	3-1	1.61	6.96	Flowability **3.23**
Angle of Respose (θ)	50-0 (°)	36.43	**2.71**	
Powder Flow (F)	20-0 (s)	*NF*	**0.00**	
Loss on Drying (LOD)	0-10 (%)	3.10	6.90	Lubricity/ Stability 8.08
Hygroscopicity (%H)	20-0 (%)	1.46	9.27	
Particles <50µm (%F_m)	50-0 (%)	69.22	**-3.84**	Lubricity/ Dosage 5.20
Homogeneity Index (Iθ)	0-0.02	0.03	14.23	

***NF**:* *NF (No Flow) indicates no flow was present and therefore no experimental value could be calculated. By default the minimum value was assigned to the parameter.*

Viewing the factors calculated for gliclazide, the dimensional factor (ɟ$_b$ and ɟ$_t$) is seen as acceptable, even though the bulk density value is below 5; but this is corrected for by the higher value obtained from the tapped density (6.48 g/mL). The compressibility factor indicates that gliclazide will most probably display good compressibility despite the fact that the cohesion index only achieved a hardness value of 35 N. Flowability is the factor depicting the most unacceptable value (3.23), which was not unexpected as the Hausner ratio, angle of repose and the flow rate indicated that gliclazide has poor to extremely poor flowability (Table 4.2, section 4.2.2) according to the set standards of the BP (2016). Interestingly, the Hausner ratio depicted an acceptable radius value of 6.96 afforded by the SeDeM Diagram Expert System, whereas according to the BP (2016) standards, the obtained value of 1.61, renders gliclazide as having extremely poor powder flow. On the other hand, the lubricity/stability factor (LOD and %H) presented with the highest value of 8.08. This indicates that the powderôs moisture content is more than suitable for direct compression (Suñé-Negre *et al.*, 2011a). Predominantly this factor can be controlled by regulating the humidity level of the storage and work areas; as well as drying the material if the moisture content is too high. Last, the lubricity/dosage factor (%F$_m$ and Iɗ) obtained an acceptable result, but this is due to two contrasting results. Gliclazide consists of too many particles smaller than 50 µm (69.22%) rendering a negative radius value of -3.84; whereas a radius value of 14.23 was acquired for the homogeneity index parameter. Again, the only way to improve the parameter is by increasing the particle size. This may be accomplished by, for example extrusion-spheronisation, or physically blending gliclazide with an excipient having a larger particle size.

Subsequently, the PI, PPI and GCI were calculated to determine whether the SeDeM Diagram Expert System will render gliclazide powder as acceptable for direct compression. These values are tabled in Table 4.10.

Table 4.10: *PI, PPI and GCI values and acceptability for gliclazide powder as per SeDeM Diagram Expert System*

Index	Value	Acceptability
Parameter Index (PI)	0.5833	Acceptable
Parametric Profile Index (PPI)	5.2893	Acceptable
Good Compression Index (GCI)	5.0509	Acceptable

From this table it may be concluded that the PI (>0.5), PPI (>5) and GCI (>5) values for the gliclazide powder indicated the powder acceptable for direct compression. There are however 5 parameters that may be improved by means of the addition of excipients with increased flowability.

4.3.2 Evaluation of selected filler formulations as per SeDeM Diagram Expert System

The SeDeM Diagram Expert System was applied to the individual selected filler powders as well as beads formulated from the individual filler powders, which either included, or omitted 10% w/w gliclazide (samples). These samples were tested and the 12 parameters evaluated to ascertain their suitability for direct compression. As established in section 4.3.1, gliclazide on its own is not a suitable powder for direct compression, and therefore the addition of a suitable filler is recommended. Results obtained for the individual SeDeM parameters, factors and index values for each sample are presented in Tables 4.11ï 4.20, respectively. Once again, the values printed in bold signify unacceptable values according to the criteria of the SeDeM Diagram Expert System. Polygons for all of the samples were successively constructed and may be viewed in Figures 4.5ï 4.20.

Results obtained for CombiLac® powder and bead samples are tabled in Table 4.11. The dimensional factor of the pure CombiLac® powder depicts fair results with an average value of 5.24, indicating the powder is of suitable size and shape to conform to the densities suggested (Ó0.5 g/mL) by the SeDeM Diagram Expert System. This value is relatively similar to the dimensional factor obtained for the gliclazide powder (5.26). The compressibility factor for the

CombiLac® powder, although averaging a value of 5.59, depicts two parameters (inter-particle porosity ï 3.17 and Carrôs index ï 3.59) that did not meet the requirements set by SeDeM. These results are possibly due to the natural packing formation of the CombiLac® powder particles. The two parameter values were corrected through the relatively high value obtained by the cohesion index parameter, rendering the acceptable compressibility factor. This value indicates that CombiLac® powder will probably be suitable for direct compression according to the set standards of the SeDeM Diagram Expert System. Comparing the results achieved for CombiLac® powder with the gliclazide powder results, it is evident that the CombiLac® powder portrayed a higher cohesion index, yet lower inter-particle porosity and Carrôs index values. By mixing these powders, flow of both CombiLac® and gliclazide may possibly be synergistically improved.

Table 4.11: *Experimental (V) and radius (r) values for all CombiLac® formulations utilising the SeDeM Diagram Expert System.*

	CombiLac® Samples Tested											
	Powder			API* Powder			Beads			API* Beads		
Parameter	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor
ρ_b	0.47	**4.72**	Dim. 5.24	0.48	**4.76**	Dim. 5.51	0.93	9.29	Dim. 9.55	0.64	6.40	Dim. 6.79
ρ_t	0.57	5.75		0.63	6.25		0.98	9.81		0.72	7.18	
Ie	0.38	**3.17**	Comp. 5.59	0.50	**4.17**	Comp. 5.48	0.06	**0.47**	Comp. **3.13**	0.17	**1.42**	Comp. **3.03**
CI	17.93	**3.59**		23.81	**4.76**		5.28	**1.06**		10.87	**2.17**	
Icd	210	10		150.00	7.50		157.00	7.85		110.00	5.50	
HR	1.22	8.91	Flow. 8.06	1.31	8.44	Flow. 7.32	1.06	9.72	Flow. 8.40	1.12	9.39	Flow. 8.08
θ	19.31	6.14		27.36	**4.53**		19.73	6.05		21.48	5.70	
F	1.77	9.12		2.04	8.98		1.15	9.43		1.68	9.16	
LOD	4.07	5.93	Lub./St. 7.10	6.34	**3.66**	Lub./St. 6.23	3.03	6.97	Lub./St. 7.99	19.97	**0.00**	Lub./St. **4.84**
%H	3.48	8.26		2.43	8.79		1.97	9.01		0.65	9.68	
%F_m	2.26	9.55	Lub./Do. 6.28	7.15	8.57	Lub./Do. 5.80	0.00	10.00	Lub./Do. 10.00	1.11	9.78	Lub./Do. 9.89
Iθ	0.01	**3.00**		0.01	**3.03**		0.23	10.00		0.05	10.00	

**API*: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

***Dim.**: Dimensional Factor; **Comp.**: Compressibility Factor; **Flow.**: Flowability Factor; **Lub./St.**: Lubricity/Stability Factor; **Lub./Do.**: Lubricity/Dosage Factor*

The flowability factor of CombiLac® powder presented an extremely high value that is indicative of good flowability. Again, by mixing gliclazide with CombiLac® powder, the flow properties of the active ingredient may be significantly improved. The lubricity/stability and lubricity/dosage factors both displayed satisfactory values for the CombiLac® powder. The lubricity/stability factor, characterised by the loss on drying (LOD) and hygroscopicity index (%H) parameters, denoted a good indication of future stability as well as the ability to lubricate the tablet press. CombiLac® powder has an adequate moisture content, similar to that of gliclazide, and portrays sufficient hygroscopic properties, indicating that the powder will not easily degrade. Although, the lubricity/dosage factor of the CombiLac® powder depicted a higher value compared to the gliclazide powder, it displayed a significantly lower homogeneity index value and a notably higher percentage particles <50 εm parameter value. Thus, the CombiLac® powder has relatively larger particles compared to the gliclazide powder, but these particles have a wider size distribution according to the criteria of the SeDeM Diagram Expert System that will negatively influence the lubricity/dosage factor. However, these stipulations are in direct contrast to the powder property results obtained for the CombiLac® powder (Section 4.2), which showed that CombiLac® has a narrower span compared to gliclazide. Furthermore, these particles are more spherical compared to the gliclazide particles and therefore, this effect demonstrated by SeDeM will in all probability not have such a remarkable effect on the compressibility of the CombiLac® powder as expected by the SeDeM Diagram Expert System.

Figure 4.5 displays the superimposed SeDeM diagrams of CombiLac® powder and gliclazide. By superimposing the SeDeM diagrams, the degree of similarity or differences between the two powders can easily be utilised to establish the suitability for direct compression. It is evident from this figure that the CombiLac® powder will most probably enhance the powder flowability of the gliclazide powder.

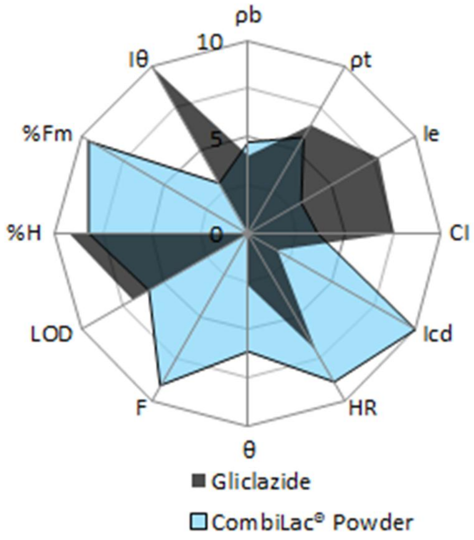


Figure 4.5: *Superimposed SeDeM Diagrams for CombiLac® powder and gliclazide*

CombiLac® powder was physically mixed with 10% w/w gliclazide (CombiLac®/API powder). Subsequent analysis was conducted on this mixture in order to establish the influence that the addition of gliclazide would exude on CombiLac® powder. The results are portrayed in Table 4.11 and the superimposed SeDeM diagrams of the CombiLac® powder and CombiLac®/API powder are displayed in Figure 4.6.

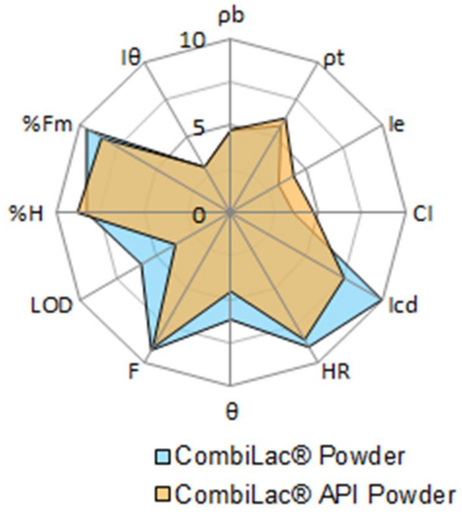


Figure 4.6: *Superimposed SeDeM Diagrams for* CombiLac® powder and *CombiLac®/API powder*

Six of the twelve parameters (bulk density, inter-particle porosity, Carr's index, angle of repose, loss on drying and the homogeneity index) did not adhere to the set value of 5 for the CombiLac®/API powder. These parameter values that did not meet the expectations of the SeDeM Diagram Expert System were similar to those parameter values depicted by the individual gliclazide and CombiLac® powders, with the exception of LOD. A relatively large decrease in LOD is seen once gliclazide is mixed with the CombiLac® powder, which might be due to the hygroscopic properties of the 10% w/w native white corn starch incorporated into this powder that was influenced by the weather conditions during experimentation. Comparing the CombiLac® powder and CombiLac®/API powder factors, the dimensional factor increased slightly when gliclazide was added to the filler. The improvement of this factor might be due to the difference in particle sizes of the individual powders in the mixture that influenced both the bulk and tapped densities, which in turn improved the packing formation of the mixture. All of the other factors displayed relatively lower values for the CombiLac®/API powder, compared to the factor values of the CombiLac® powder. This could, however, not be stated as being significant. Again, the flowability factor depicted the highest value, indicating that the CombiLac®/API powder has acceptable flow properties in order to be directly compressed according to the SeDeM Diagram Expert System.

The SeDeM Diagram Expert System is generally used in formulation studies to develop direct compressible tablets (Suñé-Negre *et al.*, 2008). Recently, researchers have shown increased interest in multi-particulate delivery systems to improve oral drug delivery and to improve the performance of pharmaceutical active ingredients (Pagariya and Patil, 2013). Multi-particulate delivery systems include, amongst others, beads (Barakat & Ahmad, 2008). As stated before, beads offer various technological advantages over conventional dosage forms, including spherical particles with smooth surfaces and low friability, narrow particle size distribution and improved powder flowability (Reddy *et al.*, 2011). Beads may be either filled into capsules, or compressed into tablets. However, some challenges may be experienced, especially in terms of content uniformity and weight variation during tableting when beads are mixed with other excipients. An additional limitation may be the fragmentation of beads during compression into tablets (Hamman *et al.*, 2017; Reddy *et al.*, 2011). During this study beads were formulated and subjected to the SeDeM Diagram Expert System in order to establish whether this system is able to also predict the suitability of beads for direct compression.

CombiLac® beads and CombiLac®/API beads (containing 10% w/w gliclazide) were produced by means of extrusion-spheronisation as described in section 3.3.2. These bead formulations were examined by means of the SeDeM Diagram Expert System and results procured may be viewed in Table 4.11. Following, polygons were constructed for each bead formulation and these SeDeM diagrams were separately superimposed on the CombiLac® powder SeDeM diagram as well as on each other (Figure 4.7).

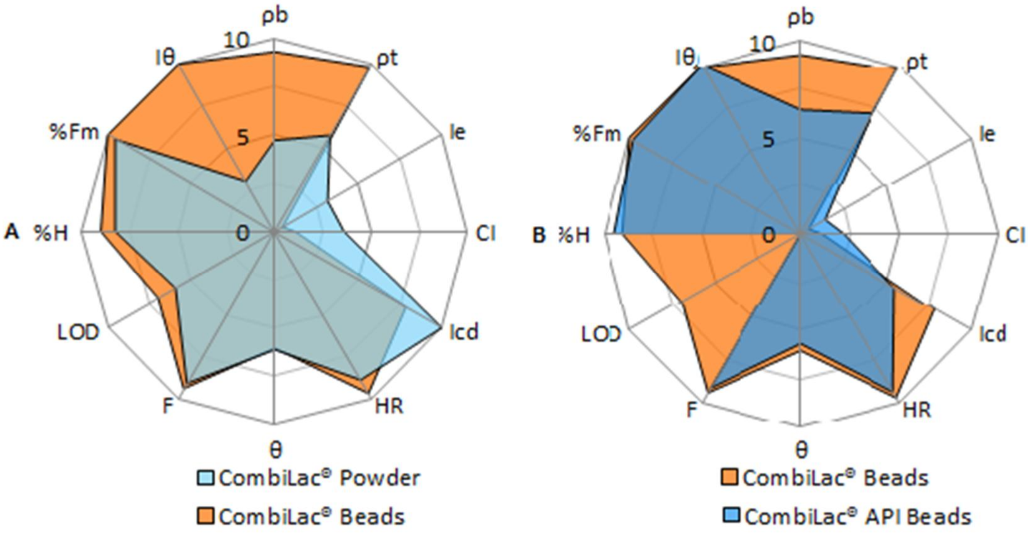


Figure 4.7: *Superimposed SeDeM Diagrams for (A) CombiLac® powder and CombiLac® beads; and (B) CombiLac® beads and CombiLac®/API beads*

According to values obtained in Table 4.11, it is clear that the production of CombiLac® beads notably increased the dimensional, flowability, lubricity/stability and lubricity/dosage factors, regardless the inclusion of gliclazide into the beads. The dimensional factor showed the greatest improvement, with the value increasing to 9.55 and 6.79, for CombiLac® beads and CombiLac®/API beads, respectively. The formulation of beads leads to more uniform particle size, size distribution and lower weight variation (Reddy *et al.*, 2011); and consequently improved both the bulk and tapped densities. Improvement of the flowability, lubricity/stability and lubricity/dosage factors supports the notion that beads will most likely be able to better incorporate gliclazide than a physical powder mixture of CombiLac® powder and gliclazide, which in turn will assist in masking the weaker flow properties of gliclazide. The compressibility factor was however decreased by an approximate value of 2.46 for both CombiLac® beads and CombiLac®/API beads, which could especially be attributed to the inter-particle porosity and Carr's index parameters. The cohesion index showed a slight improvement, which may be due to the increased powder flowability associated with beads that leads to improved dye filling and subsequently a harder, more densely packed tablet (Dawoodbhai & Rhodes, 2008). As mentioned, the SeDeM Diagram Expert System was specifically developed to assist in formulation studies of direct compressible tablets and not tablets containing beads. Thus, the low compressibility factor might not be a true reflection of the bead formulationsô ability to be directly compressed. Hamman *et al.* (2017) confirmed this statement as they concluded that although the SeDeM Diagram Expert System could be successfully applied to beads of different sizes, the compressibility factor was identified as a potential shortcoming of this System.

After the addition of 10% w/w gliclazide to the CombiLac® bead formulation a slight decrease in all factors was observed. The CombiLac®/API bead formulation displayed a larger average particle size and a narrower particle size distribution compared to the bead formulation containing no gliclazide (Table 4.1). Thus, these particles are considered more uniform in size which suggests that the void spaces between individual beads are less likely to be filled by smaller beads. This occurrence will affect particle packing and therefore the difference between the bulk and tapped densities of the CombiLac®/API bead formulation will be smaller (as observed in Table 4.11), rendering a lower dimensional factor value. No substantial difference between the compressibility factor values for the CombiLac® beads and CombiLac®/API beads could be observed. However, a trend is detected where the cohesion index value decreases upon the addition of gliclazide. Additionally, no considerable differences could be established between the flowability and lubricity/dosage factors post the incorporation of gliclazide into CombiLac® beads. The lubricity/dosage factor (including the particles <50 εm and homogeneity index parameters) portrayed the highest value for both the CombiLac® beads and CombiLac®/API beads when compared to all of the CombiLac® samples. Again, these results obtained may be attributed to the fact that bead formulations possess larger, more uniformly shaped particles that are usually larger than 50 εm. The most substantial decrease in factor value for the bead formulations could be observed for the lubricity/stability factor (decrease of 3.15). This considerable decrease was more specifically due to the noteworthy decrease in the loss on drying parameter value, which could possibly have been caused by insufficient drying of the beads after spheronisation.

Subsequently, the PI, PPI and GCI were calculated to determine whether the SeDeM Diagram Expert System will render CombiLac® formulations as acceptable for direct compression. These values are tabled in Table 4.12.

Table 4.12: *Parameter index (PI), parametric profile index (PPI) and good compression index GCI values and acceptability for* CombiLac® formulations *as per SeDeM Diagram Expert System*

	CombiLac® Samples Tested							
	Powder		**API* Powder**		**Beads**		**API* Beads**	
	Value	Acceptability	Value	Acceptability	Value	Acceptability	Value	Acceptability
PI	0.667	Acceptable	0.500	Acceptable	0.833	Acceptable	0.750	Acceptable
PPI	6.509	Acceptable	6.119	Acceptable	7.472	Acceptable	6.365	Acceptable
GCI	6.216	Acceptable	5.843	Acceptable	7.135	Acceptable	6.078	Acceptable

****API***: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

From this table it may be concluded that all formulations of CombiLac® were found acceptable for direct compression as all of the formulations (Table 4.12) displayed GCI values >5. From these formulations, the bead formulation (with the omission of gliclazide) showed the highest GCI value. However it may be noted that although both the powders and beads showed a decrease in their GCI values after the addition of gliclazide, an increase in GCI is seen when the type of sample is changed from powder to beads.

Results obtained from the formulations containing MicroceLac® 100 as filler that were subjected to the SeDeM Diagram Expert System may be viewed in Table 4.13. With regards to the dimensional factor, the MicroceLac® 100 powder showed an average value of 5.68 which is an indication of sufficient densities that will assist in the direct compression process. This powder shows an improved dimensional factor when compared to gliclazide powder. As seen with the CombiLac® formulations, an increase in the dimensional factor is often accompanied by a decrease in the compressibility factor, especially the inter-particle porosity and the Carr's index parameters. The higher the densities, the lower the inter-particle porosity parameter; and Carr's index is calculated using the difference in density values. Thus, a smaller difference between the bulk and tapped densities will produce a lower Carr's index, which is benefits flowability, but negatively affects the compressibility factor according to the SeDeM Diagram Expert System. Due to the densities being suitable for direct compression, the cohesion index displays quite a high value.

Table 4.13: *Experimental (V) and radius (r) values for all MicroceLac® 100 formulations utilising the SeDeM Diagram Expert System.*

	MicroceLac® 100 Samples Tested											
	Powder			API* Powder			Beads			API* Beads		
Parameter	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor
ρ_b	0.51	5.10	Dim. 5.68	0.51	5.05	Dim. 5.70	0.87	8.74	Dim. 8.91	0.76	7.63	Dim. 7.84
ρ_t	0.63	6.25		0.63	6.34		0.91	9.07		0.80	8.04	
Ie	0.36	**3.00**	Comp. 5.56	0.40	**3.34**	Comp. 5.47	0.04	**0.36**	Comp. **3.70**	0.07	**0.56**	Comp. **3.81**
CI	18.38	**3.68**		20.38	**4.08**		3.73	**0.75**		5.09	**1.02**	
Icd	220	10.00		180.00	9.00		212.00	10.00		197.00	9.85	
HR	1.23	8.87	Flow. 8.26	1.26	8.72	Flow. 7.33	1.04	9.81	Flow. 8.64	1.05	9.73	Flow. 8.46
θ	16.89	6.62		27.25	**4.55**		16.73	6.65		18.29	6.34	
F	1.44	9.28		2.53	8.73		1.06	9.47		1.39	9.31	
LOD	0.44	9.56	Lub./St. 8.39	4.78	5.22	Lub./St. 7.24	3.44	6.56	Lub./St. 8.12	20.80	**0.00**	Lub./St. **4.88**
%H	5.59	7.21		1.49	9.25		0.64	9.68		0.49	9.75	
%F_m	4.44	9.11	Lub./Do. 5.99	0.70	9.86	Lub./Do. 9.93	0.00	10.00	Lub./Do. 10.00	0.70	9.86	Lub./Do. 9.93
Iθ	0.01	**2.88**		0.05	10.00		1.00	10.00		0.05	10.00	

***API**:* *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*
***Dim.**: Dimensional Factor; **Comp.**: Compressibility Factor; **Flow.**: Flowability Factor; **Lub./St.**: Lubricity/Stability Factor; **Lub./Do.**: Lubricity/Dosage Factor*

.

This may be due to effective packing of the particles, which during direct compression, leads to a harder tablet. The high value of the cohesion index increases the value of the compressibility factor to an acceptable value of 5.56. Compared to the gliclazide powder, the flowability factor of the MicroceLac® 100 powder demonstrates outstanding results, averaging a value of 8.26. This may be due to the larger particle size of MicroceLac® 100 powder. A suitable level of moisture content in MicroceLac® 100 powder was demonstrated through an acceptable lubricity/stability factor (8.39); and the lubricity/dosage factor shows an exceptional value for the particles <50 εm parameter (9.11). The homogeneity index parameter value (2.88) was not ideal. This may be due to a less than optimal particle size distribution.

A visual comparison of the results obtained for the SeDeM Diagram Expert System between the MicroceLac® 100 powder and gliclazide powder can be observed in Figure 4.8, which displays the superimposed polygons. Upon addition of 10% w/w gliclazide to MicroceLac® 100 powder, a modified SeDeM profile can be witnessed that indicates how gliclazide influences the physical properties of the MicroceLac® 100 powder (Figure 4.9). The results pertaining to MicroceLac® 100/API powder are summarised in Table 4.13.

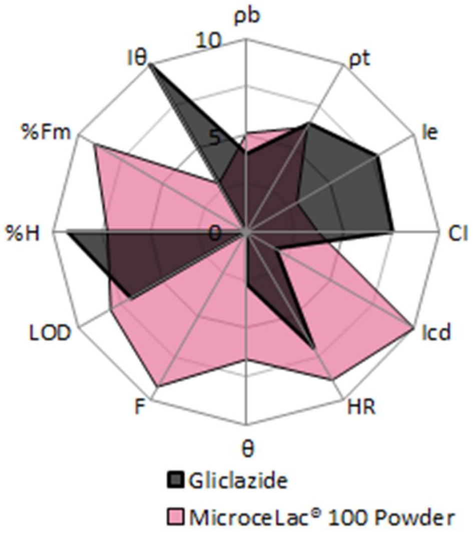


Figure 4.8: *Superimposed SeDeM Diagrams for MicroceLac® 100 powder and gliclazide.*

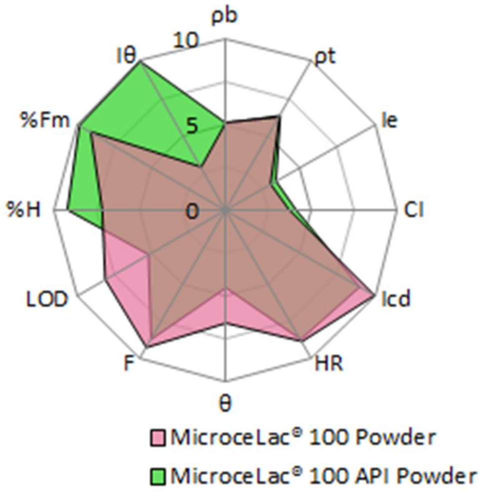


Figure 4.9: *Superimposed SeDeM Diagrams for MicroceLac® 100 powder and MicroceLac® 100/API powder.*

The addition of gliclazide to the MicroceLac® 100 powder did not have a substantial effect on the dimensional factor as no significant increase could be established (increase of 0.02). A slight decrease with regards to the compressibility factor was however observed, whereas a more noteworthy decrease was displayed with the flowability factor. This decrease may be attributed to the substantial decrease in the angle of repose parameter (4.55 for the MicroceLac® 100/API powder vs 6.62 for MicroceLac® 100 powder), indicating that gliclazide has a remarkable effect on the flowability of the MicroceLac® 100 powder. Again, it is interesting to note that according to the BP (2016) specifications, a value of 27.25° designates excellent flowability, nonetheless, the SeDeM Diagram Expert System classifies this value as inadequate for direct compression. Next, the lubricity/stability factor indicated suitable moisture content in the powder mixture. Although the powder contained a higher level of moisture, which was lost upon drying, as seen in the loss on drying parameter (5.22), this lower value is compensated for by the increase in the hygroscopicity parameter (9.25). The subsequent increase in value may be attributed to the low levels of hygroscopicity as exhibited by gliclazide. On the other hand, the lubricity/dosage factor for this mixture depicted the most noteworthy improvement when compared to the pure MicroceLac® 100 powder. The higher value may be accredited to the increase in the homogeneity index parameter (10.00) of approximately 7.12.

An evident change in powder characteristics could be seen once MicroceLac® 100 beads were produced. In general, an increase in all of the parameter values occurred, except for the compressibility factor, which may be, as previously stated, a shortcoming in the SeDeM

Diagram Expert System (Hamman *et al.*, 2017). The trend previously observed with the compressibility factor decreasing when an increase in the dimensional factor is noted, is once again clearly detected. The dimensional factor, as previously seen with CombiLac® beads, displayed a significant improvement through the formulation of beads; and the flowability factor (8.64) showed a similar profile as observed with pure MicroceLac® 100 powder, which is remarkable, as flow is typically most affected by the manufacture of beads. The lubricity/stability factor is indicative of a more than acceptable moisture profile for the pure MicroceLac® 100 bead formulation, even though it showed a slight decrease compared to the value for the pure MicroceLac® 100 powder. A significant improvement may be observed regarding the lubricity/dosage factor (10.00) that may be due to a more uniform particle size and particle distribution, both of which are frequently observed after the formulation of beads (Aulton, 2013). Figure 4.10A depicts the superimposed SeDeM Diagrams of MicroceLac® 100 powder and MicroceLac® 100 beads.

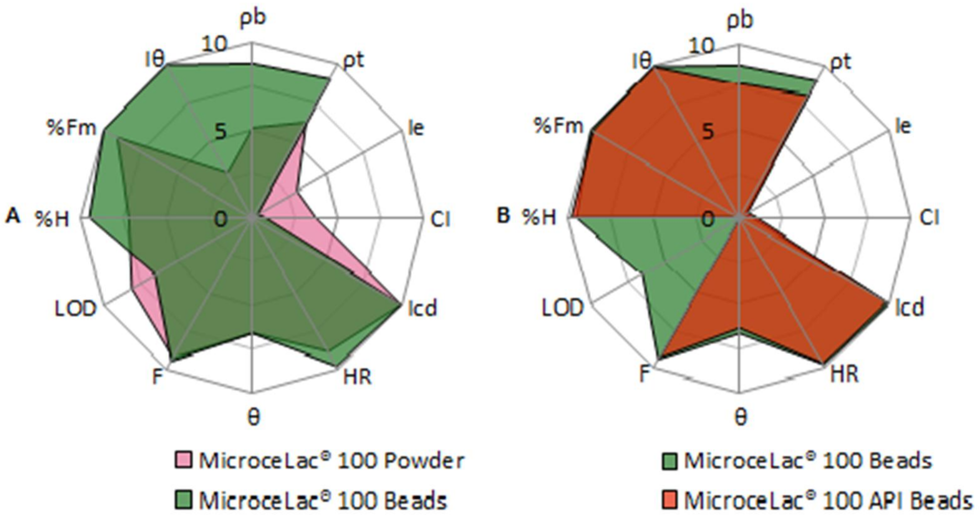


Figure 4.10: *Superimposed SeDeM Diagrams for (A) MicroceLac® 100 powder and MicroceLac® 100 beads and (B) MicroceLac® 100 beads and MicroceLac® 100/API beads.*

The influence exerted upon MicroceLac® 100 beads by gliclazide may be observed in Figure 4.10B. The addition of 10% w/w gliclazide to the MicroceLac® 100 bead formulation, marginally decreased the dimensional factor value and flowability factor value, but not to the same extent as with the lubricity/stability factor, which displayed a more visible decrease (a reduction of 3.24). Once again, the addition of gliclazide powder to the beads negatively affected the characteristics of the bead formulation, but still maintained a more than acceptable value for each of the factors, except the compressibility and lubricity/stability factors.

Compressibility was again more affected by the interparticle porosity and Carr's index parameters, as stated previously. The loss on drying parameter displayed the most notable effect on the lubricity/stability factor, which was due to the fact that the MicroceLac$^{®}$ 100/API beads retained a higher moisture level after drying compared to the MicroceLac$^{®}$ 100 beads. This may probably be corrected by extending the drying time post extrusion-spheronisation. The lubricity/dosage factor remained largely unchanged and still exhibited exceptional values with regards to direct compression, signifying that gliclazide did not affect this parameter significantly.

As observed in Table 4.14, all formulations containing MicroceLac$^{®}$ 100 showed acceptable values for direct compression as recommended by the SeDeM Diagram Expert System. The pure MicroceLac$^{®}$ 100 bead formulation obtained the best results, although both formulations containing gliclazide showed sufficient GCI values to advance into direct compression without many aspects needing improvement.

Table 4.14: Parameter index (*PI), parametric profile index (PPI) and good compression index GCI values and acceptability for* MicroceLac$^{®}$ 100 formulations *as per SeDeM Diagram Expert System*

	MicroceLac$^{®}$ 100 Samples Tested							
	Powder		**API* Powder**		**Beads**		**API* Beads**	
	Value	Acceptability	Value	Acceptability	Value	Acceptability	Value	Acceptability
PI	0.750	Acceptable	0.750	Acceptable	0.833	Acceptable	0.750	Acceptable
PPI	6.797	Acceptable	7.014	Acceptable	7.590	Acceptable	6.841	Acceptable
GCI	6.491	Acceptable	6.698	Acceptable	7.248	Acceptable	6.533	Acceptable

*****API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide.*

RetaLac$^{®}$ and all formulations thereof were analysed utilising the SeDeM Diagram Expert System (Table 4.15). RetaLac$^{®}$ powder's analysis produced five parameters (bulk density, tapped density, Carr's index, angle of repose and homogeneity index) that did not meet the minimum acceptable value of 5.

Table 4.15: *Experimental (V) and radius (r) values for all RetaLac® formulations utilising the SeDeM Diagram Expert System.*

	RetaLac® Samples Tested											
	Powder			API* Powder			Beads			API* Beads		
Parameter	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor
ρ_b	0.34	**3.42**	Dim. **3.89**	0.36	**3.58**	Dim. **4.16**	0.49	**4.86**	Dim. 5.02	0.41	**4.11**	Dim. **4.42**
ρ_t	0.44	**4.36**		0.47	**4.73**		0.52	5.17		0.47	**4.73**	
Ie	0.63	5.28	Comp. 5.45	0.68	5.67	Comp. 5.53	0.13	**1.06**	Comp. **1.20**	0.32	**2.67**	Comp. **2.07**
CI	21.64	**4.33**		24.33	**4.87**		6.15	**1.23**		13.15	**2.63**	
Icd	135.00	6.75		121.00	6.05		26.00	**1.30**		18.00	**0.90**	
HR	1.28	8.62	Flow. 7.39	1.32	8.39	Flow. 7.14	1.07	9.67	Flow. 7.60	1.15	9.24	Flow. **4.96**
θ	26.87	**4.63**		28.47	**4.31**		28.29	**4.34**		36.75	**2.65**	
F	2.19	8.91		2.58	8.71		2.43	8.78		14.03	**2.98**	
LOD	4.50	5.50	Lub./St. 7.10	7.77	**2.23**	Lub./St. **4.76**	25.02	**0.00**	Lub./St. **4.30**	30.65	**0.00**	Lub./St. **4.80**
%H	2.61	8.69		5.45	7.28		2.80	8.60		0.81	9.59	
$\%F_m$	1.77	9.65	Lub./Do. 5.92	3.29	9.34	Lub./Do. 5.58	0.00	10.00	Lub./Do. 10.00	0.00	10.00	Lub./Do. 10.00
Iθ	0.004	**2.18**		0.003	**1.81**		1.00	10.00		1.00	10.00	

****API*:* *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

***Dim.**: Dimensional Factor; **Comp.**: Compressibility Factor; **Flow.**: Flowability Factor; **Lub./St.**: Lubricity/Stability Factor; **Lub./Do.**: Lubricity/Dosage Factor*

Compared to the gliclazide powder (Figure 4.11), the RetaLac® powder exhibited only increased flowability and lubricity/dosage factor values, which is mostly due to the larger particle size of the RetaLac® powder. The dimensional factor was the only factor that did not comply with the criteria of the SeDeM Diagram Expert System. One reason for non-compliance is due to the large, irregular shape of the RetaLac® powder particles, which does not support effective packing formation.

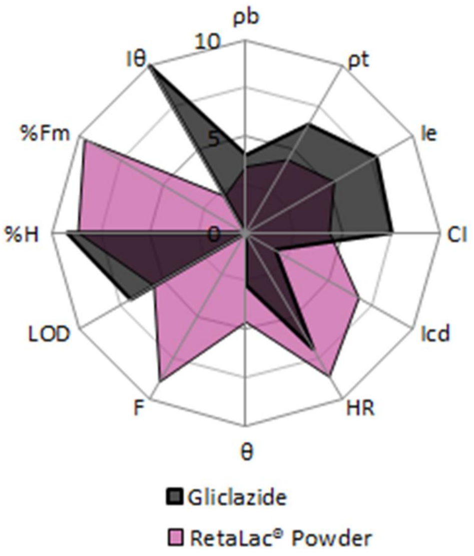


Figure 4.11: *Superimposed SeDeM Diagrams for RetaLac® powder and gliclazide.*

Subsequent addition of 10% w/w gliclazide (Figure 4.12) rendered higher values for both the dimensional and compressibility factors, however, this increase in the dimensional factor value was not sufficient to deliver an acceptable factor value. The flowability, lubricity/stability and lubricity/dosage factors were all detrimentally affected by the addition of gliclazide as was found with the other fillers, though, the lubricity/stability factor was most affected (decrease of 2.34). Parameters that did not meet the requirements were also seen as the weaker parameters in the pure RetaLac® powder formulation (with the exception of loss on drying). The loss on drying parameter’s decrease in value (an approximate decrease of 3.27 from the pure RetaLac® powder) may partly be attributed to the weather conditions as it was a humid, rainy season when the experiments were conducted; and due to RetaLac® consisting of hypromellose (Meggle, 2015c), it would more likely be prone to be affected by humidity. Again, this may easily be corrected by drying the powder mixture for extended time periods. The lower, but still acceptable lubricity/dosage factor could be explained by the relatively lower homogeneity index parameter. RetaLac® powder depicted a more irregular particle shape and its span was relatively wider compared to the other fillers tested. These properties cause the RetaLac® powder not to mix as homogeneously with gliclazide as the other fillers did.

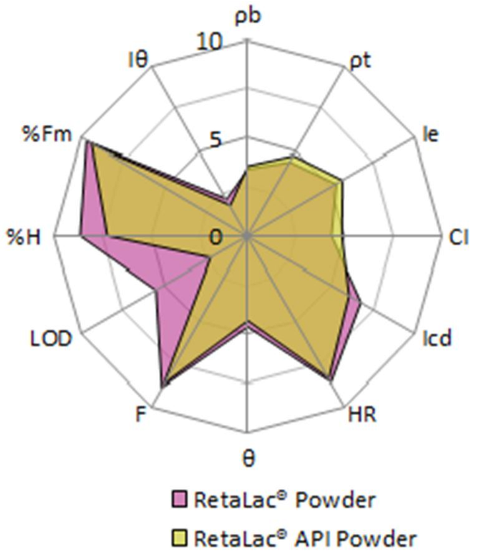


Figure 4.12: *Superimposed SeDeM Diagrams for RetaLac® 100 powder and RetaLac® 100/API powder*

Upon formulation of beads containing pure RetaLac® powder, a clear difference can be observed in the results obtained (Table 4.15). The dimensional factor exhibited a noteworthy improvement and could be deemed acceptable due to the fact that the density values of the beads were more acceptable according to the SeDeM Diagram Expert System. Contradictory to these results, the compressibility factor showed a substantial decrease as all of the parameters pertaining to this factor (inter-particle porosity, Carr's index and the cohesion index) displayed notably reduced values. The inter-particle porosity parameter value declined due to the irregular and elongated shape of the RetaLac® beads. As previously mentioned, the beads did not spheronise, but instead formed rods, which may inhibit effective packing thus creating larger cavities between the particles. The Carr's index value, as previously stated exhibits a contradiction, wherein a smaller difference between bulk and tapped densities positively influence flow, but have a negative impact on the compressibility parameter. The cohesion index parameter (1.30) also portrayed a noteworthy decline, which may be due to ineffective dye filling, owing to the particle shape, or the property of hypromellose forming a colloidal solution with cold water that is prone to elastic recovery (Eyjolfsson, 2015). As supporting evidence, the loss on drying parameter displayed a notable amount of moisture present in the RetaLac® bead formulation that additionally rendered an unacceptable lubricity/stability factor.

Once more a prolonged drying time may improve this factor. The flowability factor (7.60), on the other hand, increased upon the production of beads, nonetheless it was largely negatively influenced by the angle of repose parameter. Angle of repose is affected by the particle size and shape of a sample. Thus, the large, irregular shape of RetaLac® beads negatively influenced this parameter. The lubricity/dosage factor showed optimal results (10.00) for both the particles >50 µm and the homogeneity index parameters, signifying particle size and size distribution that are ideal for the SeDeM Diagram Expert System. Therefore, according to this System tablets produced from these RetaLac® beads will possess a homogeneous content. A superimposed SeDeM Diagram may be viewed in Figure 4.13A where one may discern the influence exerted by the formation of beads.

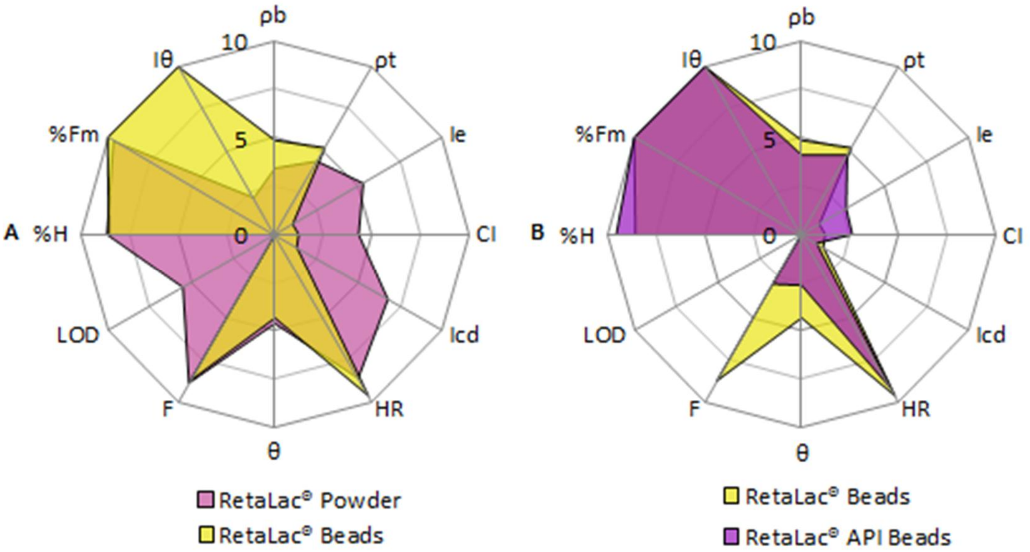


Figure 4.13: *Superimposed SeDeM Diagrams for (A) RetaLac® powder and RetaLac® beads and (B) RetaLac® 100 beads and RetaLac®/API beads.*

Subsequently, gliclazide was incorporated into RetaLac® bead formulations and the results obtained are summarised in Table 4.15. These results were compared with RetaLac® beads comprising no active ingredient by constructing a superimposed SeDeM Diagram as seen in Figure 14.14B. According to this figure and the results acquired, it is clear that the incorporation of gliclazide into RetaLac® beads remarkably influenced the flowability factor as indicated by the flow rate and angle of repose parameters. These results are in concurrence with previously attained findings. As previously stated the decrease seen in the flowability may be attributed to the shape and varying size of the RetaLac®/API beads (Figure 4.3C III), which may promote interlocking of the beads and thus inhibit flow (Aulton, 2013).

Overall, RetaLac® formulations showed more variance between results obtained for the individual formulations than seen with both CombiLac® and MicroceLac® formulations. The various RetaLac® formulations furthermore displayed more unacceptable parameters compared to the other formulations. The acceptability for all of the RetaLac® formulations for direct compression may be observed in Table 4.16.

Table 4.16: *Parameter index (PI), parametric profile index (PPI) and good compression index GCI values and acceptability for RetaLac® formulations as per SeDeM Diagram Expert System*

	RetaLac® Samples Tested							
	Powder		**API* Powder**		**Beads**		**API* Beads**	
	Value	Acceptability	Value	Acceptability	Value	Acceptability	Value	Acceptability
PI	0.583	Acceptable	0.500	Acceptable	0.500	Acceptable	0.333	Acceptable
PPI	6.025	Acceptable	5.580	Acceptable	5.418	Acceptable	4.959	**Not acceptable**
GCI	5.753	Acceptable	5.328	Acceptable	5.173	Acceptable	4.735	**Not acceptable**

*****API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

From this table it may be noted that although RetaLac® exhibited a large variation in the parameter values, which is moreover unacceptable given the SeDeM Diagram Expert System, all but one formulation (RetaLac®/API beads), was deemed acceptable for direct compression, according to the PI, PPI and GCI values. The RetaLac®/API bead formulation may be improved by implementing the changes as suggested in the previous discussions. These improvements may lead to an acceptable formulation. The inclusion of a binder and a lubricant may also increase the compressibility and flowability factors, respectively, which may aid the formulation's suitability for direct compression.

Pharmacel® 101 powder was also characterised utilising the SeDeM Diagram Expert System. Results are displayed in Table 4.17 and the superimposed SeDeM Diagram for the Pharmacel® 101 powder and gliclazide is seen in Figure 4.14. Five parameters (bulk density, tapped density, angle of repose, loss on drying and particles <50 εm) measured for the Pharmacel® 101 powder did not meet the requirements, rendering an unacceptable dimensional factor (4.03) and lubricity/dosage factor (4.15). The highest valued factor is the compressibility factor, indicating suitable values for direct compression. Contrary, the lowest value depicted is the dimensional factor. The trend previously seen regarding the relationship between the dimensional factor and the compressibility factor can be confirmed, whereby a decrease in the dimensional factor leads to an increase in Carrôs index and indirectly improves the compressibility factor. The unacceptable value of the lubricity/dosage factor can be mainly ascribed to the particles <50 εm parameter that indicated that Pharmacel® 101 consists of a too high percentage particles that are too small according to the SeDeM Diagram Expert System. This characteristic renders the powder inadequate for direct compression. However, through an increase in particle size by means, for example extrusion-spheronisation, this problem as well as the unacceptable value for the dimensional factor may be rectified. According to Figure 4.14, the Pharmacel® 101 powder may theoretically be able to improve the suitability of gliclazide for direct compression.

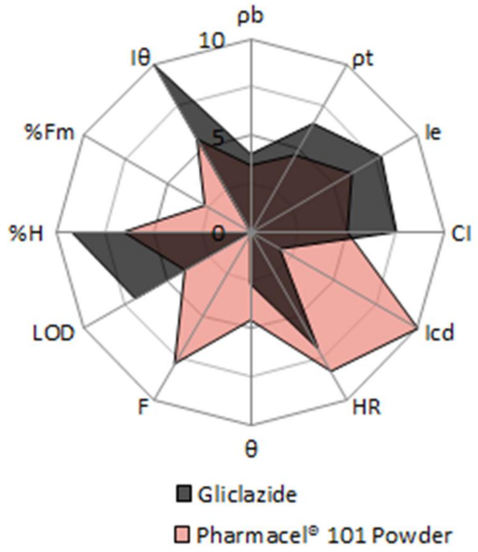


Figure 4.14: *Superimposed SeDeM Diagrams for Pharmacel® 101 powder and gliclazide.*

Table 4.17 *Experimental (V) and radius (r) values for all Pharmacel® 101 formulations utilising the SeDeM Diagram Expert System.*

	Pharmacel® 101 Samples Tested											
	Powder			API* Powder			Beads			API* Beads		
Parameter	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor
ρ_b	0.34	**3.45**	Dim. **4.03**	0.36	**3.61**	Dim. **4.16**	0.72	7.21	Dim. 7.32	0.71	7.11	Dim. 7.33
ρ_t	0.46	**4.60**		0.47	**4.70**		0.74	7.43		0.75	7.54	
Ie	0.73	6.05	Comp. 7.02	0.64	5.31	Comp. 6.09	0.04	**0.33**	Comp. **0.72**	0.08	**0.67**	Comp. **0.99**
CI	25.05	5.01		23.02	**4.60**		2.89	**0.58**		5.69	**1.14**	
Icd	212.00	10.00		167.00	8.35		25.00	**1.25**		23.00	**1.15**	
HR	1.33	8.33	Flow. 6.93	1.30	8.50	Flow. 5.94	1.03	9.85	Flow. 8.68	1.06	9.70	Flow. 8.39
θ	27.14	**4.57**		25.12	**4.98**		16.07	6.79		18.38	6.32	
F	4.24	7.88		11.31	**4.35**		1.21	9.39		1.72	9.14	
LOD	6.06	**3.94**	Lub./St. 5.26	6.93	**3.07**	Lub./St. 5.16	38.23	**0.00**	Lub./St. **3.74**	26.79	**0.00**	Lub./St. **4.76**
%H	6.86	6.57		5.53	7.24		5.04	7.48		0.97	9.51	
$\%F_m$	36.25	**2.75**	Lub./Do. **4.15**	42.55	**1.49**	Lub./Do. **2.97**	0.00	10.00	Lub./Do. 10.00	0.00	10.00	Lub./Do. 10.00
Iθ	0.01	5.55		0.01	**4.44**		0.98	10.00		1.00	10.00	

**API*: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

***Dim.**: Dimensional Factor; **Comp.**: Compressibility Factor; **Flow.**: Flowability Factor; **Lub./St.**: Lubricity/Stability Factor; **Lub./Do.**: Lubricity/Dosage Factor*

Figure 4.15 displays the comparison between the superimposed SeDeM Diagrams for Pharmacel® 101 powder and Pharmacel® 101/API powder. It is evident that mixing gliclazide into Pharmacel® 101 powder only slightly increased (0.13) the dimensional factor. This may be due to the smaller particles of gliclazide being able to fill the voids between the larger Pharmacel® 101 powder during compaction, thus, increasing the overall densities, but not to such an extent as to deem the powder mixture acceptable for direct compression. This increase in the densities furthermore displayed a slight, expected decrease in the Carr's index and increase in the Hausner ratio parameters (Gao *et al.*, 2002). All other factors were detrimentally affected.

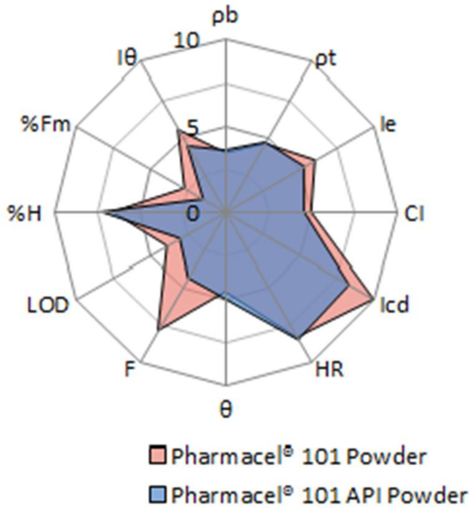


Figure 4.15: *Superimposed SeDeM Diagrams for Pharmacel® 101 powder and the Pharmacel® 101/API powder.*

The production of beads with Pharmacel® 101 (Figure 4.16A) rendered results that followed the same trend as observed with all of the other filler formulations where the dimensional, flowability and lubricity/dosage factors increased; and both the compressibility and lubricity/stability factors decreased to such an extent that they are considered unacceptable according to the SeDeM Diagram Expert System. Flowability was increased due to the formation of larger and more spherical particles (Figure 4.3D I), which in turn lowered inter-particular attraction forces between the particles due to a decrease in the contact surface of the particles. The lubricity/dosage factor displayed an ideal value (10.00) which is due to the uniformity of the particle size and the equal distribution thereof. Overall, the Pharmacel® 101 bead formulation displayed a noteworthy improvement in the powder characteristics compared to the Pharmacel® 101 powder, except for the compressibility factor. Once more, this observation indicates that the compressibility factor of the SeDeM Diagram Expert System cannot be accurately applied to bead formulations (Hamman *et al.*, 2017).

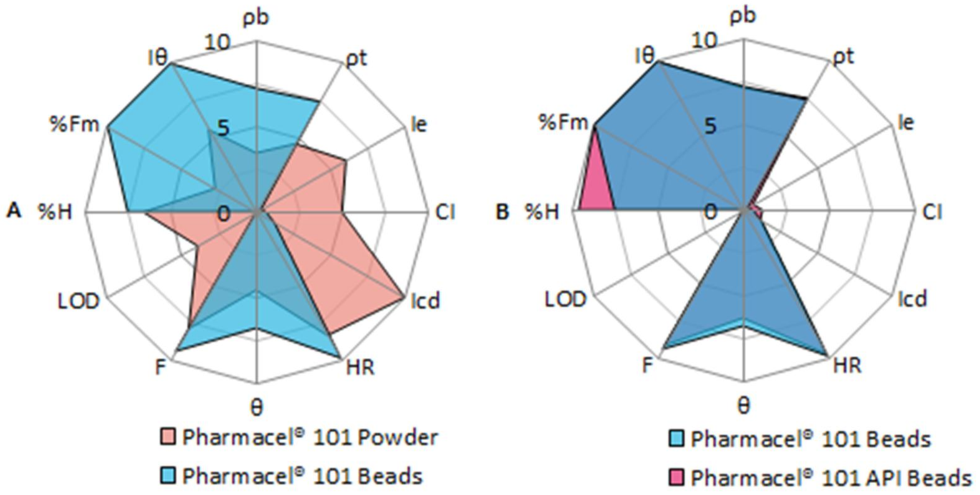


Figure 4.16: *Superimposed SeDeM Diagrams for (A) RetaLac® powder and RetaLac® beads and (B) RetaLac® 100 beads and RetaLac®/API beads.*

The addition of 10% w/w gliclazide to the Pharmacel® 101 bead formulation (Figure 4.16B) generally displayed little variation compared to the Pharmacel® 101 bead formulation containing no gliclazide, with the exception of the hygroscopicity factor. The lower hygroscopicity of the Pharmacel® 101/API bead formulation, increased the hygroscopicity parameter value (1.02), however it was not high enough to merit an acceptable lubricity/stability factor.

Upon examination of all the Pharmacel® 101 formulations, Table 4.18 was compiled detailing the acceptability of these formulations for direct compression. Initial calculations indicated all indexes as acceptable, except for the PI and GCI of the Pharmacel® 101/API powder. From the analysed formulas, it may be noted that Pharmacel® 101/API beads displayed the most suitable value for direct compression (5.752) and will thus likely be able to deliver more suitable tablets in further experimentation.

Table 4.18 *Parameter index (PI), parametric profile index (PPI) and good compression index GCI values and acceptability for Pharmacel® 101 formulations as per SeDeM Diagram Expert System*

	Pharmacel® 101 Samples Tested							
	Powder		**API* Powder**		**Beads**		**API* Beads**	
	Value	Acceptability	Value	Acceptability	Value	Acceptability	Value	Acceptability
PI	0.583	Acceptable	0.333	**Not acceptable**	0.667	Acceptable	0.667	Acceptable
PPI	5.726	Acceptable	5.0526	Acceptable	5.860	Acceptable	6.023	Acceptable
GCI	5.468	Acceptable	4.825	**Not acceptable**	5.595	Acceptable	5.752	Acceptable

*****API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

Cassava starch was physically blended with HPMC in an 80:20 ratio. During the mixing process, this powder displayed visual adhesion to the glass containers. This would serve as an indication to the flowability of the powder mixture, but conformation could only be obtained after analysis utilising the SeDeM Diagram Expert System (Table 4.19). All of the factors, excluding the flowability factor depicted acceptable values, although only five parameters showed adequate results. Thus, the visual observation of poor flowability could be confirmed by the results obtained. Cassava starch comprises extremely small particles (an average of 50.139 µm), a characteristic that increases the contact surface area, which in turn increases the inter-particular attraction forces between individual particles, decreasing flowability. Interestingly the acceptable parameter values were high enough to correct the notably lower unacceptable values in order to attain suitable factor values. For example the high homogeneity index parameter (10.00) corrected the lubricity/dosage factor despite the inadequate particles <50 εm parameter (0.00). This powder mixture may possibly not be able to increase the compressibility of gliclazide as seen in Figure 4.17.

Table 4.19: *Experimental (V) and radius (r) values for all Cassava starch/HPMC formulations utilising the SeDeM Diagram Expert System.*

	Cassava starch/HPMC Samples Tested											
	Powder			API* Powder			Beads			API* Beads		
Parameter	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor	ñVò	ñrò	Factor
ρ_b	0.50	**4.95**	Dim. 5.56	0.48	**4.82**	Dim. 5.41	0.66	6.64	Dim. 6.84	0.62	6.23	Dim. 6.43
ρ_t	0.62	6.17		0.60	5.99		0.70	7.04		0.66	6.62	
Ie	0.40	**3.33**	Comp. 5.00	0.40	**3.36**	Comp. **4.88**	0.09	**0.72**	Comp. **0.96**	0.10	**0.80**	Comp. **0.90**
CI	19.80	**3.96**		19.45	**3.89**		5.76	**1.15**		6.00	1.20	
Icd	154.00	7.70		148.00	7.40		20.00	**1.00**		14.00	**0.70**	
HR	1.25	8.77	Flow. **3.62**	1.24	8.79	Flow. **3.48**	1.06	9.69	Flow. 8.43	1.06	9.68	Flow. 7.81
θ	39.58	**2.08**		41.77	**1.65**		18.66	6.27		25.78	**4.84**	
F	20.00	**0.00**		20.00	**0.00**		1.33	9.34		2.17	8.92	
LOD	5.97	**4.03**	Lub./St. 5.86	14.43	**0.00**	Lub./St. **3.73**	19.84	**0.00**	Lub./St. **4.76**	25.19	**0.00**	Lub./St. **4.88**
%H	4.64	7.68		5.08	7.46		0.97	9.52		0.49	9.76	
$\%F_m$	69.39	**0.00**	Lub./Do. 5.00	68.30	**0.00**	Lub./Do. 5.00	0.00	10.00	Lub./Do. 10.00	0.00	10.00	Lub./Do. 10.00
$I\theta$	0.03	10.00		0.02	10.00		1.00	10.00		1.00	10.00	

***API**: *API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*
***Dim.**: Dimensional Factor; **Comp.**: Compressibility Factor; **Flow.**: Flowability Factor; **Lub./St.**: Lubricity/Stability Factor; **Lub./Do.**: Lubricity/Dosage Factor*

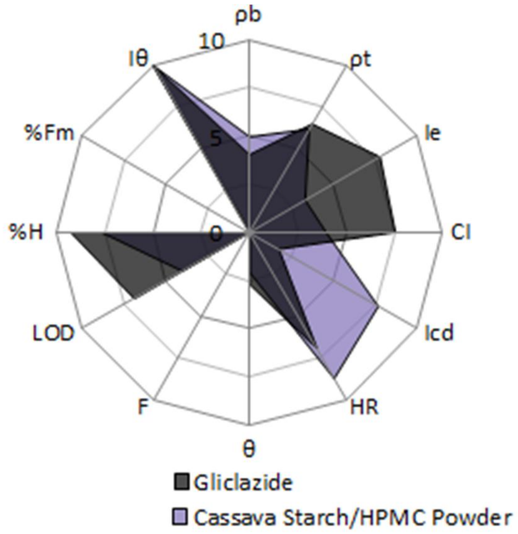


Figure 4.17: *Superimposed SeDeM Diagrams for Pharmacel® 101 powder and gliclazide.*

The only factor that remained unchanged with the addition of 10% w/w gliclazide is the lubricity/dosage factor (Table 4.19). All of the other factors decreased in value, and most visibly, the lubricity/stability factor (decrease of 2.13). This was due to a decrease in the loss on drying parameter, indicating that the combination of Cassava starch/HPMC with gliclazide produces a powder mixture with higher moisture retention properties as depicted in Figure 4.18.

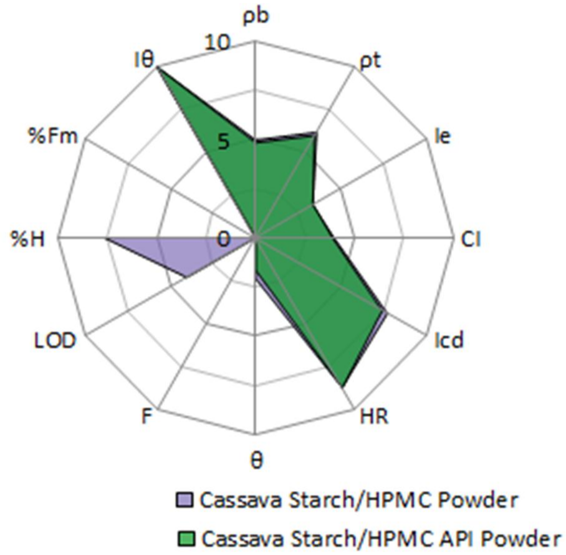


Figure 4.18: *Superimposed SeDeM Diagrams for Cassava starch/HPMC powder and Cassava starch/HPMC API powder.*

The manufacture of beads increased the dimensional, flowability and lubricity/dosage factors substantially. All of these factors were improved due to the formation of larger beads that are more uniform in size and shape compared to the Cassava starch/HPMC powder mixture. It is however important to note that the beads that formed are not spherical, but rather rod-shaped, much like RetaLac® beads. Beads created from Cassava starch/HPMC do not differ significantly from beads produced by RetaLac® in terms of particle shape; they do however display a diverse internal structure (Figure 4.3C and E). The Cassava starch/HPMC beads are more densely packed compared to the RetaLac® beads, rendering relatively harder, less compressible beads as indicated by the compressibility factor (0.96). It is evident from the hygroscopicity parameter that the formation of beads increased this factor remarkably compared to the value obtained for the Cassava starch/HPMC powder. During the extrusion-spheronisation process, the powder mixture is wetted; and the hygroscopic property of both Cassava starch and HPMC enables the mixture to absorb the added moisture. This moisture is retained during and after the drying procedure, therefore, excess atmospheric moisture is not absorbed after the subsequent manufacturing process, rendering a higher hygroscopicity parameter value. However, during execution of the loss on drying experiment, a substantial percentage moisture is lost, causing a lower loss on drying parameter value that influences the lubricity/stability factor negatively. These results are displayed in Figure 4.19A.

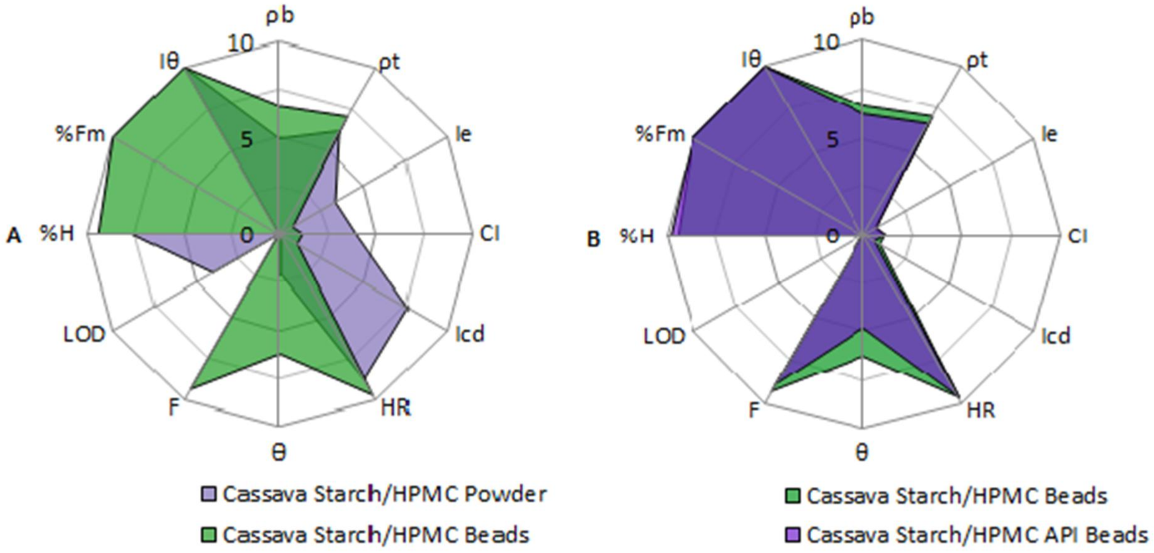


Figure 4.19: *Superimposed SeDeM Diagrams for (A) Cassava starch/HPMC powder and Cassava starch/HPMC beads and (B) Cassava starch/HPMC beads and Cassava starch/HPMC API beads.*

Figure 4.19B (and Table 4.19) compares the SeDeM Diagrams of Cassava starch/HPMC beads and Cassava starch/HPMC API beads. From this figure it is evident that the addition of gliclazide did not have a significant effect on the different SeDeM parameters. Only the angle of repose parameter showed a marginally decrease in value, which suggests that the inclusion of gliclazide in Cassava starch/HPMC beads leads to relatively poorer powder flowability of the beads. The parameter values were utilised to calculate the PI, PPI and GCI values in order to determine the suitability of the Cassava starch/HPMC formulations for direct compression. The PI, PPI and GCI values for these formulations are tabled in Table 4.20. All of the Cassava starch/HPMC powder formulations were deemed unfit for direct compression whereas the bead formulations were found acceptable. The primary concern with the powder formulations is the poor flowability, which may possibly be improved upon with the inclusion of a glidant and/or lubricant, such as magnesium stearate (Kikuta & Kitamori, 1994; Bolhuis *et al.*, 1981). Moreover, the addition of gliclazide reduced the acceptability of the powder mixture, yet not to such an extent where the addition of specialised excipients cannot compensate for the flaws. The Cassava starch/HPMC bead formulations depicted higher acceptable values, though the other filler formulations that were tested performed better according to the GCI values obtained.

Table 4.20: *Parameter index (PI), parametric profile index (PPI) and good compression index GCI values and acceptability for Cassava starch/HPMC formulations as per SeDeM Diagram Expert System*

	Cassava starch/HPMC Samples Tested							
	Powder		**API* Powder**		**Beads**		**API* Beads**	
	Value	Acceptability	Value	Acceptability	Value	Acceptability	Value	Acceptability
PI	0.417	**Not acceptable**	0.417	**Not acceptable**	0.667	Acceptable	0.583	Acceptable
PPI	4.890	**Not acceptable**	4.447	**Not acceptable**	5.947	Acceptable	5.729	Acceptable
GCI	4.669	**Not acceptable**	4.247	**Not acceptable**	5.679	Acceptable	5.471	Acceptable

*****API**: API Powder and API Beads refer to a mixture of 90% w/w filler and 10% w/w gliclazide*

Comparing the GCI values for all of the selected filler formulations, it could be recognised that MicroceLac® 100 beads (with the omission of gliclazide) presented the highest value, closely followed by CombiLac® beads (no gliclazide). However, overall it could be concluded that formulations containing MicroceLac® 100 as filler depicted the highest GCI values regardless the type of formulation or the inclusion of gliclazide, indicating that this filler is the most suitable for direct compression according to the SeDeM Diagram Expert System. The following rank order could be established for the suitability for direct compression of the selected fillers: MicroceLac® 100 > CombiLac® > Pharmacel® 101 ÓRetaLac® ÓCassava starch/HPMC.

4.4 Evaluation of tablet properties

Upon analysis of the results obtained through the SeDeM Diagram Expert System, tablets were formulated utilising a full factorial design. The SeDeM Diagram Expert System recommended the inclusion of a lubricant which could benefit the flowability of the different powder mixtures. Additionally, a binder may improve the compressibility (as seen lacking in most of the bead formulations). The SeDeM Diagram Expert System recommends the incorporation of magnesium stearate if the flowability parameter is below 5 (Suñé-Negre *et al.*, 2011a). However, increased lubricant concentrations may lead to the formation of weaker tablets (Zuurman *et al.*, 1999). Therefore, a full factorial design was employed to analyse which minimum level of lubricant concentration (either 0.5% or 1.0%) is needed to compensate for the weak flowability without compromising the integrity of the tablet. The binder concentration was furthermore varied (0%, 2% and 5%) to obtain a suitable concentration that would render acceptable tablet formulations. The tablets were tableted with a weight of approximately 300 mg and all tablets contained either 0.5 or 1.0% magnesium stearate; as well as 0, 2 or 5% Kollidon® 90F. These formulations were either prepared by mixing 10% w/w gliclazide with one of the selected fillers, or beads were produced that contained 10% w/w gliclazide and a selected filler (section 3.6). The formulations manufactured (and the abbreviations assigned to each formulation) may be viewed in Table 4.21. Some of the bead formulations did not produce tablets that could be tested and these formulations are indicated as a black cell in Table 4.21.

Table 4.21: *Table depicting abbreviations used for each formula. Blocks coloured in black indicate that the beads did not produce tablets suitable for testing.*

				Filler type:									
				CombiLac®		**MicroceLac® 100**		**RetaLac®**		**Pharmacel® 101**		**Cassava starch / HPMC**	
				P*	**B***	**P***	**B***	**P***	**B***	**P***	**B***	**P***	**B***
Magnesium stearate (% w/w)	**0.5**	**Kollidon® 90F (% w/w)**	**0**	0.5CL0	■	0.5ML0	0.5ML0	0.5RL0	0.5RL0	0.5PC0	■	0.5CS0	■
			2	0.5CL2	0.5CL2	0.5ML2	0.5ML2	0.5RL2	0.5RL2	0.5PC2	0.5PC2	0.5CS2	■
			5	0.5CL5	0.5CL5	0.5ML5	0.5ML5	0.5RL5	0.5RL5	0.5PC5	0.5PC5	0.5CS5	■
	1.0		**0**	1CL0	■	1ML0	1ML0	1RL0	1RL0	1PC0	■	1CS0	1CS0
			2	1CL2	1CL2	1ML2	1ML2	1RL2	1RL2	1PC2	1PC2	1CS2	■
			5	1CL5	1CL5	1ML5	1ML5	1RL5	1RL5	1PC5	1PC5	1CS5	■

***P:** *P is indicative of Powder tablet formulations*

***B:** *B is indicative of Bead tablet formulations*

A black cell indicates that the formulation did not produce tablets

4.4.1 Tablet morphology

Figure 4.20 represents SEM micrographs depicting the internal morphology of selected formulated tablets. It may be observed that the tablets comprising beads are less densely packed than their respective powder counterparts. Due to this property, it may result in the bead tablets depicting a lower crushing strength value than the powder tablets. Regarding the powder tablets (Figure 4.20 I) a similar structure to the corresponding beads may be detected, but these tablets are more densely packed, leading to increased hardness, and may result in a higher content uniformity when compared to the bead tablets of identical content. The bead tablets for CombiLac®, MicroceLac® 100 and RetaLac® beads display a similar internal structure with well-defined beads still visible within the tablet. Thus, minimal bead deformation occurred. The RetaLac® bead tablets, on the other hand, portray a more loosely packed bead structure. This may be indicative of a tablet depicting decreased hardness, even when compared to the other bead tablet formulations.

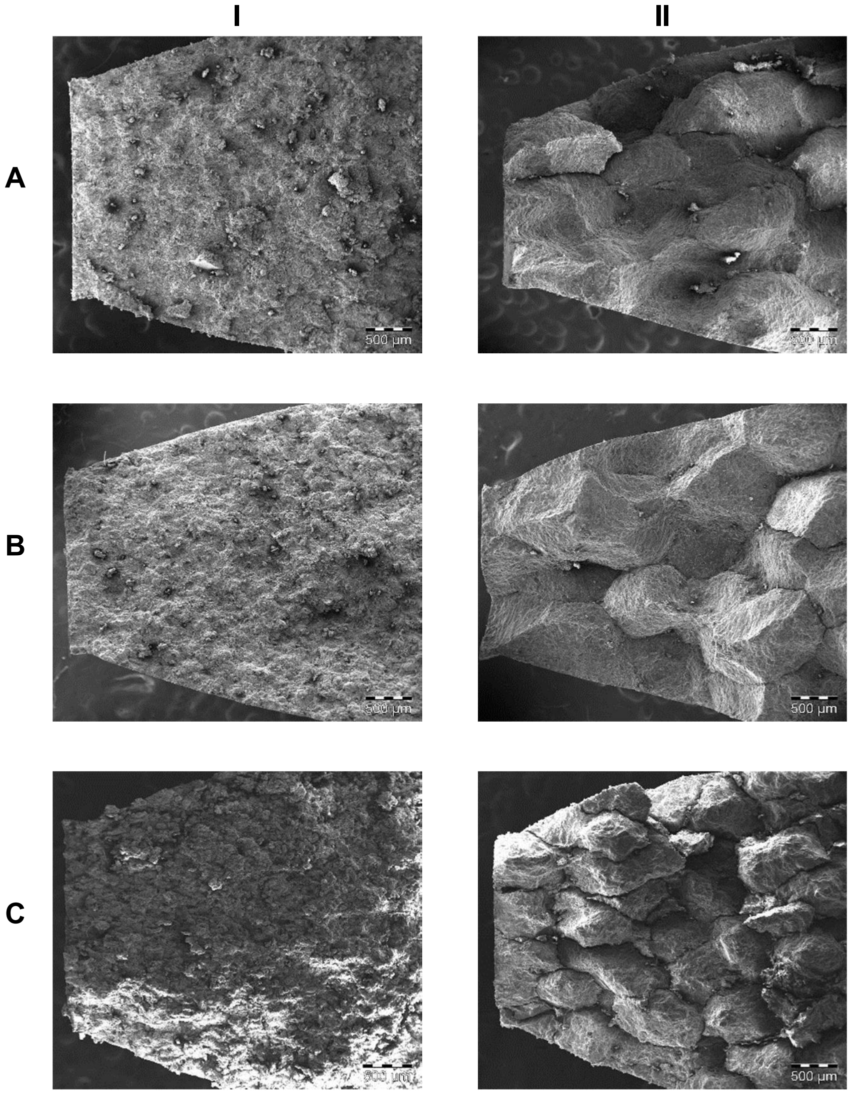


Figure 4.20: *SEM micrographs of A) CombiLac®, B) MicroceLac® 100 and C) RetaLac® tablets taken at 75X magnification showing I) powder tablets, and II) bead tablets containing 10% w/w gliclazide, 1% w/w magnesium stearate and 2% w/w Kollidon® 90F.*

4.4.2 Evaluation of the friability of the different bead formulations

The official test to ascertain the mechanical strength of the manufactured beads was conducted in accordance with section 3.7.2. Beads comprised 10% w/w gliclazide and 90% w/w of the selected filler, thus, no binder was included. Results obtained from the assessment are tabled in Table 4.22.

Table 4.22 *Results obtained from bead friability testing, indicating the % mass lost*

Filler	% Friability
CombiLac®	0.00
MicroceLac® 100	0.42
RetaLac®	0.05
Pharmacel® 101	0.00
Cassava starch/HPMC	0.00

From this table, it may be noted that all the formulations indicated acceptable values in accordance with the BP (2016) standards. Formulations that contained CombiLac®, Pharmacel® 101 and Cassava starch/HPMC as fillers, produced beads that displayed no loss in mass, indicating beads formed that displayed increased mechanical strength. During preformulation studies to manufacture tablets from these bead formulations, it could be clearly seen that all of these formulations were not able to produce tablets that could be rendered acceptable. Throughout the tableting process the beads that comprised either CombiLac®, Pharmacel® 101 or Cassava starch/HPMC did not deform and then bind sufficiently to form a viable tablet. Thus, no tablets were produced and it was decided to include a binder utilising a full factorial design.

4.4.3 Tablet Evaluation

Tablets were consequently manufactured in accordance with the full factorial design (as described in section 3.6.1) and subjected to testing in accordance with the BP (2016) criteria. The purpose of a full factorial design is to estimate the interactions between different factors and levels of these factors. In this way an impartial and systematic decision may be made as to which of the various excipients; and at what concentrations they should be incorporated in order to obtain the most acceptable tablet formulation. Therefore, a summary of the average values for each level of the selected variables of each response that were included in the full factorial design are listed in Table 4.23.

Table 4.23 *Results obtained from testing according to the BP (2016). The results printed in bold represent the best results obtained from the respective parameters.*

Variable		Mass Variation (%RSD)	Friability (%)	Tensile Strength ($N.mm^{-2}$)	Disintegration (sec)
Fillers	CombiLac®	**1.667**	**0.937**	**2.1**	772.4
	MicroceLac®	2.183	1.707	**2.1**	847.9
	RetaLac®	1.853	17.863	1.3	**900.0**
	Pharmacel® 101	2.130	1.454	2.0	**900.0**
	Cassava starch/HPMC	2.230	1.607	1.7	**900.0**
Binder	0% Kollidon® 90F	**1.651**	1.953	1.6	839.5
	2% Kollidon® 90F	2.151	**1.273**	**2.0**	870.6
	5% Kollidon® 90F	2.141	12.100	1.9	**874.2**
Lubricant	0.5% Magnesium stearate	2.006	**5.171**	1.8	824.0
	1.0% Magnesium stearate	**1.995**	5.412	**1.9**	**900.0**
Production Method	Powder tablets	**1.358**	**0.686**	**2.5**	836.6
	Bead tablets	2.918	11.877	0.8	**900.0**

According to Table 4.23 it is evident that the production method did play an evident role in the physical properties of the different tablet formulations. Although all of the tablets displayed acceptable mass variation values, the formulations that contained CombiLac® as filler varied slightly less in mass compared to the other fillers, thus, more uniform tablets in terms of weight were produced. Formulations which did not include any binder (Kollidon® 90F) depicted slightly more uniform tablet weights. However, the inclusion of Kollidon® 90F, did not show a trend as no significant difference in the mass variation values could be obtained, irrespective of the concentration included. The inclusion of magnesium stearate into the different formulations produced mixtures with good flowability as the %RSD for mass variation were considered relatively small and thus relatively uniform tablets were tableted. However, an increase in lubricant concentration did not significantly influence mass variation and it can therefore be concluded that the incorporation of 1% w/w magnesium stearate in terms of weight variation, is impractical. Interestingly, powder formulations delivered a more uniform tablet weight compared to the bead formulations. Nonetheless, this was only a relatively minor observation.

Considering friability of the different tablet formulations, it was remarkable that the type of filler indicated that only formulations which contained CombiLac® as filler were deemed acceptable. This observation may be misleading as a more in-depth study (Annexure D) showed that the method of production played a more prominent role. Furthermore, RetaLac® bead formulations displayed the most unacceptable friability results as most of these formulations portrayed a percentage friability of more than 5%. Powder formulations produced tablets that were considered suitable, whereas bead formulations presented an average friability value of 17.31 times higher than that of the powder formulations. The incorporation of magnesium stearate expectedly delivered poor friability results, indicating that these formulations produced tablets that were highly brittle. The level of lubricant concentration, again, did not display any noteworthy difference in terms of friability; and thus again it would rather be more meaningful to include magnesium stearate in a lower concentration according to these findings. Addition of Kollidon® 90F provided no trend in the percentage friability obtained for the different tablet formulations. Although the formulations comprising 2% w/w Kollidon® 90F presented the lowest average friability value, the method of production again exerted a more distinctive influence (Annexure D). As stated the different bead formulations formed highly friable tablets that did not adhere to the BP (2016) specifications.

The average tensile strength values obtained followed the same trend as the friability values. Conversely, here the type of filler that indicated the highest tensile strength could not be clearly identified. Interestingly formulations containing fillers that consist of MCC (CombiLac®, MicroceLac® 101 and Pharmacel® 101) provided harder tablets. Once more the type of production method played a more noteworthy role in the average tensile strength of the different tablet formulations, whereas the concentrations lubricant and binder were considered unimportant.

For disintegration analysis pertaining to this study, an average disintegration time longer than 900 s (15 min) was deemed appropriate as the objective was to produce tablets with sustained release properties. Tablets considered as non-disintegrating are expected to assist in the extended release of the active ingredient (van Rooyen, 2017). Contradicting to all other results achieved, the average disintegration values indicated that formulations which were manufactured utilising bead formation by means of extrusion-spheronisation, and which comprised 1% w/w magnesium stearate and 5% w/w Kollidon® 90F exhibited the most acceptable values. These results were expected as beads are harder and more difficult to erode once exposed to an aqueous media (it is a multi-stage disintegration process, i.e. from tablet to bead to smaller particles); magnesium stearate is known to delay disintegration due to its hydrophobic nature (Bolhuis *et al.*, 1981) and therefore may postpone water penetration into the tablet which facilitates disintegration; and Kollidon® 90F forms a gel matrix when in solution that may also retard disintegration (Bühler, 1992).

Through experimentation and implementation of the factorial design, it could be seen that the binder and lubricant concentrations were indicative of certain ratios amounting to formulations displaying more appropriate properties to not only obtain acceptable tablets, but that are furthermore able to provide sustained release of the active ingredient. Overall, it could be concluded that the inclusion of magnesium stearate was necessary. Although the concentration was deemed less important through evaluation of most of the tablet properties, according to the disintegration analysis, a 1% w/w concentration will suffice. According to the full factorial design, the inclusion of a binder did not play a significant role, but the inclusion of Kollidon® 90F rendered diverse results where the exclusion of the binder favourably improved mass variation results; the 2% w/w concentration produced tablet formulations that exhibited harder and more resilient tablets; and formulations comprising 5% w/w Kollidon® 90F delivered tablets which depicted delayed disintegration properties. Additionally, the type of filler included exerted some effect on tablet properties, though this was not as conspicuous as the method of production. Powder formulations generally displayed more favourable tablet properties, except for the disintegration characteristic where the bead formulations were considered more ideal. Permitting these results obtained, formulations comprising 1% w/w magnesium stearate and 2% w/w Kollidon® 90F were selected to further investigate their swelling and erosion properties as well as their drug release profiles in order to establish which formulations portray sustained or modified release of gliclazide.

4.4.4 Swelling and erosion

Swelling and erosion experiments were conducted on the selected formulations (powder tablets, beads and bead tablets) in accordance with section 3.7.6. From the results obtained, Figures 4.21ï 4.23 were constructed to display the swelling characteristics for the selected formulations; and Table 4.24 was constructed to indicate the erosive properties thereof. The same abbreviations used as previously indicated in the full factorial design with now added suffixes (PT indicating powder tablets, B indicating beads and BT indicating bead tablets) were utilised to describe the different formulations.

As seen in Figure 4.21, the powder tablet formulations depicted a limited swelling capability, with RetaLac® exhibiting the highest swelling propensity of 22.26%. This may be attributed to the hypromellose, which is a hygroscopic powder and has a tendency to retain absorbed moisture (Eyjolfsson, 2015). This property may also lead to the establishment of a hydrophobic matrix, once in solution that may prolong drug release. This hydrated matrix forms a protective barrier of the content, and therefore the tablet shape may be maintained. The tablet may therefore not experience erosion during exposure to the aqueous medium (Sriamornsak *et al.*, 2007). Cassava starch/HPMC tablets portrayed a maximum swelling percentage of 14.28%, rendering these tablets the second most susceptible formulation towards swelling. This powder mixture contains 17.4% w/w HPMC and therefore the same reasoning may be followed as with RetaLac® powder tablet formulations. Generally, all other powder tablet formulations displayed limited swelling, which was only achieved over an extended time period (Esterhuizen-Rudolph, 2015; Sriamornsak *et al.*, 2007). MicroceLac® 100 powder tablet formulations portrayed relatively low swelling (maximum of 2.31%) and rather eroded as indicated in Table 4.24 as well as with the disintegration analysis (section 4.4.2).

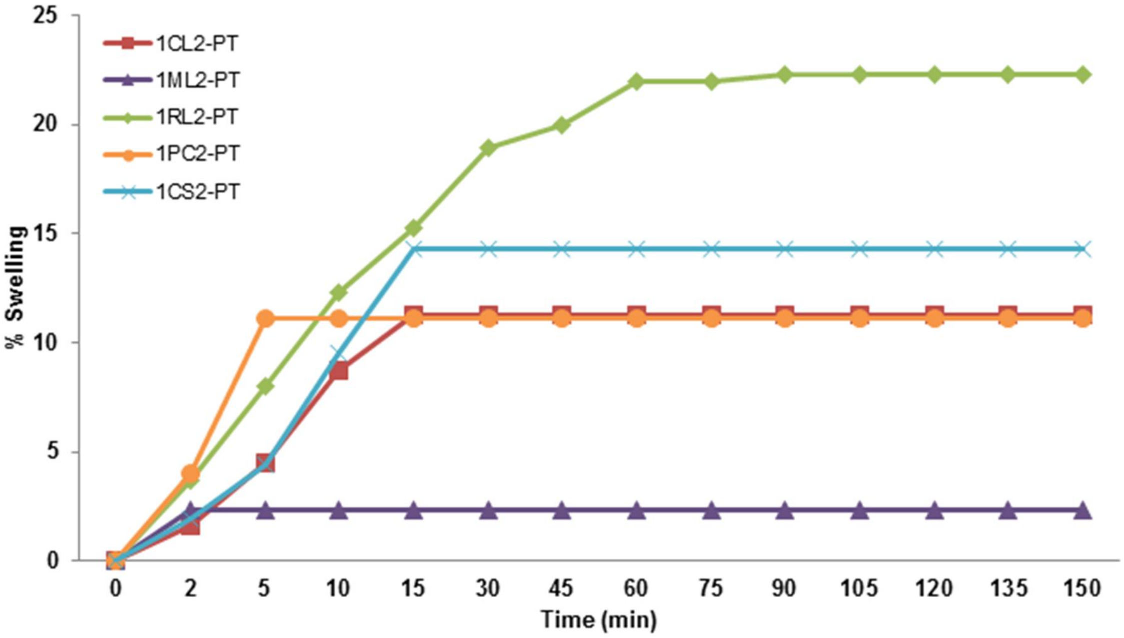


Figure 4.21: *Graphs depicting the percentage swelling for all the respective powder tablet formulations*

The bead formulations exhibit a higher level of swelling for most formulations (Figure 4.22), with RetaLac® beads having a lower swelling percentage relative to the related powder tablet formulations. This may be attributed to the smaller size of the beads rendering a larger surface area exposed to the aqueous media when compared to the tablet formulations. Thus, RetaLac® beads are able to absorb moisture, but simultaneously form the hydrophobic barrier more quickly, which in turn leads to slower swelling of the individual beads. Swelling of MicroceLac® 100 beads were comparatively higher than the respective powder tablet formulations. Contradictory to what transpired with the powder tablet formulations, the bead formulations did not erode in any way. Beads that consisted of Cassava starch/HPMC portrayed a relatively high percentage swelling (17.76%) during the first 10 min after which these beads remained intact, but did not display any additional swelling characteristics. The Pharmacel® 101 and CombiLac® beads exhibited similar initial swelling rates, however, CombiLac® beads only swelled for 10 min, whereas Pharmacel® 101 beads depicted swelling up until 30 min, rendering a maximum swelling percentage of 14.74%.

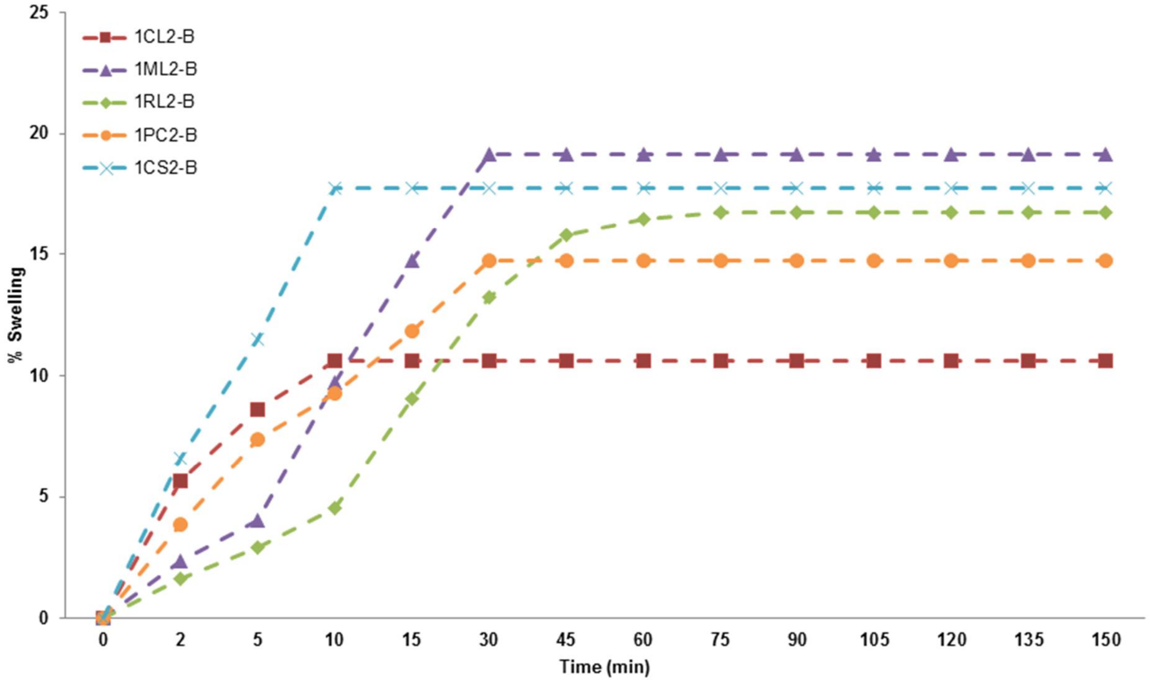


Figure 4.22: *Graphs depicting the percentage swelling for all the respective bead formulations*

Bead tablets were subsequently manufactured and tested to analyse their swelling properties, but neither Pharmacel® 101 nor Cassava starch/HPMC beads were successfully tableted. Figure 4.23 was constructed after subsequent swelling experiments of the bead formulations that could be tableted. RetaLac® once again depicted the highest swelling value with regards to the percentage moisture that was absorbed, which once again, may be attributed to the same reasoning followed with the comparative RetaLac® powder tablets, and bead formulations. CombiLac® bead tablets also displayed a similar trend as its related powder tablets and bead formulations. These results obtained are thus an indication that, regardless the production method, CombiLac® formulations display a constant and predictable rate of moisture absorption. MicroceLac® 100 bead tablets exhibited the lowest rate of moisture absorption, with a subsequent maximum swelling percentage of approximately 8.723%. This percentage swelling was furthermore only achieved after 120 min, depicting a slow, steady fluid uptake rather than fast absorption, as seen with the other fillers.

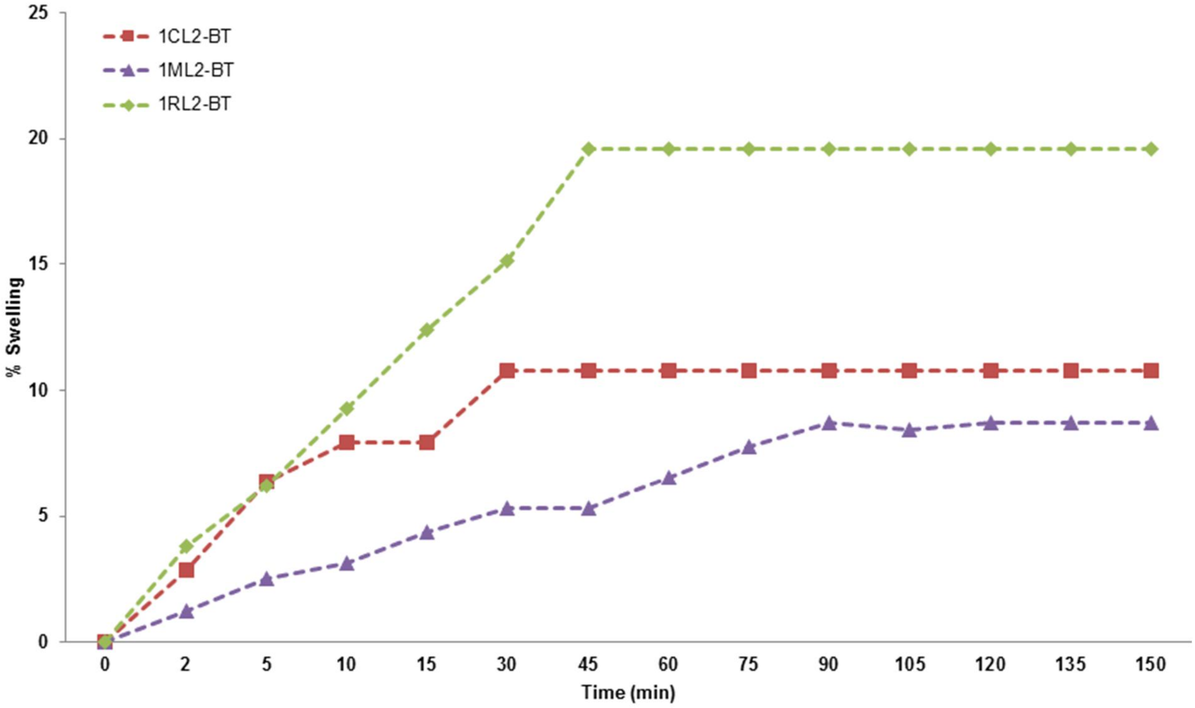


Figure 4.23: *Graphs depicting the percentage swelling for all the respective bead tablet formulations*

Following swelling analysis, erosion experiments were performed on the formulations that did not erode in the aqueous media by subjecting the formulations to oven drying (section 3.7.6). The powders were dried until no mass variation was observed for 3 consecutive measurements and the results tabled in Table 4.24.

Table 4.24: *Percentage erosion of the analysed formulations*

Filler	Formulation	Percentage erosion (%)
CombiLac®	Powder tablets	13.87
	Beads	5.63
	Bead tablets	23.49
MicroceLac® 100	Powder tablets	100
	Beads	11.41
	Bead tablets	23.05
RetaLac®	Powder tablets	19.93
	Beads	23.55
	Bead tablets	24.39
Pharmacel® 101	Powder tablets	31.21
	Beads	14.42
Cassava starch/HPMC	Powder tablets	37.14
	Beads	81.91

As observed, the method of production played a relative role during erosion analysis due to the fact that the bead tablets of the formulations that could be tableted illustrated the highest percentage erosion. Powder tablets obtained from formulations that consisted of MCC (CombiLac®; MicroceLac® 100; and Pharmacel® 101) portrayed higher erosion values compared to powder tablets comprising hypromellose or HPMC (RetaLac® and Cassava starch/HPMC). This was expected as the last mentioned formulations absorbed more moisture during swelling analysis. CombiLac® formulations showed a constant rate and volume of moisture absorption during swelling analysis, however, varying results were obtained during the erosion experiments. The following rank order for percentage erosion of CombiLac® formulations could be created: bead formulations Ó Beads >> powder tablets. MicroceLac® 100 formulations displayed a similar tendency, however, the powder tablet formulation did not erode, but rather disintegrated completely (100%) during swelling experiments. No significant difference in erosion values could be seen between RetaLac® beads and bead tablets. Cassava starch/HPMC formulations exhibited the highest mass loss and consequently percentage erosion, possibly due to the hygroscopicity of HPMC, which retains fluid in a similar way to hypromellose.

4.4.5 Assay

Gliclazide content was tested for all powder tablets, beads as well as bead tablet formulations (Table 4.25) according to section 3.7.8. All of the samples (i.e. tablet and 100 mg beads) were formulated to each contain 10% w/w gliclazide (10 mg). No conspicuous differences could be detected between the individual powder tablets, beads or bead tablets produced from a selected filler. All of the different samples, except for the RetaLac® formulations adhered to the criteria set by the BP (2016) where it is indicated that formulations containing gliclazide may vary in content between 85ï 115%. RetaLac® formulations deviated by more than 30% in terms of gliclazide content. Furthermore, distinguishing between the formulations in terms of the filler that was incorporated, it is clear that RetaLac® formulations overall depicted the lowest gliclazide content, regardless the method of production that was employed. All other formulations illustrated similar gliclazide content, with MicroceLac® 100 formulations displaying the highest gliclazide content obtained.

Table 4.25: *Gliclazide content of the assayed formulations*

		Gliclazide Mass (mg)	% Content
CombiLac®	Powder Tablets	9.488	94.937
	Beads	9.512	95.357
	Bead Tablets	9.637	96.832
MicroceLac® 100	Powder Tablets	9.746	97.961
	Beads	9.687	96.351
	Bead Tablets	9.961	99.621
RetaLac®	Powder Tablets	6.401	64.083
	Beads	6.813	68.198
	Bead Tablets	6.429	64.796
Pharmacel® 101	Powder Tablets	9.501	95.344
	Beads	9.648	96.783
Cassava starch/HPMC	Powder Tablets	9.333	93.612
	Beads	9.218	92.918

4.4.6 Drug release analysis

Dissolution studies are conducted to analyse the drug release profile of a tested formulation. This is a critical step, especially pertaining to the absorption and bioavailability of a drug (Maggi *et al.*, 2005). The selected formulations were subjected to dissolution analysis under the conditions explained in section 3.7.9 and subsequently analysed with regards to the gliclazide content utilising ultraviolet spectrophotometry (section 3.8). The values obtained for each formulation during the assay experiments were noted as 100% dissolution; and the percentage dissolution for the various formulations were related to this value.

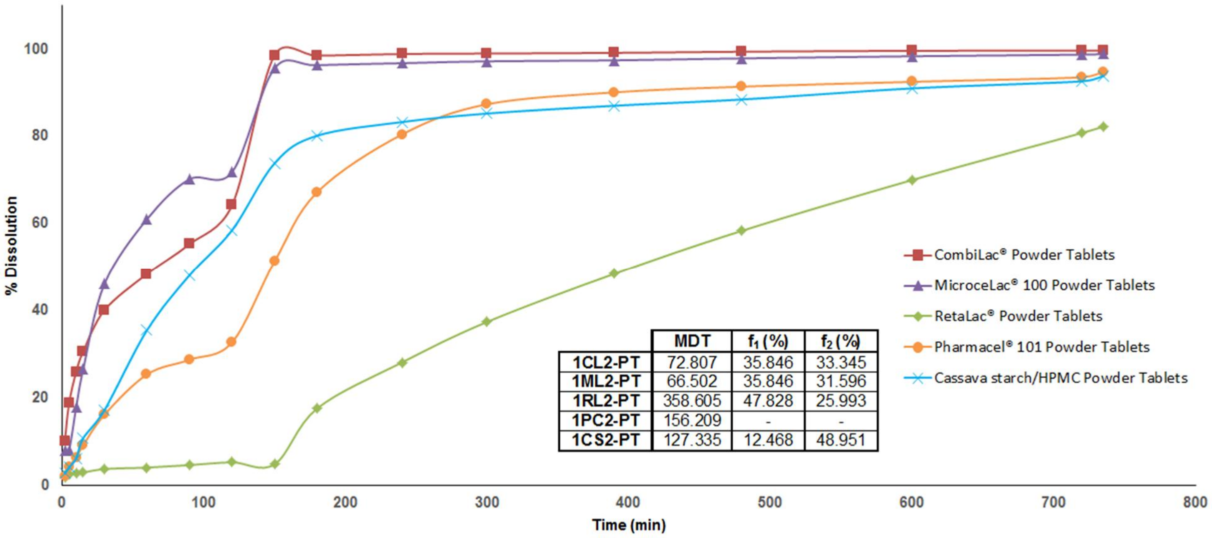
Mean dissolution time (MDT) may be defined as the average dissolution time of the percentage drug released at all the tested time intervals during dissolution studies. A higher MDT value is indicative of a slower drug release profile (Esterhuizen-Rudolph, 2015; Qiu, 2009) The f_1- and f_2-values of each formulation were calculated relative to the Pharmacel® 101 powder tablet formulation to establish whether the drug release profiles displayed a significant difference comparative to the said formulation. No statistical difference is observed when the f_1-value is less than 15% and f_2-value is higher than 50% (Costa & Lobo, 2001; Moore & Flanner, 1996).

During drug release studies, the powder tablet formulations exhibited varying results (Figure 4.24). Pharmacel® 101 powder tablets displayed a relatively fast rate of drug release during the first 2 h in the acidic media. As soon as the media was changed to a more neutral pH (pH 6.8), the rate of release increased even more rapidly. After 300 min the dissolution rate declined until the maximum amount of gliclazide was released. CombiLac® powder tablet formulations depicted a faster initial rate of release during the first 2 h compared to the Pharmacel® 101 powder tablets. This could be observed again until the media was changed to a pH of 6.8. Thereafter almost the entire remaining drug was released before the next interval. The gliclazide release profile of this formulation was considered statistically significantly different from the Pharmacel® 101 powder tablet formulation due to an f_1-value of 35.846% and an f_2-value of 33.345% that were calculated. This may be due to the fact that the CombiLac® powder tablet formulation competitively displayed an increased drug release rate (i.e. faster release) and a higher amount of gliclazide released.

MicroceLac® 100 powder tablets exhibited a similar drug release profile as the CombiLac® powder tablet formulations; however it illustrated an even faster initial drug release rate and a MDT value of 66.502 min, which indicates that the MicroceLac® 100 powder tablet formulation released gliclazide the fastest. The f_1-and f_2-values for this formulation, furthermore, are relatively similar to that of CombiLac® powder tablets, illustrating that this formulation also display statistical significant differences in their gliclazide release profiles when compared to Pharmacel® 101 powder tablets. RetaLac® powder tablets depicted the lowest concentration gliclazide released as well as the lowest percentage dissolution obtained (82.225%). It additionally displayed a relatively slow initial gliclazide release rate and its MDT value signified the slowest overall dissolution time (358.61 min). However, the rate of release was considerably increased after the media was adjusted to pH 6.8, i.e. from time t = 150 min (as seen in Figure 4.24). A near-linear rate of release ($R^2 = 0.9868$) from time, t = 150 min to t = 720 min, was obtained for the RetaLac® powder tablet formulation, which for these powder tablet formulations, is the most ideal gliclazide release profile that could be achieved for this study.

As previously stated, RetaLac® consists of, amongst others, hypromellose which is a hydrophilic cellulose ether that forms a swellable matrix; and this powder is normally utilised in modified release dosage forms due to the fact that it is able to effectively gel and subsequently decrease drug release rates, i.e. prolong therapeutic effect (van Rooyen, 2017). Upon contact with the dissolution medium, it promptly absorbs water that penetrates the polymer through various pores, causing hydration. The polymer uncoils and hydrogen bonds between chains are broken, leading to the activation of addition hydrogen bonding with more water molecules. (Bettini *et al.*, 2001; Kim & Fassihi, 1997). A gel-like layer is formed and the pores are blocked, which causes reduced water uptake. Consequently the gel-layer prohibits the drug from dissolving too rapidly as dilution and erosion is decreased. Thus slower diffusion and drug release occur (van Rooyen, 2017). For a poorly water-soluble drug, such as gliclazide, the rate-limiting factor for release of the drug is influenced by self-erosion as a release mechanism (Costa & Lobo, 2001). Again, the fit-factors specified statistical significant differences in the gliclazide release profiles of the RetaLac® powder tablet formulation and the Pharmacel® 101 powder tablet formulation.

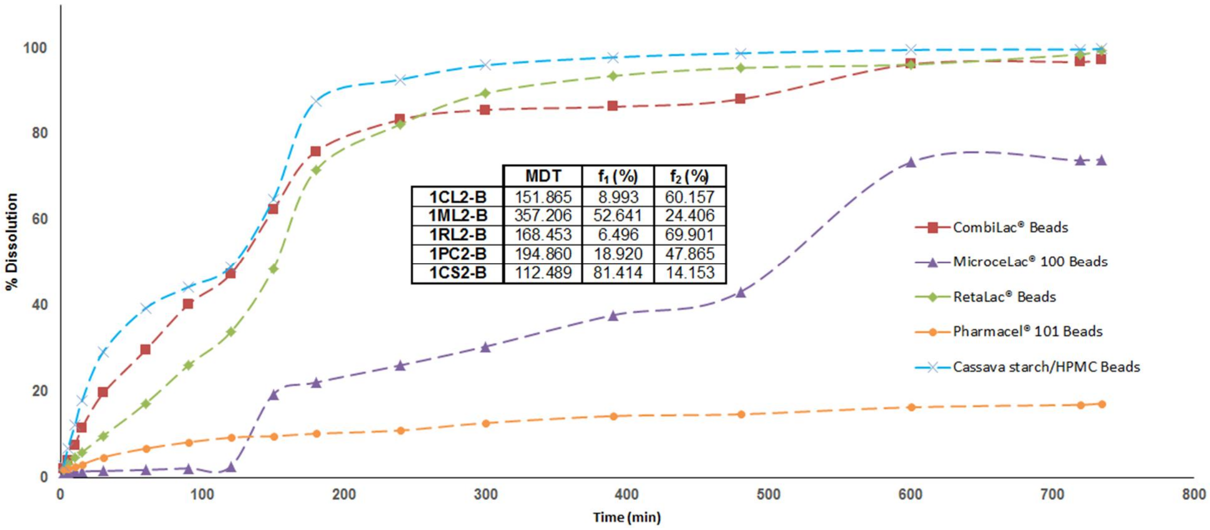
Interestingly, the Cassava starch/HPMC powder formulation, which likewise comprises hypromellose and which was included in a higher concentration, did not exhibit the same drug release profile as observed with the RetaLac® powder tablet formulation. In fact, this formulation illustrated an initial near-linear release rate ($R^2 = 0.9918$) up until t = 150 min, where approximately 75% gliclazide was already released and in solution from the formulation. No definite conclusive results were obtained in terms of the fit-factors as the f_1-value indicated no statistical significant difference between the Cassava starch/HPMC powder formulation and the Pharmacel® 101 powder tablet formulation, whereas the f_2-value did show a statistical significant difference in the drug release profiles.



	MDT	f_1 (%)	f_2 (%)
1CL2-PT	72.807	35.846	33.345
1ML2-PT	66.502	35.846	31.596
1RL2-PT	358.605	47.828	25.993
1PC2-PT	156.209	-	-
1CS2-PT	127.335	12.468	48.951

Figure 4.24: *Dissolution profiles of the tested powder tablet formulations*

Upon the construction of the drug release curves for the bead formulations (Figure 4.25), all the formulations were likewise statistically compared to the Pharmacel® 101 powder tablet formulation utilising the difference and similarity factors (f_1 and f_2). Generally, the formation of beads, except for the RetaLac® bead formulation, portrayed higher MDT-values which is indicative of slower drug release from the selected bead formulations. The effect observed after the media was changed to pH 6.8 for the powder tablet formulations, could not be seen here, except for the MicroceLac® 100 bead formulation. CombiLac® and Cassava starch/HPMC bead formulations followed similar trends as was depicted by the accordingly related powder tablet formulations. Although these formulations portrayed similar dissolution profiles as the powder tablet formulations, the CombiLac® bead formulation is not considered statistically significantly different ($f_1 = 8.993\%$; $f_2 = 60.157\%$) from the Pharmacel® 101 powder tablet formulation, whereas the Cassava starch/HPMC bead formulation may be deliberated as statistically significantly different.

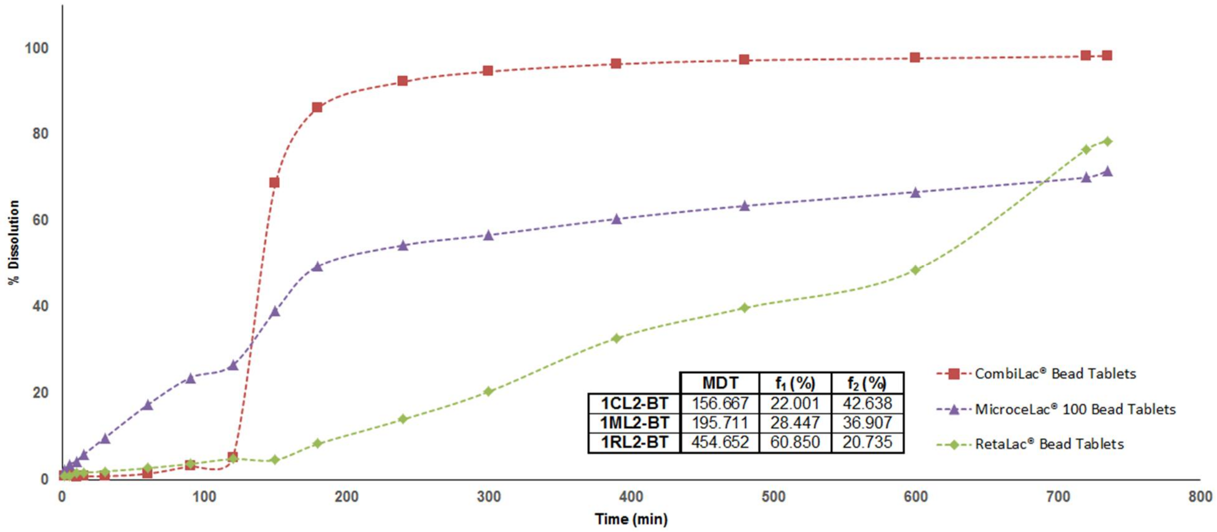


	MDT	f_1 (%)	f_2 (%)
1CL2-B	151.865	8.993	60.157
1ML2-B	357.206	52.641	24.406
1RL2-B	168.453	6.496	69.901
1PC2-B	194.860	18.920	47.865
1CS2-B	112.489	81.414	14.153

Figure 4.25: *Dissolution profiles of the tested bead formulations*

Viewing the drug release profile of the MicroceLac® 100 bead formulation, the formation of beads hindered initial gliclazide release as this formulation displayed a relatively different release profile (slowed) when compared to the MicroceLac® 100 powder tablet formulation. Compacted beads were more densely packed compared to the powder tablet formulation, thus further inhibiting dissolution media penetration. This formulation depicted a slow initial rate of gliclazide release, until the dissolution media was changed to pH 6.8. The increase in the rate of drug release may be attributed to the insolubility of MCC. Due to this insolubility, dissolution of gliclazide is more reliant on pure diffusion (Kranz *et al.*, 2009). Gliclazide depicts increased solubility in the more neutral medium, and therefore displayed a higher rate of dissolution from the bead formulation after the change in dissolution media. Compared to the powder tablet formulation, the RetaLac® bead formulation displayed a near-sigmoidal rate of drug release. This formulation did not depict modified release properties pertaining to Figure 4.25, but rather followed a more immediate drug release profile as approximately all of the gliclazide was released and in dissolution within 5 h. The increased rate of drug release from this formulation may probably be attributed to the smaller size of the RetaLac® beads, thus eroding faster than a powder tablet would have. The Pharmacel® 101 bead formulation did not release gliclazide to the same extent as the other formulations as a maximum percentage dissolution of only 17.288% was obtained. A MDT value of 194.860 min indicates that this formulation released gliclazide relatively slower than the Pharmacel® 101 powder tablet formulation and other bead formulations, except for the Cassava starch/HPMC bead formulation. A more modified drug release profile was therefore obtained with this formulation, however, due to the inadequate total amount of gliclazide released this formulation is deemed unacceptable. Overall, the MicroceLac® 100, Pharmacel® 101 and Cassava starch/HPMC bead formulations portrayed statistical significant differences (f_1 >15%; f_2 <50%) in their dissolution profiles compared to the Pharmacel® 101 powder tablet formulation. On the other hand, according to the fit-factors, the CombiLac® and RetaLac® bead formulations could be considered having similar (f_1 <15%; f_2 >50%) dissolution profiles to that of the Pharmacel® 101 powder tablet formulation.

CombiLac®, MicroceLac® 100 and RetaLac® bead formulations were successfully tableted and analysed with regards to the drug release profiles (Figure 4.26). Overall, bead tablet formulations compared to the powder tablet formulations displayed higher MDT values, signifying that gliclazide was expectedly more slowly release from the bead tablet formulations. Relating the bead tablet formulations to the bead formulations, the MDT values showed that once tableted, the bead tablet formulations were not necessarily able to delay gliclazide release. The mean dissolution time for CombiLac® formulations did not vary significantly. These formulations released gliclazide at a relatively similar rate. MicroceLac® 100 bead tablet formulations released gliclazide at a higher rate compared to the bead formulation. The RetaLac® bead tablet formulation was the only bead tablet formulation that was able to prolong the release of gliclazide. All of the bead tablet formulations depicted statistically significantly different (f_1 >15%; f_2 <50%) drug release profiles when related to the Pharmacel® 101 powder tablet formulation. Again the CombiLac® bead tablet formulation displayed a delayed release profile up to 120 min, thereafter almost a burst release is seen (Figure 4.26) where approximately all of the gliclazide is released within an hour. The MicroceLac® 100 bead tablet formulation did release gliclazide more slowly than a conventional tablet, however only a maximum concentration of 71.69% could be released, rendering it undesirable for this study. The RetaLac® bead tablet formulation was the only bead tablet formulation able to follow a more sustained release drug release profile, but as with the MicroceLac® 100 bead tablet formulation, this formulation was not able to fully release the entire amount of gliclazide. In future it might be wise to extend the dissolution experiment's time to determine whether the RetaLac® bead tablet formulation might be able to fully release the gliclazide dose.



	MDT	f_1 (%)	f_2 (%)
1CL2-BT	156.667	22.001	42.638
1ML2-BT	195.711	28.447	36.907
1RL2-BT	454.652	60.850	20.735

Figure 4.26: *Dissolution profiles of the tested bead tablet formulations*

Overall, the various methods of manufacture each presented formulations that did not perform optimally. The powder tablet formulations generally exhibited faster drug release profiles where more gliclazide was obtained in solution (i.e. 100% released). Bead and bead tablet formulations, generally illustrated more modified release profiles (either delayed release or slow release), but none of the formulations exhibited a definite sustained release profile. However, none of these formulations were able to release gliclazide completely. The RetaLac® bead tablet formulation depicted the most modified release profile.

* * *

Chapter 5:
SUMMARY AND FUTURE PROSPECTS

5.1 Summary

The aim of the study was to ascertain whether a multiple-unit sustained release dosage form for gliclazide could be formulated utilising beads manufactured by means of extrusion-spheronisation.

Considering the objectives set in section 1.3, the following were met:

- The selected fillers (CombiLac®, MicroceLac®, RetaLac®, Pharmacel® 101 and a mixture of Cassava starch and HPMC) were successfully characterised with regards to their physical properties and morphology.
- Beads were effectively formulated utilising the abovementioned fillers and 10% w/w gliclazide by means of extrusion-spheronisation.
- The selected fillers (with and without gliclazide), were analysed and a profile for each filler tested was constructed (by means of the SeDeM Diagram Expert System) to evaluate their suitability for direct compression. Most of the powders were deemed acceptable for direct compression with the exception of Cassava starch/HPMC, which proved to be adequate for direct compression upon the addition of a lubricant and a binder.
- The efficacy of the SeDeM Diagram Expert System was evaluated for use with pharmaceutical beads. Although most beads were deemed acceptable for direct compression it was noted that the Pharmacel® 101 and Cassava starch/HPMC beads did not successfully produce beads after a full factorial design was employed to determine the optimum formulations. It was similarly noted that the compressibility factor of the SeDeM Diagram Expert System was not adequate for the analysis of beads which was also noted by Hamman *et al.* (2017).
- All manufactured beads were assessed with regards to their physical properties, internal and external morphology, and the drug content. All of the bead formulations tested depicted a modified release profile, though not sustained release as intended.

Physically, the beads were deemed acceptable when subjected to the criteria required by the BP (2016).

- Concave tablets (9 mm diameter) could be manufactured from most of the powder and bead mixtures (as seen in Table 4.21) without the use of unnecessary excipients.
- The subsequent tablet formulations were evaluated with regards to their physical properties (including hardness, diameter, thickness, tensile strength, friability, disintegration, and mass variation) and morphology. All the manufactured tablets depicted acceptable results pertaining to the BP (2016) criteria as well as the standards set by this study. The beads that did not amount to tablets proved to be relatively rigid and did not display deformation when subjected to direct compression, thus tablets could not be formed.
- Tablets (both powder and bead tablets) and beads were analysed and compared with regards to their drug release profiles over a 12 h period. All of the drug release profiles of the tested formulations depicted modified release, rather than sustained release. Overall, the various methods of manufacture each presented formulations that did not perform optimally. The powder tablet formulations generally exhibited faster drug release profiles where more gliclazide was obtained in solution (i.e. 100% released). Bead and bead tablet formulations, mostly depicted modified release profiles (either delayed release or slow release), but none of the formulations demonstrated a distinct sustained release profile. None of these formulations were able to release gliclazide completely, however, the RetaLac® bead tablet formulation depicted the most appropriate modified release profile.

Therefore, a multiple-unit modified release dosage form for gliclazide could be formulated utilising beads manufactured by means of extrusion-spheronisation. Al-Kassas *et al.* (2007) found that rapid intestinal absorption may lead to enhanced gliclazide action, and thus it may benefit from a delayed release dosage form as opposed to a sustained release dosage form. In view of this study, it may be more beneficial to rather enhance the modified drug release capabilities of the formulated dosage form, than reformulate to obtain sustained drug release.

5.2 Future prospects

After completion of this study, the following recommendations can be made regarding future investigations:

- The influence exerted by the size of the beads in the various formulations should be investigated. This may be done by comparing tablets manufactured from 0.5, 1.0 and 1.5 mm beads by means of the SeDeM Diagram Expert System, the physical properties of the different formulations, as well as comparing the different drug release profiles.
- Dissolution or drug release experiments should be extended to between 18ï 24 h in order to ensure optimal dissolution of each manufactured dosage form.
- The possibility of obtaining tablet formulations depicting pulsatile release when a mixture of coated and uncoated beads is directly compressed should be investigated.
- One should consider exploring the inclusion of other different excipients, such as other binders (e.g. Kollidon® VA64, Kollidon® 30, HPMC, etc.), lubricants (e.g. talc, Pruv®, Aerosil®, etc.) and even fillers.
- A comparison between physically blended formulations and co-processed fillers should be studied.
- The SeDeM Diagram Expert System should be revised to better accommodate bead formulations with regards to the compressibility factor. This may be accomplished by reviewing the parameters and implementing adequate changes to the acceptable limits of the different parameters.

* * *

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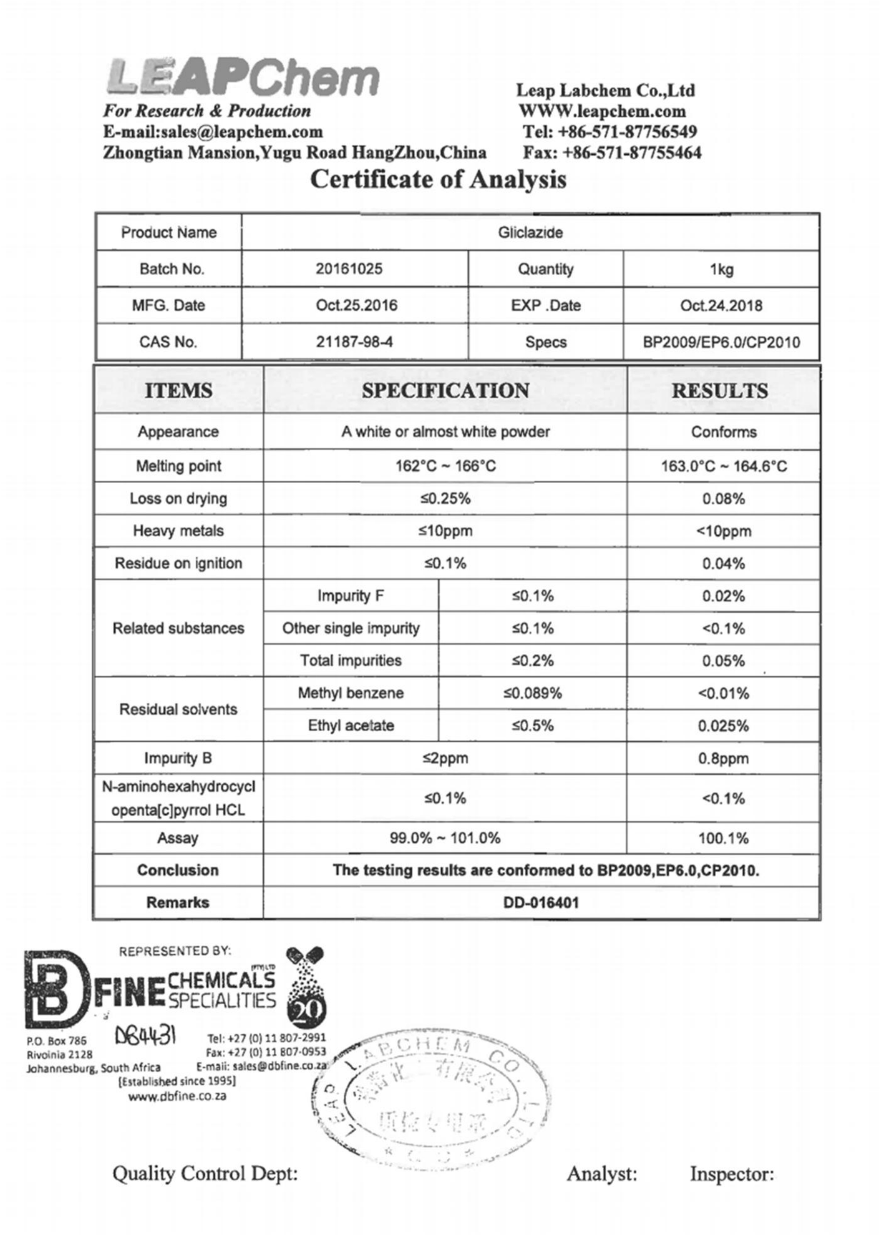
Annexure A:
Gliclazide Certificate of Analysis

* * *



LEAPChem

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Certificate of Analysis

Product Name	Gliclazide		
Batch No.	20161025	Quantity	1kg
MFG. Date	Oct.25.2016	EXP .Date	Oct.24.2018
CAS No.	21187-98-4	Specs	BP2009/EP6.0/CP2010

ITEMS	SPECIFICATION		RESULTS
Appearance	A white or almost white powder		Conforms
Melting point	162°C ~ 166°C		163.0°C ~ 164.6°C
Loss on drying	≤0.25%		0.08%
Heavy metals	≤10ppm		<10ppm
Residue on ignition	≤0.1%		0.04%
Related substances	Impurity F	≤0.1%	0.02%
	Other single impurity	≤0.1%	<0.1%
	Total impurities	≤0.2%	0.05%
Residual solvents	Methyl benzene	≤0.089%	<0.01%
	Ethyl acetate	≤0.5%	0.025%
Impurity B	≤2ppm		0.8ppm
N-aminohexahydrocyclopenta[c]pyrrol HCL	≤0.1%		<0.1%
Assay	99.0% ~ 101.0%		100.1%
Conclusion	**The testing results are conformed to BP2009,EP6.0,CP2010.**		
Remarks	**DD-016401**		

REPRESENTED BY:
DB FINE CHEMICALS (PTY) LTD SPECIALITIES
DB4431
P.O. Box 786
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Johannesburg, South Africa
Tel: +27 (0) 11 807-2991
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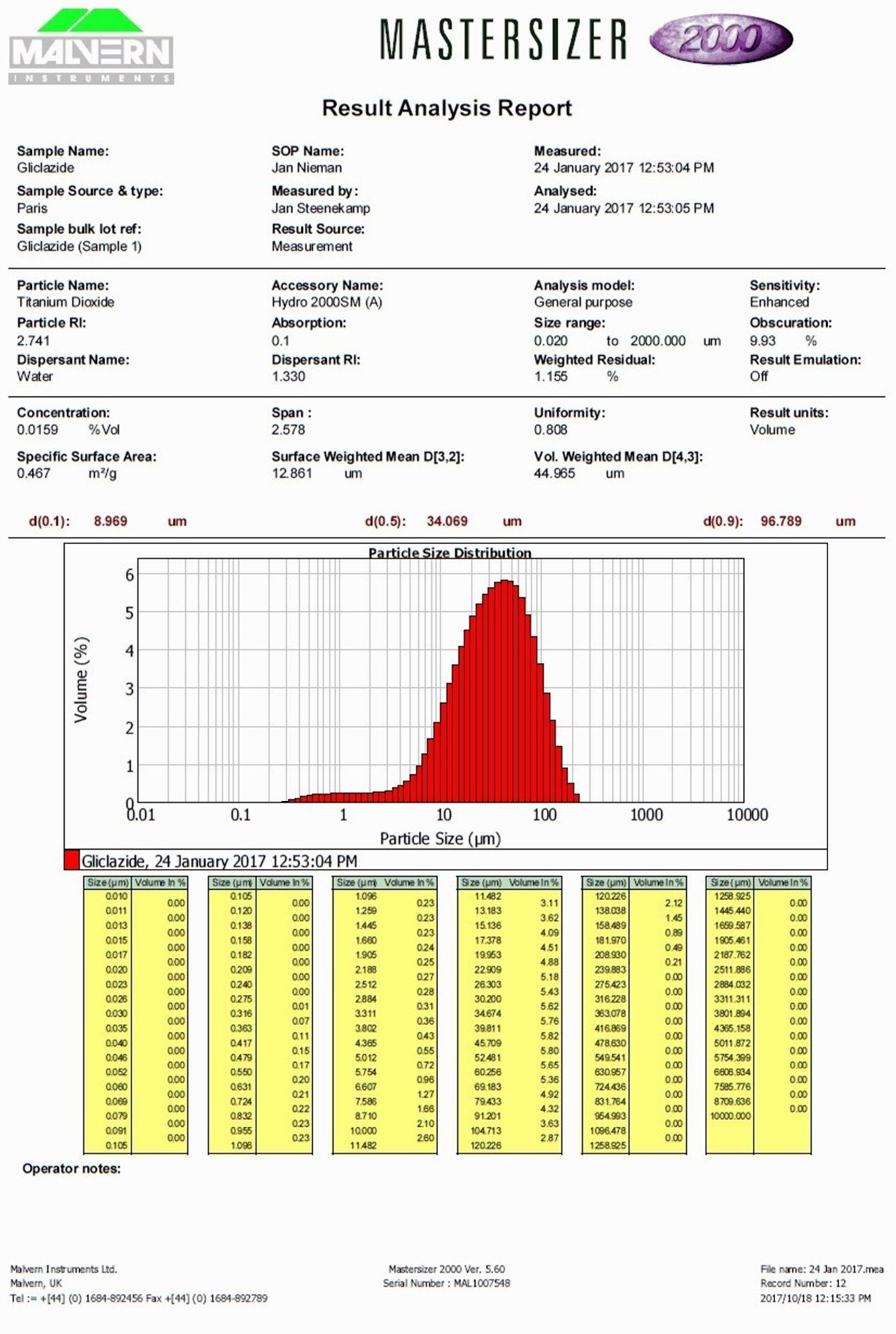
E-mail: sales@dbfine.co.za
[Established since 1995]
www.dbfine.co.za

Quality Control Dept: Analyst: Inspector:

Annexure B:
Malvern® Mastersizer Data Sheets

Annexure B1: Malvern® Mastersizer Data Sheets (Gliclazide Powder Sample 1)



Result Analysis Report

Sample Name:
Gliclazide

Sample Source & type:
Paris

Sample bulk lot ref:
Gliclazide (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
24 January 2017 12:53:04 PM

Analysed:
24 January 2017 12:53:05 PM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Water

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.330

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
1.155 %

Sensitivity:
Enhanced

Obscuration:
9.93 %

Result Emulation:
Off

Concentration:
0.0159 %Vol

Specific Surface Area:
0.467 m²/g

Span :
2.578

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

Uniformity:
0.808

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

Result units:
Volume

d(0.1): 8.969 um **d(0.5): 34.069 um** **d(0.9): 96.789 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	

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	0.01
0.316	0.07
0.363	0.11
0.417	0.15
0.479	0.17
0.550	0.20
0.631	0.21
0.724	0.22
0.832	0.23
0.955	0.23
1.096	

Size (μm)	Volume In %
1.096	0.23
1.259	0.23
1.445	0.23
1.660	0.24
1.905	0.25
2.188	0.27
2.512	0.28
2.884	0.31
3.311	0.36
3.802	0.43
4.365	0.55
5.012	0.72
5.754	0.96
6.607	1.27
7.586	1.66
8.710	2.10
10.000	2.60
11.482	

Size (μm)	Volume In %
11.482	3.11
13.183	3.62
15.136	4.09
17.378	4.51
19.953	4.88
22.909	5.18
26.303	5.43
30.200	5.62
34.674	5.76
39.811	5.82
45.709	5.80
52.481	5.65
60.256	5.36
69.183	4.92
79.433	4.32
91.201	3.63
104.713	2.87
120.226	

Size (μm)	Volume In %
120.226	2.12
138.038	1.45
158.489	0.89
181.970	0.49
208.930	0.21
239.883	0.00
275.423	0.00
316.228	0.00
363.078	0.00
416.869	0.00
478.630	0.00
549.541	0.00
630.957	0.00
724.436	0.00
831.764	0.00
954.993	0.00
1096.478	0.00
1258.925	

Size (μm)	Volume In %
1258.925	0.00
1445.440	0.00
1659.587	0.00
1905.461	0.00
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	

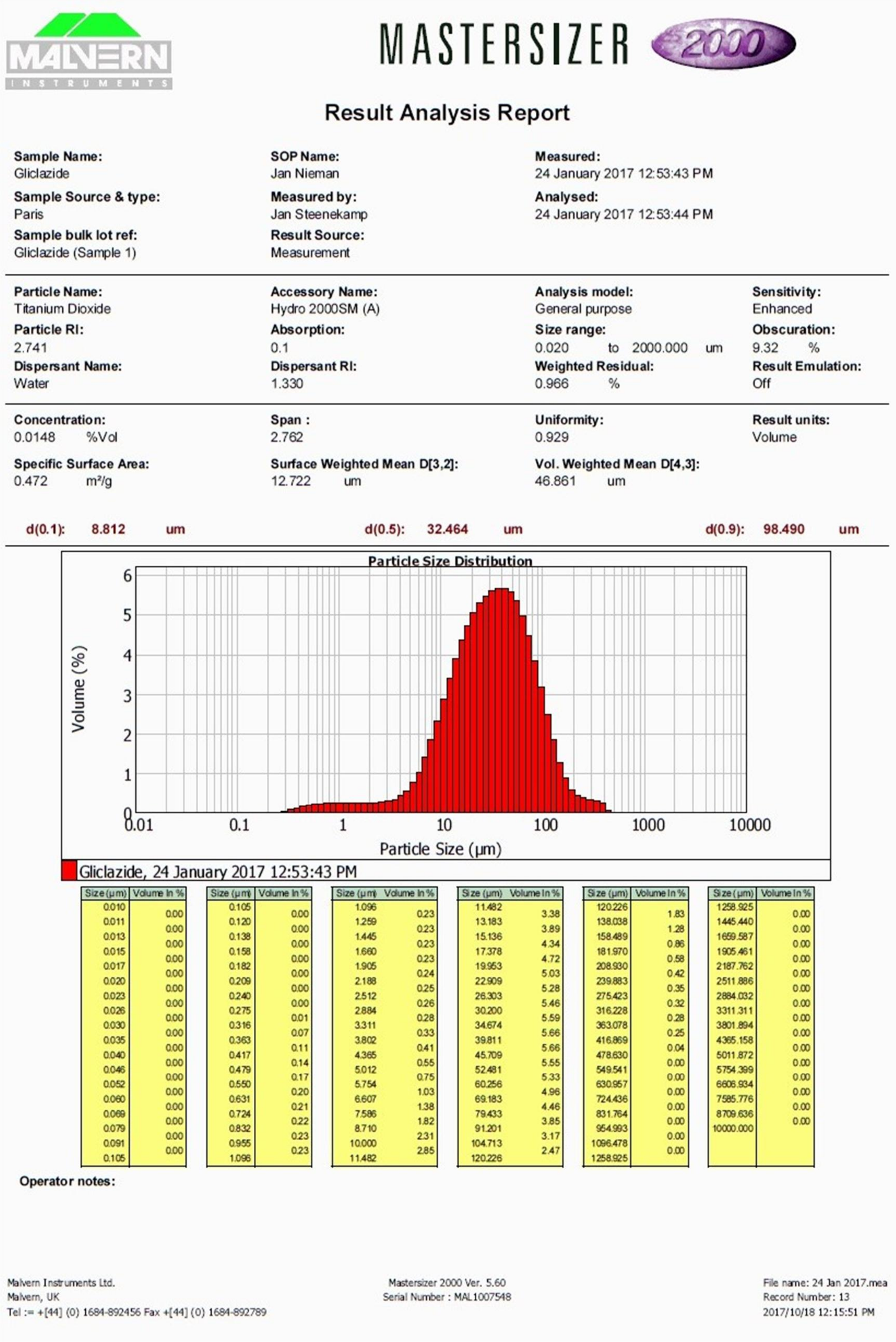
Operator notes:

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: 24 Jan 2017.mea
Record Number: 12
2017/10/18 12:15:33 PM

Annexure B2: Malvern® Mastersizer Data Sheets (Gliclazide Powder Sample 2)



MASTERSIZER 2000

Result Analysis Report

Sample Name:
Gliclazide

Sample Source & type:
Paris

Sample bulk lot ref:
Gliclazide (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
24 January 2017 12:53:43 PM

Analysed:
24 January 2017 12:53:44 PM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Water

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.330

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
0.966 %

Sensitivity:
Enhanced

Obscuration:
9.32 %

Result Emulation:
Off

Concentration:
0.0148 %Vol

Specific Surface Area:
0.472 m²/g

Span :
2.762

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

Uniformity:
0.929

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

Result units:
Volume

d(0.1): 8.812 um **d(0.5):** 32.464 um **d(0.9):** 98.490 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	0.23	11.482	3.38	120.226	1.83	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.23	13.183	3.89	138.038	1.28	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.23	15.136	4.34	158.489	0.86	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.23	17.378	4.72	181.970	0.58	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.24	19.953	5.03	208.930	0.42	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.25	22.909	5.28	239.883	0.35	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.26	26.303	5.46	275.423	0.32	2884.032	0.00
0.026	0.00	0.275	0.01	2.884	0.28	30.200	5.59	316.228	0.28	3311.311	0.00
0.030	0.00	0.316	0.07	3.311	0.33	34.674	5.66	363.078	0.25	3801.894	0.00
0.035	0.00	0.363	0.11	3.802	0.41	39.811	5.66	416.869	0.04	4365.158	0.00
0.040	0.00	0.417	0.14	4.365	0.55	45.709	5.55	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.17	5.012	0.75	52.481	5.33	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.20	5.754	1.03	60.256	4.96	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.21	6.607	1.38	69.183	4.46	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.22	7.586	1.82	79.433	3.85	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.23	8.710	2.31	91.201	3.17	954.993	0.00	10000.000	
0.091	0.00	0.955	0.23	10.000	2.85	104.713	2.47	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

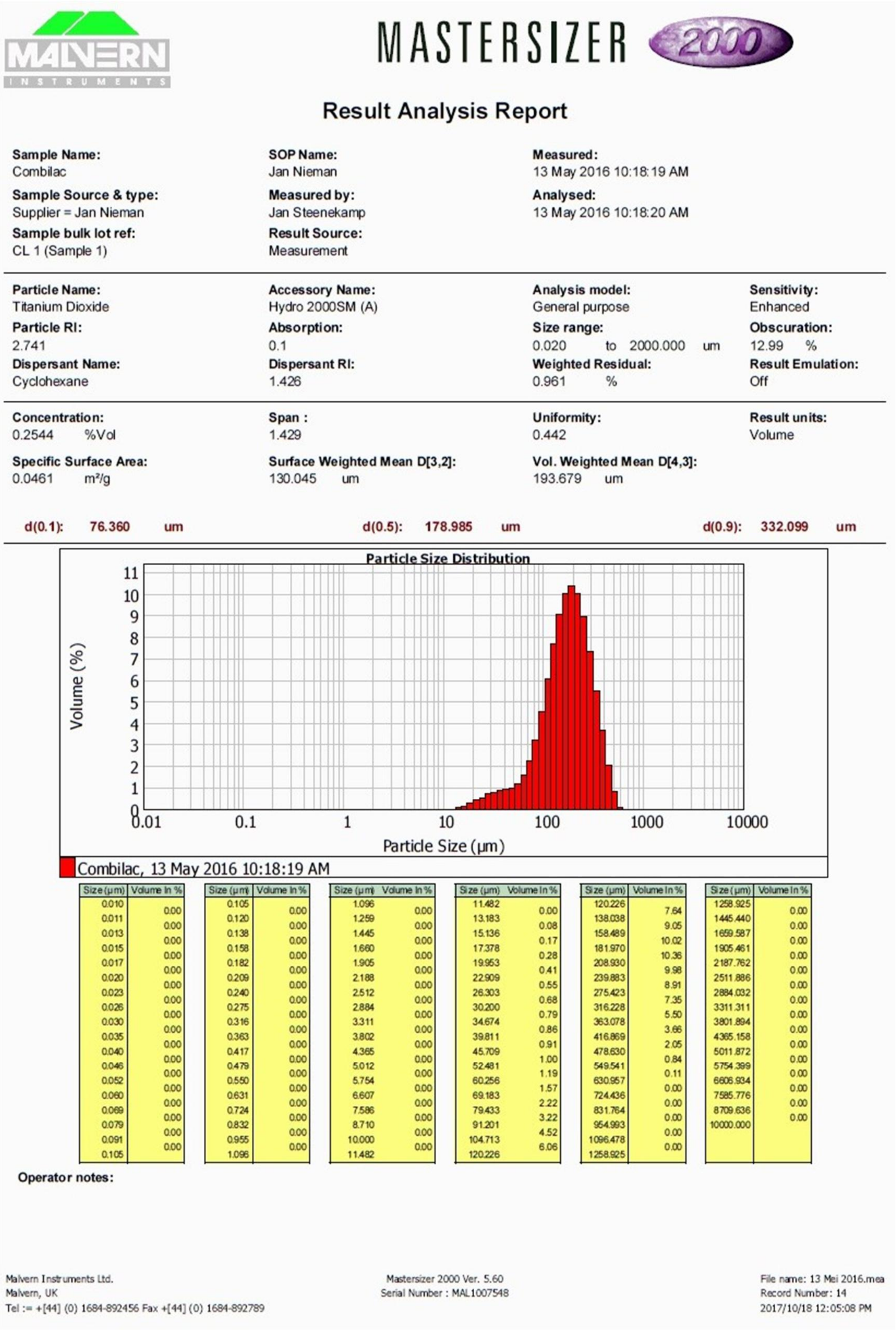
Operator notes:

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: 24 Jan 2017.mea
Record Number: 13
2017/10/18 12:15:51 PM

Annexure B3: Malvern® Mastersizer Data Sheets (CombiLac® Powder Sample 1)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
Combilac

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
CL 1 (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
13 May 2016 10:18:19 AM

Analysed:
13 May 2016 10:18:20 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:
0.961 %

Sensitivity:
Enhanced

Obscuration:
12.99 %

Result Emulation:
Off

Concentration:
0.2544 %Vol

Specific Surface Area:
0.0461 m²/g

Span :
1.429

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

Uniformity:
0.442

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

Result units:
Volume

d(0.1): 76.360 um **d(0.5):** 178.985 um **d(0.9):** 332.099 um

Particle Size Distribution

🟥 Combilac, 13 May 2016 10:18:19 AM

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	7.64	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.08	138.038	9.05	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.17	158.489	10.02	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.28	181.970	10.36	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.41	208.930	9.98	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.55	239.883	8.91	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.68	275.423	7.35	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.79	316.228	5.50	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.86	363.078	3.66	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.91	416.869	2.05	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.00	478.630	0.84	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.19	549.541	0.11	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.57	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.22	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.22	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.52	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	6.06	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

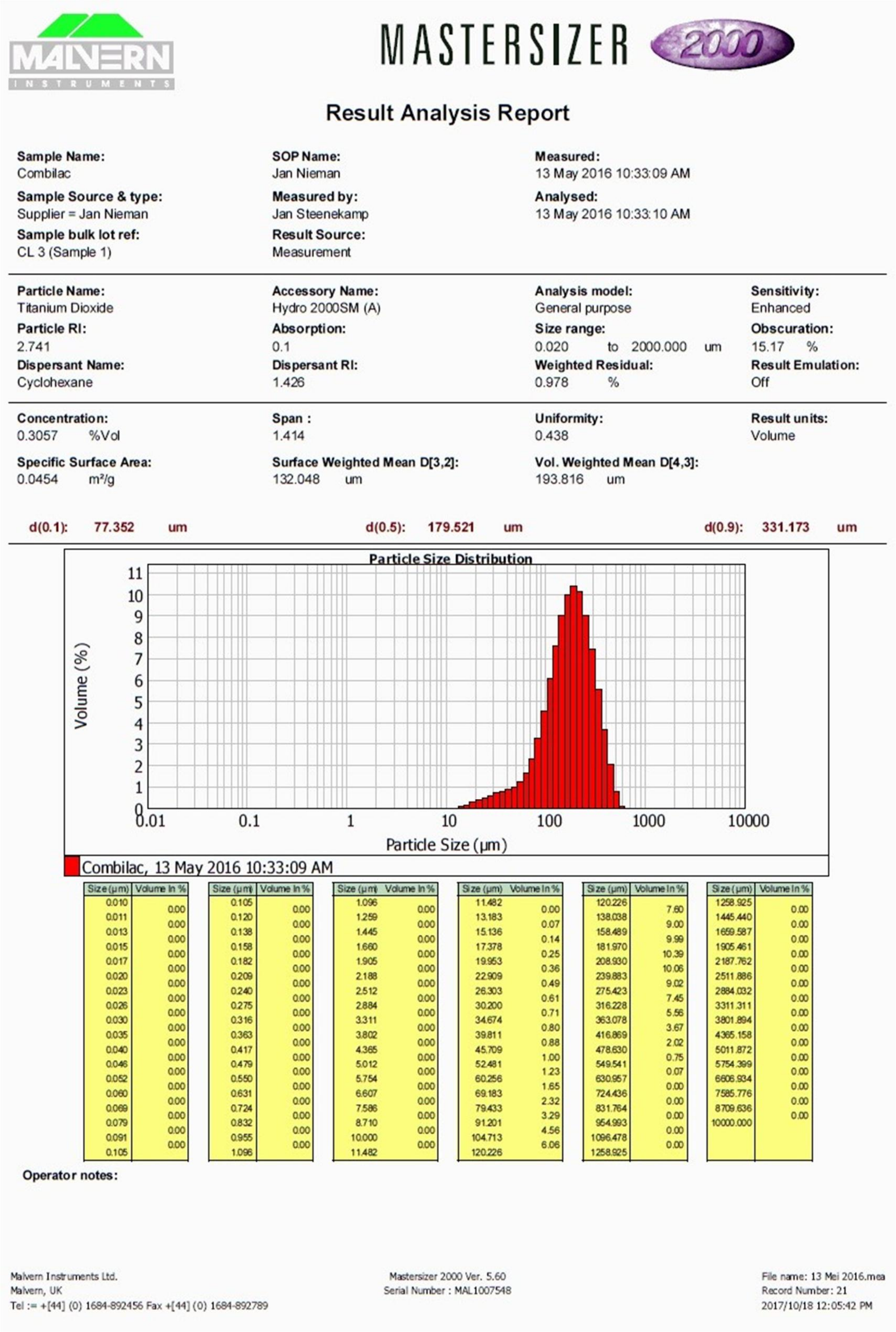
Operator notes:

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: 13 Mei 2016.mea
Record Number: 14
2017/10/18 12:05:08 PM

Annexure B4: Malvern® Mastersizer Data Sheets (CombiLac® Powder Sample 2)



Result Analysis Report

Sample Name:
Combilac

SOP Name:
Jan Nieman

Measured:
13 May 2016 10:33:09 AM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
13 May 2016 10:33:10 AM

Sample bulk lot ref:
CL 3 (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:
15.17 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
0.978 %

Result Emulation:
Off

Concentration:
0.3057 %Vol

Span :
1.414

Uniformity:
0.438

Result units:
Volume

Specific Surface Area:
0.0454 m²/g

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

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

d(0.1): 77.352 um   **d(0.5): 179.521 um**   **d(0.9): 331.173 um**

🟥 Combilac, 13 May 2016 10:33:09 AM

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	7.60	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.07	138.038	9.00	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.14	158.489	9.99	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.25	181.970	10.39	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.36	208.930	10.06	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.49	239.883	9.02	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.61	275.423	7.45	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.71	316.228	5.56	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.80	363.078	3.67	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.88	416.869	2.02	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.00	478.630	0.75	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.23	549.541	0.07	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.65	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.32	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.29	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.56	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	6.06	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

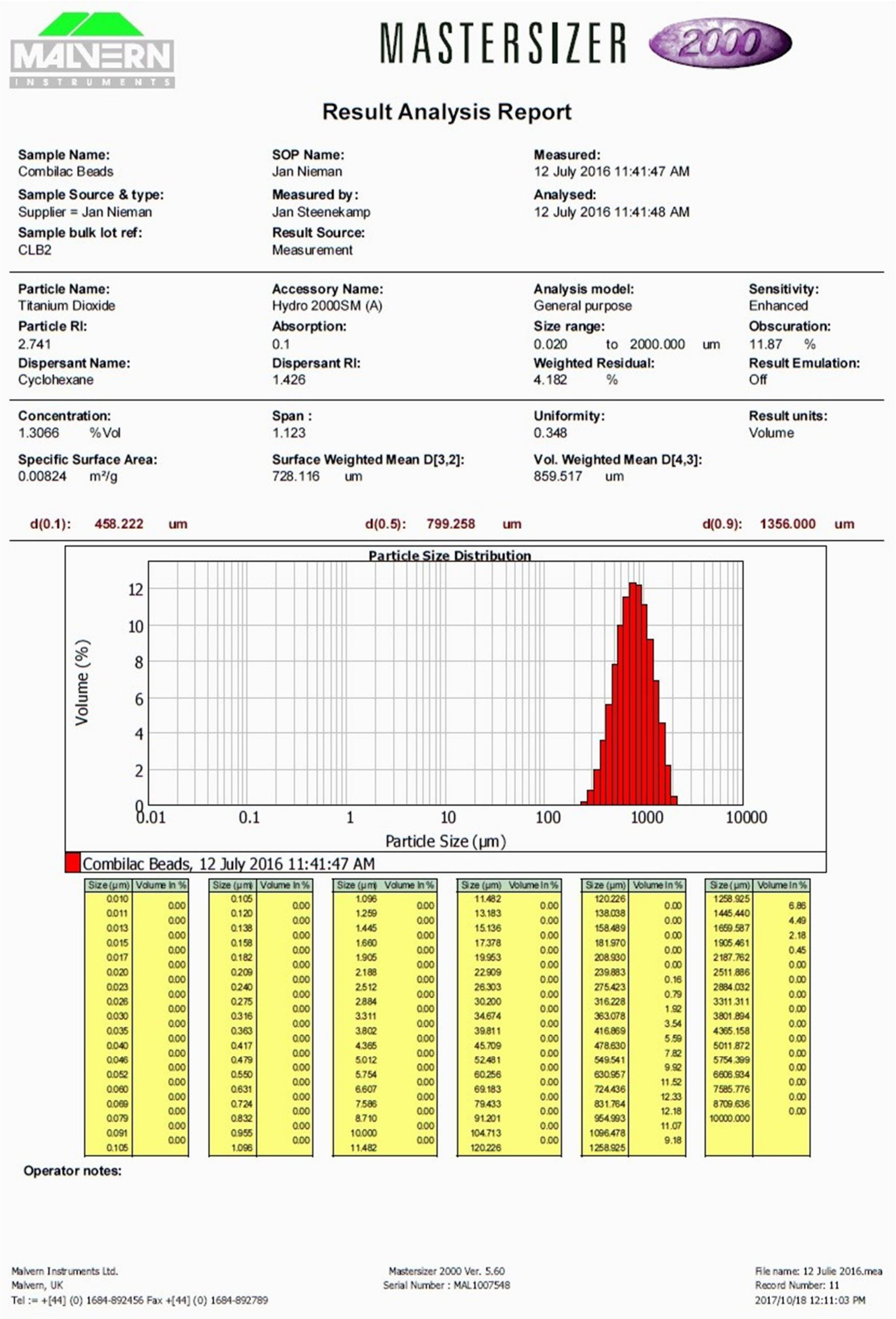
Operator notes:

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: 13 Mei 2016.mea
Record Number: 21
2017/10/18 12:05:42 PM

Annexure B5: Malvern® Mastersizer Data Sheets (CombiLac® Beads Sample 1)



MASTERSIZER 2000

Result Analysis Report

Sample Name:
Combilac Beads

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
CLB2

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
12 July 2016 11:41:47 AM

Analysed:
12 July 2016 11:41:48 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:
4.182 %

Sensitivity:
Enhanced

Obscuration:
11.87 %

Result Emulation:
Off

Concentration:
1.3066 %Vol

Specific Surface Area:
0.00824 m²/g

Span :
1.123

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

Uniformity:
0.348

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

Result units:
Volume

d(0.1): **458.222** **um** **d(0.5):** **799.258** **um** **d(0.9):** **1356.000** **um**

🟥 Combilac Beads, 12 July 2016 11:41:47 AM

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	

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	

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	

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	

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	0.16
275.423	0.79
316.228	1.92
363.078	3.54
416.869	5.59
478.630	7.82
549.541	9.92
630.957	11.52
724.436	12.33
831.764	12.18
954.993	11.07
1096.478	9.18
1258.925	

Size (μm)	Volume In %
1258.925	6.86
1445.440	4.49
1659.587	2.18
1905.461	0.45
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	

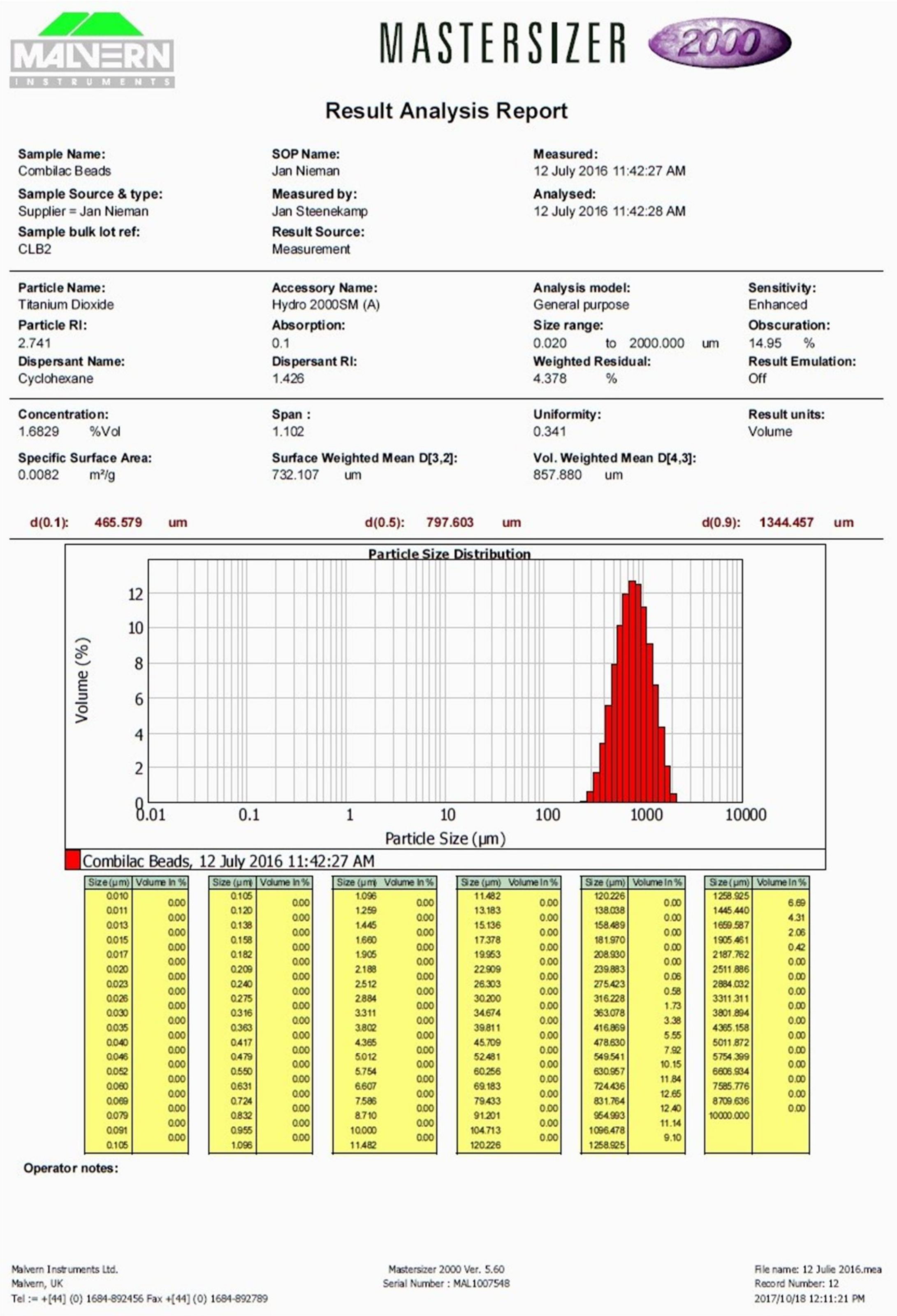
Operator notes:

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: 12 Julie 2016.mea
Record Number: 11
2017/10/18 12:11:03 PM

Annexure B6: Malvern® Mastersizer Data Sheets (CombiLac® Beads Sample 2)



Result Analysis Report

Sample Name: Combilac Beads

SOP Name: Jan Nieman

Measured: 12 July 2016 11:42:27 AM

Sample Source & type: Supplier = Jan Nieman

Measured by: Jan Steenekamp

Analysed: 12 July 2016 11:42:28 AM

Sample bulk lot ref: CLB2

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: 14.95 %

Dispersant Name: Cyclohexane

Dispersant RI: 1.426

Weighted Residual: 4.378 %

Result Emulation: Off

Concentration: 1.6829 %Vol

Span : 1.102

Uniformity: 0.341

Result units: Volume

Specific Surface Area: 0.0082 m²/g

Surface Weighted Mean D[3,2]: 732.107 um

Vol. Weighted Mean D[4,3]: 857.880 um

d(0.1): **465.579** um d(0.5): **797.603** um d(0.9): **1344.457** um

🟥 Combilac Beads, 12 July 2016 11:42:27 AM

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	6.69
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	4.31
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.06
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.42
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	0.06	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.58	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	1.73	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	3.38	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	5.55	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	7.92	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	10.15	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	11.84	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	12.65	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	12.40	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	11.14	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	9.10		
0.105		1.096		11.482		120.226		1258.925			

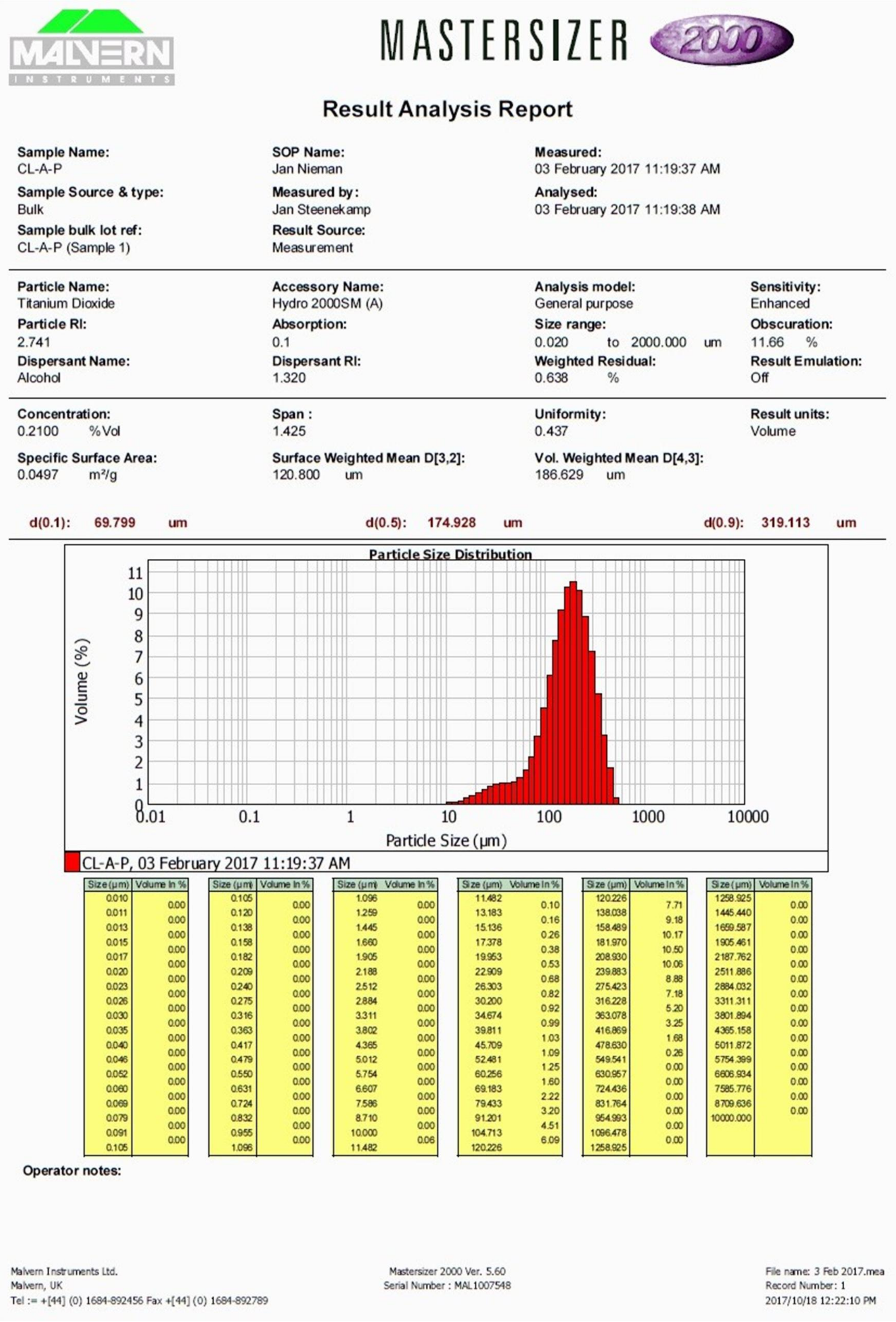
Operator notes:

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: 12 Julie 2016.mea
Record Number: 12
2017/10/18 12:11:21 PM

Annexure B7: Malvern® Mastersizer Data Sheets (CombiLac® API Powder Sample 1)



Result Analysis Report

Sample Name:
CL-A-P

Sample Source & type:
Bulk

Sample bulk lot ref:
CL-A-P (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
03 February 2017 11:19:37 AM

Analysed:
03 February 2017 11:19:38 AM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
0.638 %

Sensitivity:
Enhanced

Obscuration:
11.66 %

Result Emulation:
Off

Concentration:
0.2100 %Vol

Specific Surface Area:
0.0497 m²/g

Span :
1.425

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

Uniformity:
0.437

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

Result units:
Volume

d(0.1): 69.799 um **d(0.5): 174.928 um** **d(0.9): 319.113 um**

🟥 CL-A-P, 03 February 2017 11:19:37 AM

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	0.10	120.226	7.71	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.16	138.038	9.18	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.26	158.489	10.17	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.38	181.970	10.50	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.53	208.930	10.06	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.68	239.883	8.88	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.82	275.423	7.18	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.92	316.228	5.20	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.99	363.078	3.25	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.03	416.869	1.68	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.09	478.630	0.26	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.25	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.60	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.22	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.20	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.51	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.06	104.713	6.09	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

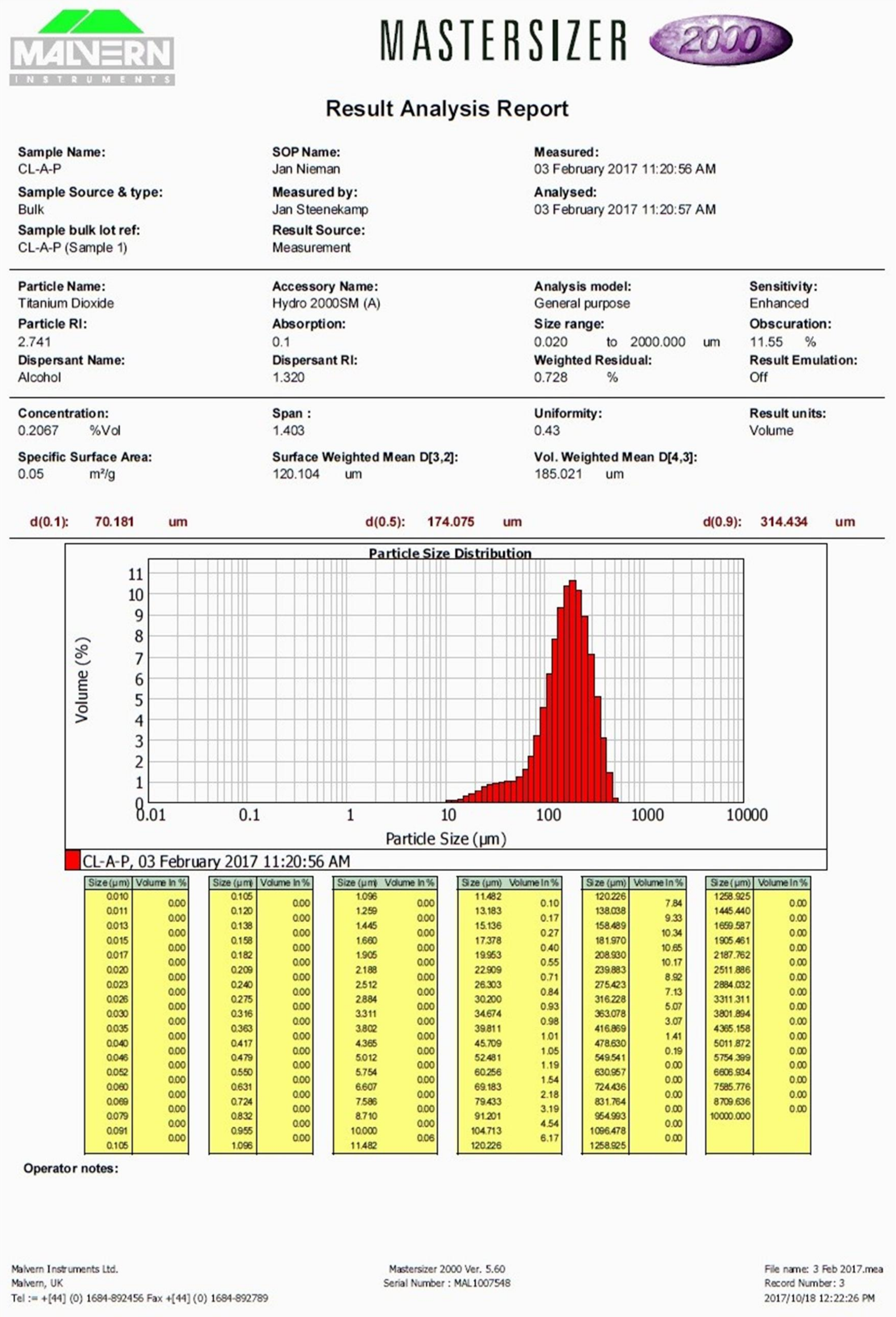
Operator notes:

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: 3 Feb 2017.mea
Record Number: 1
2017/10/18 12:22:10 PM

Annexure B8: Malvern® Mastersizer Data Sheets (CombiLac® API Powder Sample 2)



Result Analysis Report

Sample Name: CL-A-P
Sample Source & type: Bulk
Sample bulk lot ref: CL-A-P (Sample 1)
SOP Name: Jan Nieman
Measured by: Jan Steenekamp
Result Source: Measurement
Measured: 03 February 2017 11:20:56 AM
Analysed: 03 February 2017 11:20:57 AM

Particle Name: Titanium Dioxide
Particle RI: 2.741
Dispersant Name: Alcohol
Accessory Name: Hydro 2000SM (A)
Absorption: 0.1
Dispersant RI: 1.320
Analysis model: General purpose
Size range: 0.020 to 2000.000 um
Weighted Residual: 0.728 %
Sensitivity: Enhanced
Obscuration: 11.55 %
Result Emulation: Off

Concentration: 0.2067 %Vol
Specific Surface Area: 0.05 m²/g
Span : 1.403
Surface Weighted Mean D[3,2]: 120.104 um
Uniformity: 0.43
Vol. Weighted Mean D[4,3]: 185.021 um
Result units: Volume

d(0.1): **70.181** **um** **d(0.5):** **174.075** **um** **d(0.9):** **314.434** **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	0.10	120.226	7.84	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.17	138.038	9.33	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.27	158.489	10.34	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.40	181.970	10.65	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.55	208.930	10.17	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.71	239.883	8.92	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.84	275.423	7.13	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.93	316.228	5.07	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.98	363.078	3.07	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.01	416.869	1.41	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.05	478.630	0.19	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.19	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.54	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.18	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.19	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.54	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.06	104.713	6.17	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

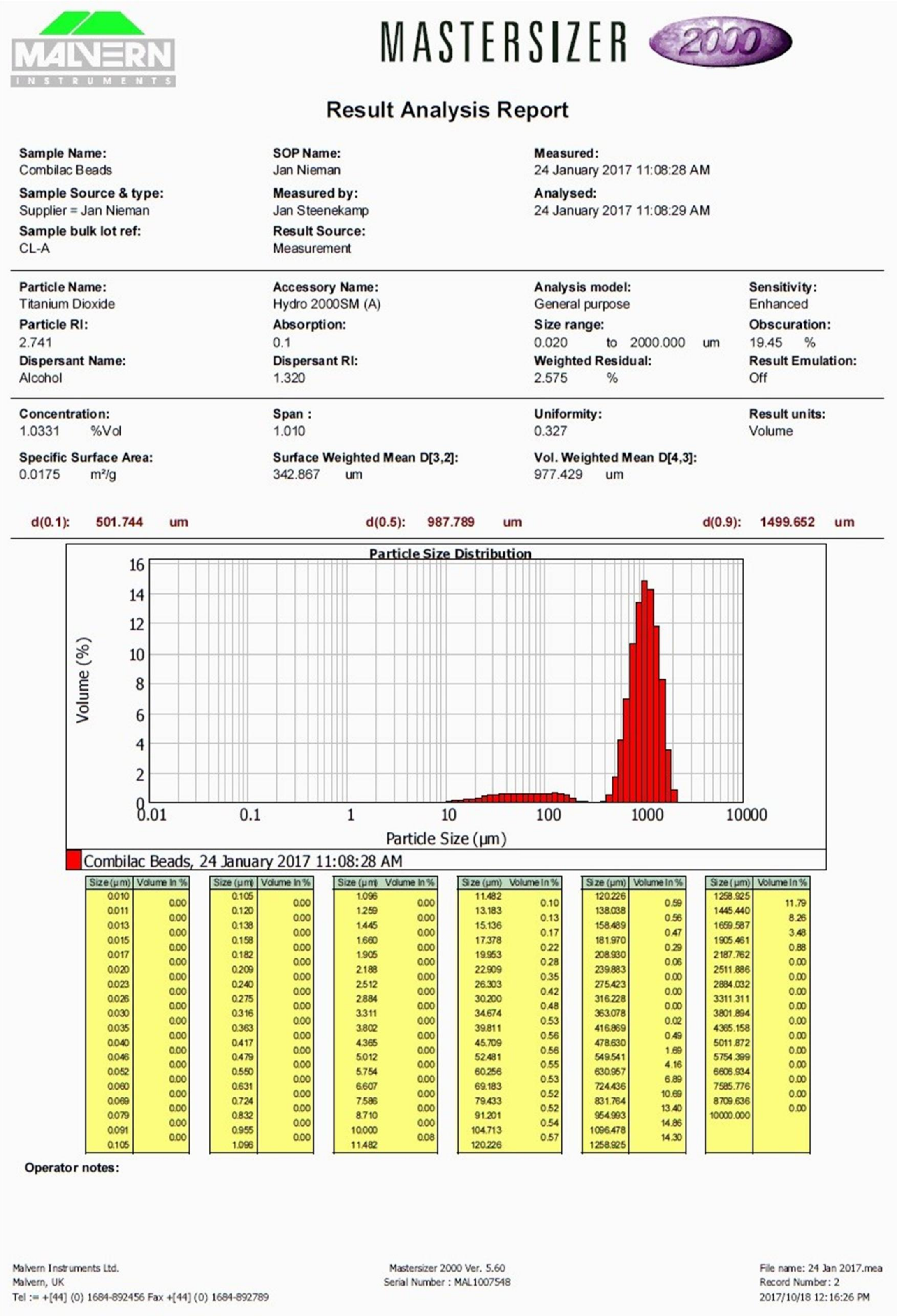
Operator notes:

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: 3 Feb 2017.mea
Record Number: 3
2017/10/18 12:22:26 PM

Annexure B9: Malvern® Mastersizer Data Sheets (CombiLac® API Beads Sample 1)



Result Analysis Report

Sample Name:
Combilac Beads

SOP Name:
Jan Nieman

Measured:
24 January 2017 11:08:28 AM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 11:08:29 AM

Sample bulk lot ref:
CL-A

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:
19.45 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
2.575 %

Result Emulation:
Off

Concentration:
1.0331 %Vol

Span :
1.010

Uniformity:
0.327

Result units:
Volume

Specific Surface Area:
0.0175 m²/g

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

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

d(0.1): 501.744 um **d(0.5): 987.789 um** **d(0.9): 1499.652 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	

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	

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	0.08
11.482	

Size (µm)	Volume In %
11.482	0.10
13.183	0.13
15.136	0.17
17.378	0.22
19.953	0.28
22.909	0.35
26.303	0.42
30.200	0.48
34.674	0.53
39.811	0.56
45.709	0.56
52.481	0.55
60.256	0.53
69.183	0.52
79.433	0.52
91.201	0.54
104.713	0.57
120.226	

Size (µm)	Volume In %
120.226	0.59
138.038	0.56
158.489	0.47
181.970	0.29
208.930	0.06
239.883	0.00
275.423	0.00
316.228	0.00
363.078	0.02
416.869	0.49
478.630	1.69
549.541	4.16
630.957	6.89
724.436	10.69
831.764	13.40
954.993	14.86
1096.478	14.30
1258.925	

Size (µm)	Volume In %
1258.925	11.79
1445.440	8.26
1659.587	3.48
1905.461	0.88
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	

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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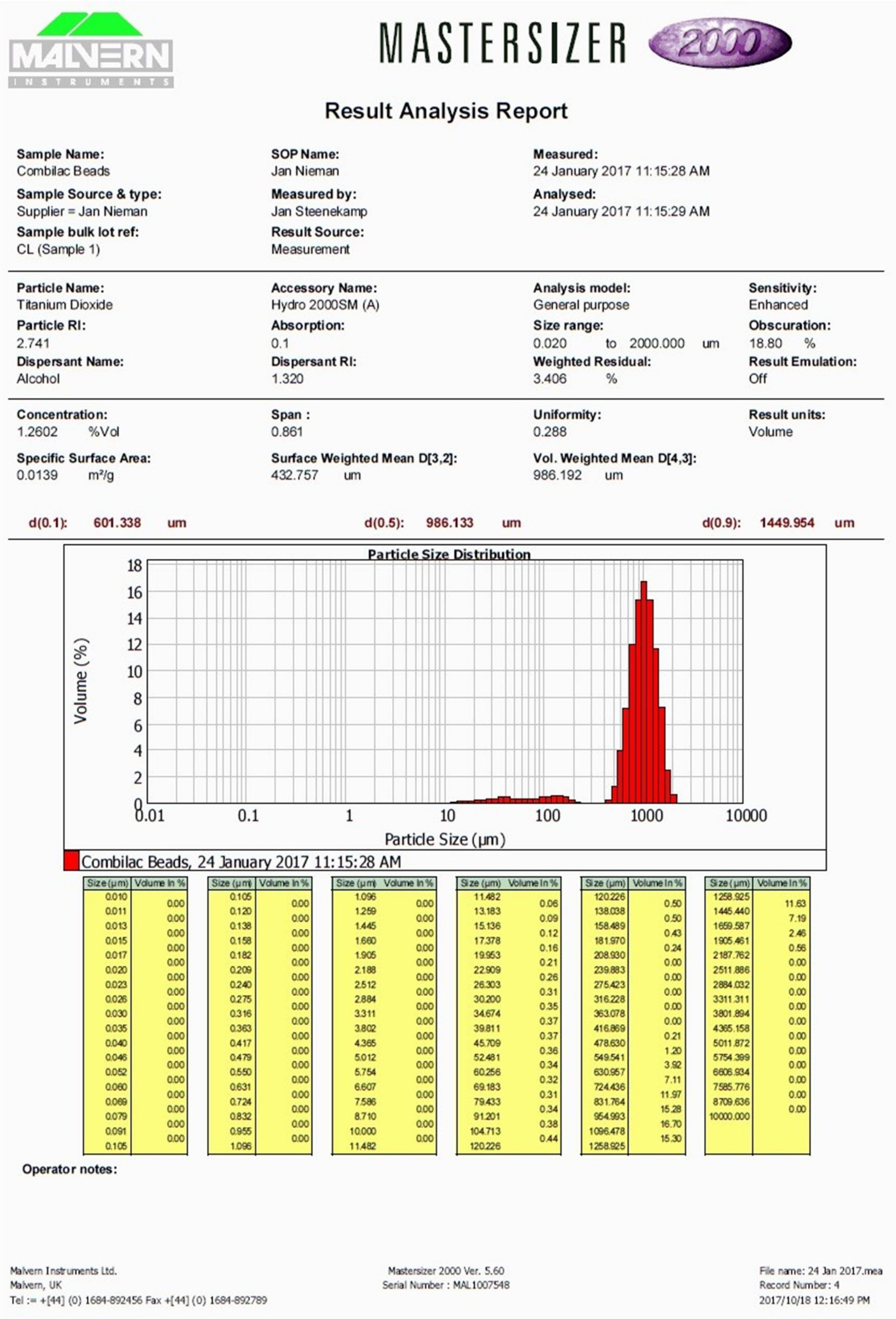
Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 24 Jan 2017.mea
Record Number: 2
2017/10/18 12:16:26 PM

Annexure B10: Malvern® Mastersizer Data Sheets CombiLac®API Beads Sample 2)



Result Analysis Report

Sample Name:
Combilac Beads

SOP Name:
Jan Nieman

Measured:
24 January 2017 11:15:28 AM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 11:15:29 AM

Sample bulk lot ref:
CL (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:
18.80 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
3.406 %

Result Emulation:
Off

Concentration:
1.2602 %Vol

Span :
0.861

Uniformity:
0.288

Result units:
Volume

Specific Surface Area:
0.0139 m²/g

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

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

d(0.1): 601.338 um **d(0.5): 986.133 um** **d(0.9): 1449.954 um**

🟥 Combilac Beads, 24 January 2017 11:15:28 AM

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	0.06	120.226	0.50	1258.925	11.63
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.09	138.038	0.50	1445.440	7.19
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.12	158.489	0.43	1659.587	2.46
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.16	181.970	0.24	1905.461	0.56
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.21	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.26	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.31	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.35	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.37	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.37	416.869	0.21	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.36	478.630	1.20	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.34	549.541	3.92	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.32	630.957	7.11	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.31	724.436	11.97	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.34	831.764	15.28	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.38	954.993	16.70	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.44	1096.478	15.30		
0.105		1.096		11.482		120.226		1258.925			

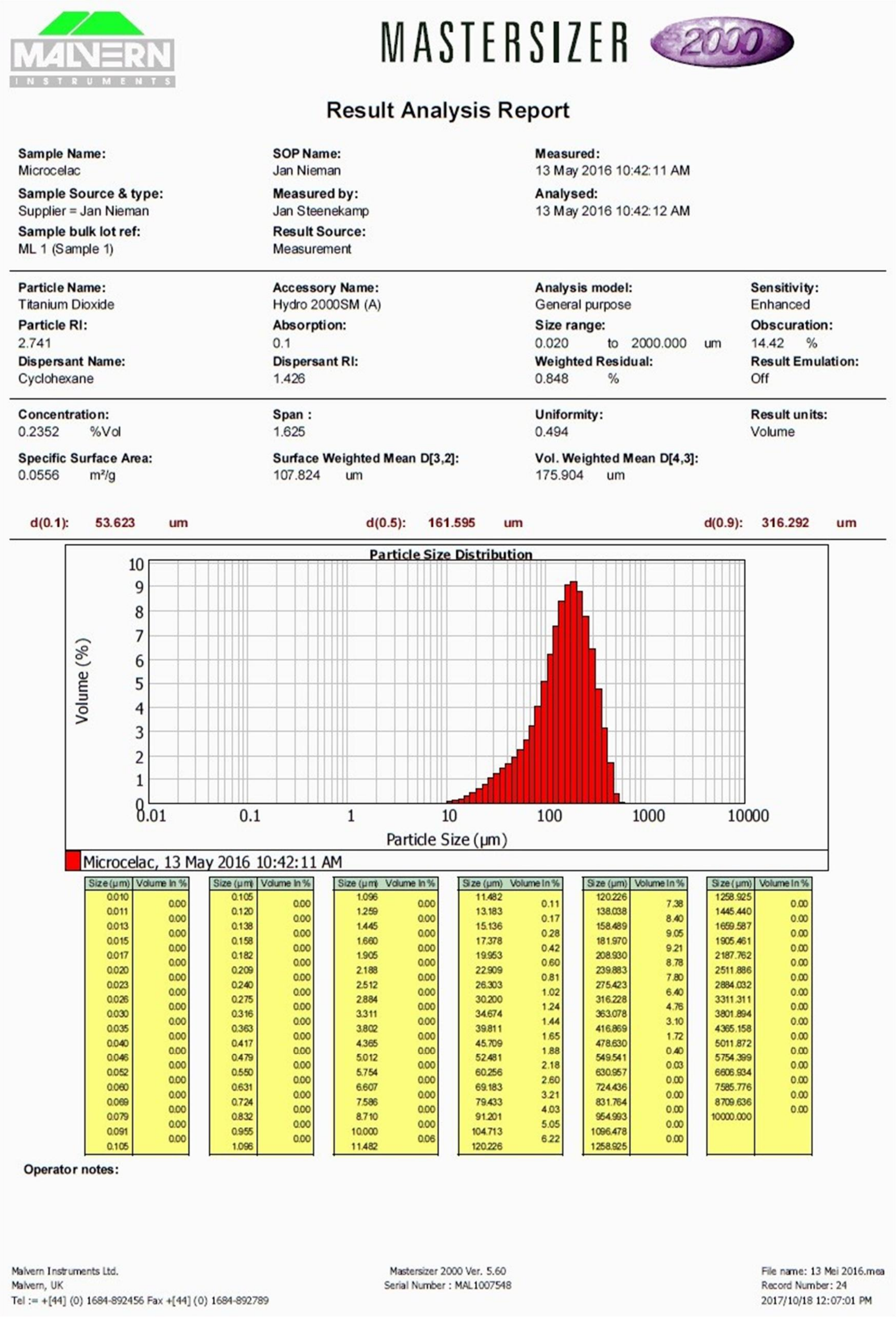
Operator notes:

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: 24 Jan 2017.mea
Record Number: 4
2017/10/18 12:16:49 PM

Annexure B11: Malvern® Mastersizer Data Sheets (MicroceLac® 100 Powder Sample 1)



MASTERSIZER 2000

Result Analysis Report

Sample Name: Microcelac	**SOP Name:** Jan Nieman	**Measured:** 13 May 2016 10:42:11 AM
Sample Source & type: Supplier = Jan Nieman	**Measured by:** Jan Steenekamp	**Analysed:** 13 May 2016 10:42:12 AM
Sample bulk lot ref: ML 1 (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:** 14.42 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 0.848 %	**Result Emulation:** Off

Concentration: 0.2352 %Vol	**Span :** 1.625	**Uniformity:** 0.494	**Result units:** Volume
Specific Surface Area: 0.0556 m²/g	**Surface Weighted Mean D[3,2]:** 107.824 um	**Vol. Weighted Mean D[4,3]:** 175.904 um	

d(0.1): 53.623 um **d(0.5):** 161.595 um **d(0.9):** 316.292 um

Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00
0.011	0.00	0.120	0.00	1.259	0.00
0.013	0.00	0.138	0.00	1.445	0.00
0.015	0.00	0.158	0.00	1.660	0.00
0.017	0.00	0.182	0.00	1.905	0.00
0.020	0.00	0.209	0.00	2.188	0.00
0.023	0.00	0.240	0.00	2.512	0.00
0.026	0.00	0.275	0.00	2.884	0.00
0.030	0.00	0.316	0.00	3.311	0.00
0.035	0.00	0.363	0.00	3.802	0.00
0.040	0.00	0.417	0.00	4.365	0.00
0.046	0.00	0.479	0.00	5.012	0.00
0.052	0.00	0.550	0.00	5.754	0.00
0.060	0.00	0.631	0.00	6.607	0.00
0.069	0.00	0.724	0.00	7.586	0.00
0.079	0.00	0.832	0.00	8.710	0.00
0.091	0.00	0.955	0.00	10.000	0.06
0.105		1.096		11.482	

Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %
11.482	0.11	120.226	7.38	1258.925	0.00
13.183	0.17	138.038	8.40	1445.440	0.00
15.136	0.28	158.489	9.05	1659.587	0.00
17.378	0.42	181.970	9.21	1905.461	0.00
19.953	0.60	208.930	8.78	2187.762	0.00
22.909	0.81	239.883	7.80	2511.886	0.00
26.303	1.02	275.423	6.40	2884.032	0.00
30.200	1.24	316.228	4.76	3311.311	0.00
34.674	1.44	363.078	3.10	3801.894	0.00
39.811	1.65	416.869	1.72	4365.158	0.00
45.709	1.88	478.630	0.40	5011.872	0.00
52.481	2.18	549.541	0.03	5754.399	0.00
60.256	2.60	630.957	0.00	6606.934	0.00
69.183	3.21	724.436	0.00	7585.776	0.00
79.433	4.03	831.764	0.00	8709.636	0.00
91.201	5.05	954.993	0.00	10000.000	
104.713	6.22	1096.478	0.00		
120.226		1258.925			

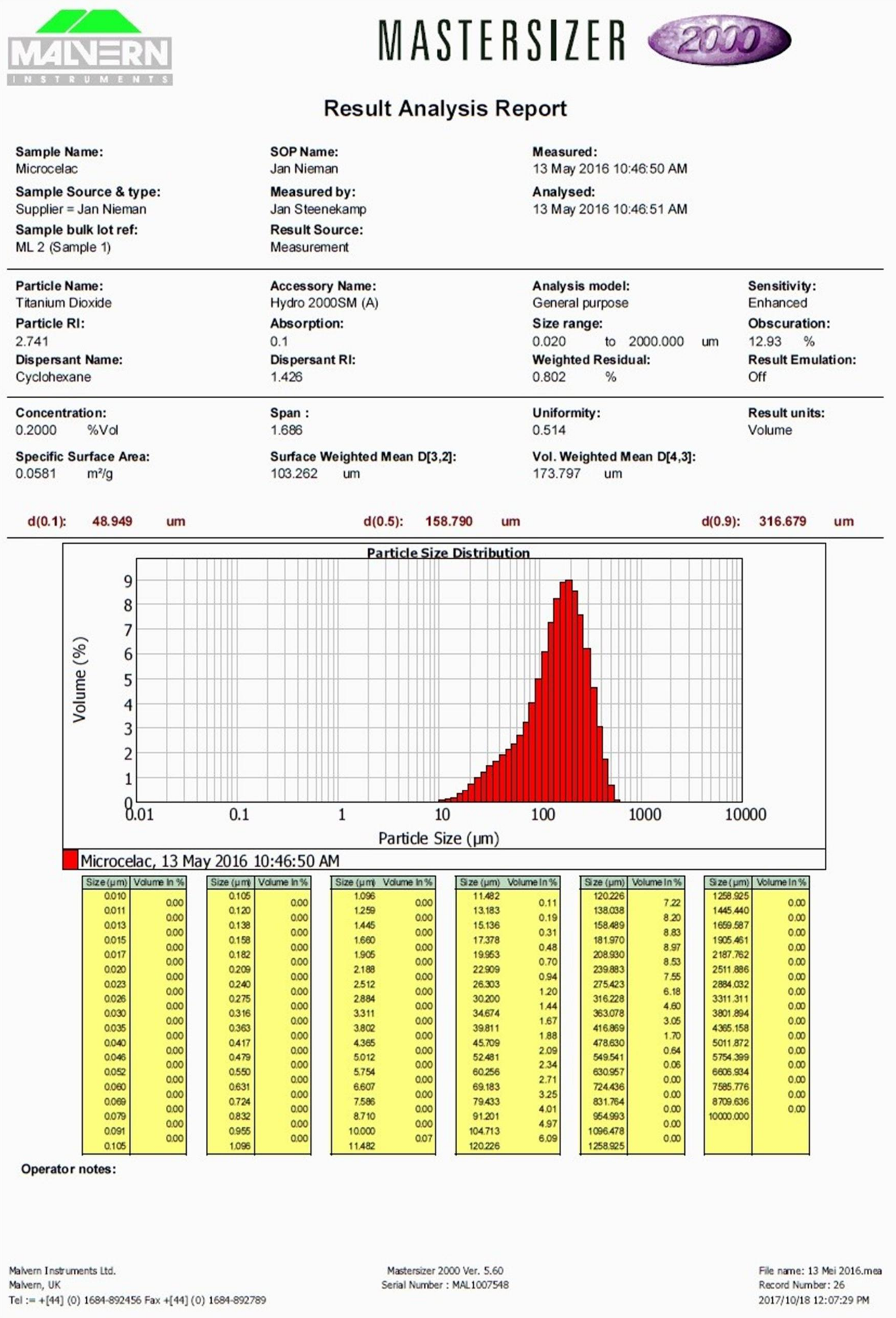
Operator notes:

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: 13 Mei 2016.mea
Record Number: 24
2017/10/18 12:07:01 PM

Annexure B12: Malvern® Mastersizer Data Sheets (MicroceLac® 100 Powder Sample 2)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Microcelac	**SOP Name:** Jan Nieman	**Measured:** 13 May 2016 10:46:50 AM
Sample Source & type: Supplier = Jan Nieman	**Measured by:** Jan Steenekamp	**Analysed:** 13 May 2016 10:46:51 AM
Sample bulk lot ref: ML 2 (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:** 12.93 %
Dispersant Name: Cyclohexane	**Dispersant RI:** 1.426	**Weighted Residual:** 0.802 %	**Result Emulation:** Off

Concentration: 0.2000 %Vol	**Span :** 1.686	**Uniformity:** 0.514	**Result units:** Volume
Specific Surface Area: 0.0581 m²/g	**Surface Weighted Mean D[3,2]:** 103.262 um	**Vol. Weighted Mean D[4,3]:** 173.797 um	

d(0.1): 48.949 um **d(0.5): 158.790 um** **d(0.9): 316.679 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	0.11	120.226	7.22	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.19	138.038	8.20	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.31	158.489	8.83	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.48	181.970	8.97	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.70	208.930	8.53	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.94	239.883	7.55	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.20	275.423	6.18	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.44	316.228	4.60	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.67	363.078	3.05	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.88	416.869	1.70	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	2.09	478.630	0.64	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	2.34	549.541	0.06	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	2.71	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	3.25	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	4.01	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.97	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.07	104.713	6.09	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

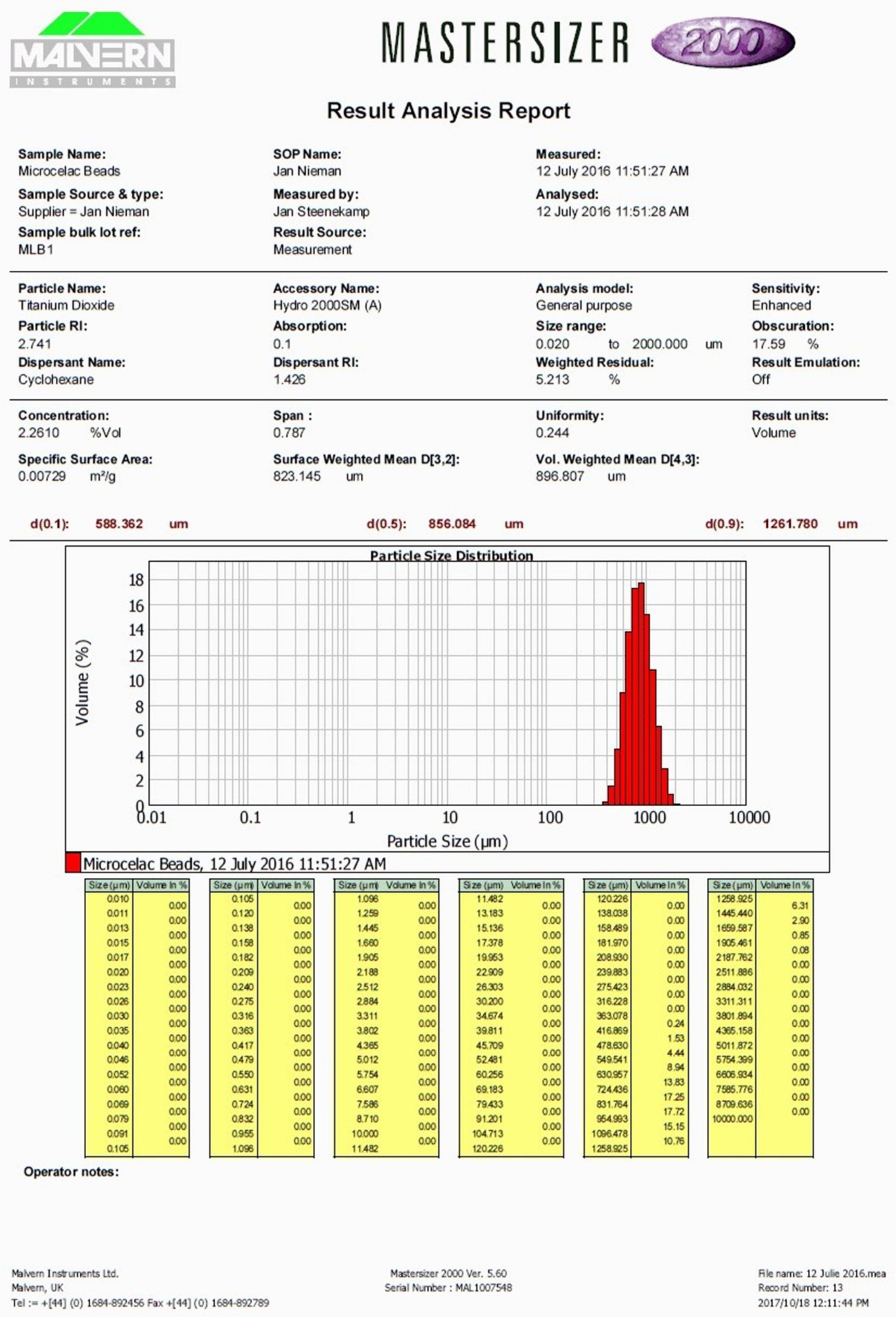
Operator notes:

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: 13 Mei 2016.mea
Record Number: 26
2017/10/18 12:07:29 PM

Annexure B13: Malvern® Mastersizer Data Sheets (MicroceLac® 100 Beads Sample 1)



Result Analysis Report

Sample Name:
Microcelac Beads

SOP Name:
Jan Nieman

Measured:
12 July 2016 11:51:27 AM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
12 July 2016 11:51:28 AM

Sample bulk lot ref:
MLB1

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:
17.59 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
5.213 %

Result Emulation:
Off

Concentration:
2.2610 %Vol

Span :
0.787

Uniformity:
0.244

Result units:
Volume

Specific Surface Area:
0.00729 m²/g

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

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

d(0.1): 588.362 um **d(0.5): 856.084 um** **d(0.9): 1261.780 um**

🟥 Microcelac Beads, 12 July 2016 11:51:27 AM

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	6.31
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	2.90
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	0.85
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	0.24	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	1.53	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.44	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	8.94	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	13.83	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	17.25	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	17.72	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	10.76		
0.105		1.096		11.482		120.226		1258.925			

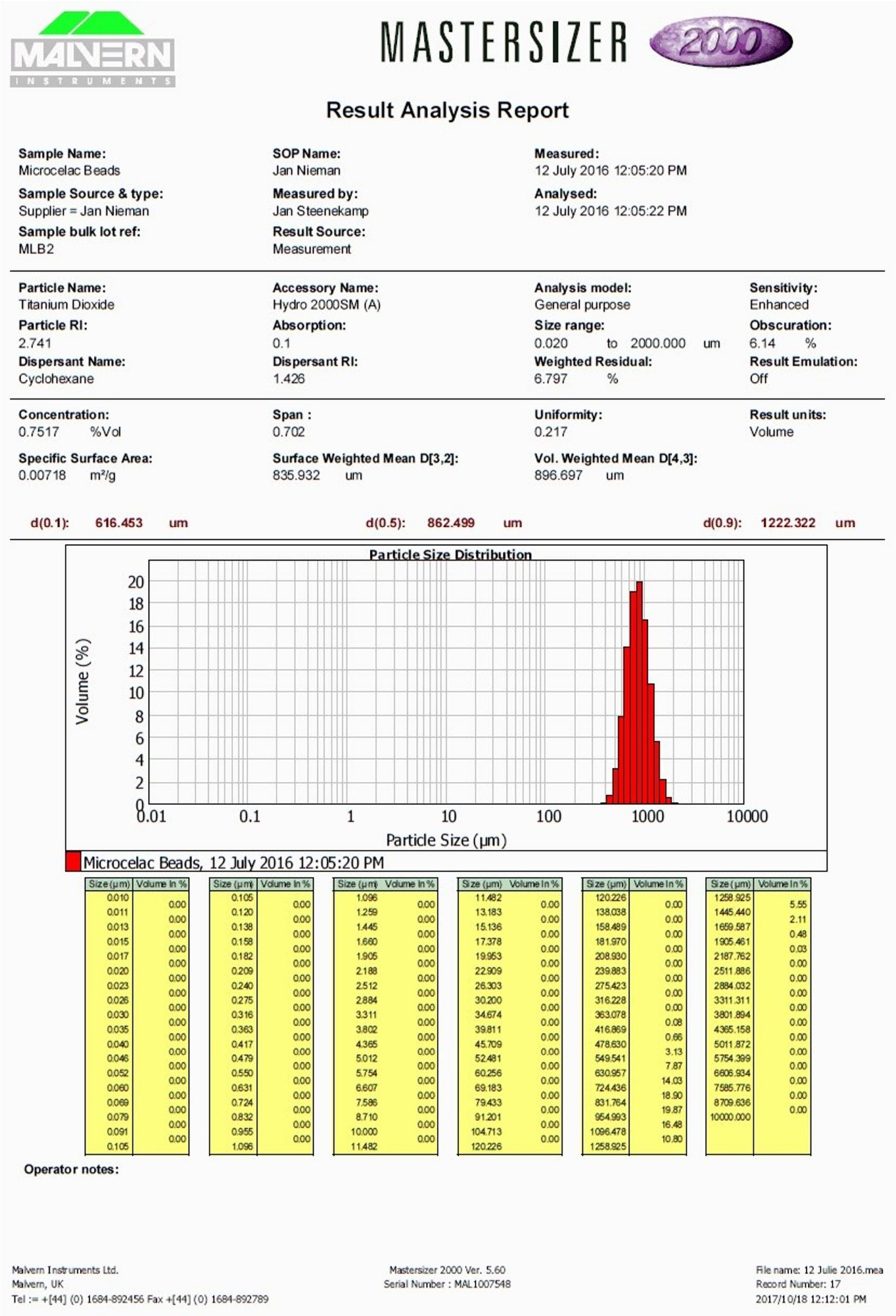
Operator notes:

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: 12 Julie 2016.mea
Record Number: 13
2017/10/18 12:11:44 PM

Annexure B14: Malvern® Mastersizer Data Sheets (MicroceLac® 100 Beads Sample 2)



Result Analysis Report

Sample Name:
Microcelac Beads

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
MLB2

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
12 July 2016 12:05:20 PM

Analysed:
12 July 2016 12:05:22 PM

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:
6.797 %

Sensitivity:
Enhanced

Obscuration:
6.14 %

Result Emulation:
Off

Concentration:
0.7517 %Vol

Specific Surface Area:
0.00718 m²/g

Span :
0.702

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

Uniformity:
0.217

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

Result units:
Volume

d(0.1): 616.453 um **d(0.5):** 862.499 um **d(0.9):** 1222.322 um

🟥 Microcelac Beads, 12 July 2016 12:05:20 PM

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	5.55
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	2.11
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	0.48
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.03
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	0.08	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.66	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	3.13	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	7.87	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	14.03	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	18.90	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	19.87	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	16.48	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	10.80		
0.105		1.096		11.482		120.226		1258.925			

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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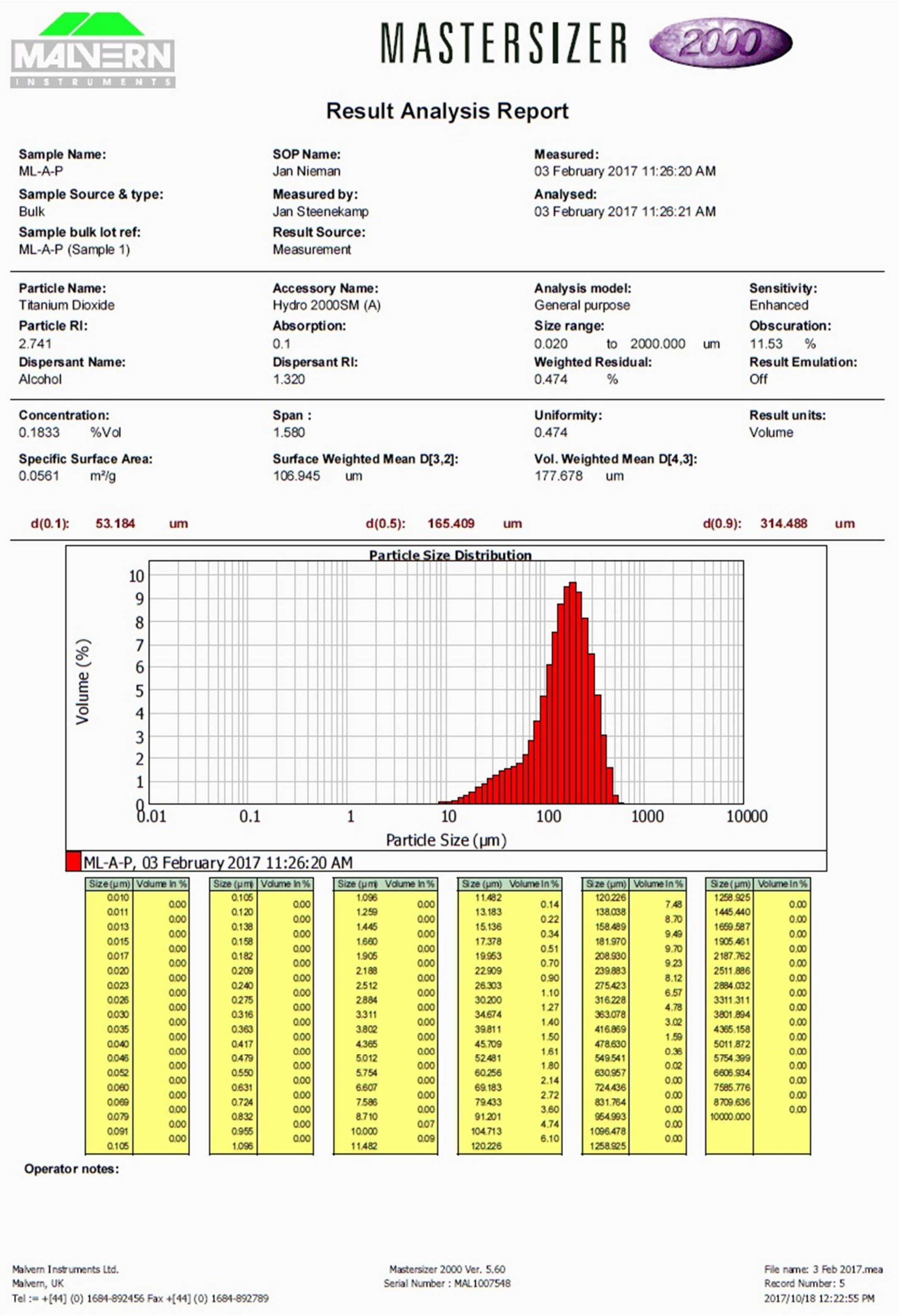
Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 12 Julie 2016.mea
Record Number: 17
2017/10/18 12:12:01 PM

Annexure B15: Malvern® Mastersizer Data Sheets (MicroceLac® 100 API Powder Sample 1)



Result Analysis Report

Sample Name:
ML-A-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:26:20 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:26:21 AM

Sample bulk lot ref:
ML-A-P (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:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
0.474 %

Result Emulation:
Off

Concentration:
0.1833 %Vol

Span :
1.580

Uniformity:
0.474

Result units:
Volume

Specific Surface Area:
0.0561 m²/g

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

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

d(0.1): 53.184 um

d(0.5): 165.409 um

d(0.9): 314.488 um

🟥 ML-A-P, 03 February 2017 11:26:20 AM

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	0.14	120.226	7.48	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.22	138.038	8.70	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.34	158.489	9.49	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.51	181.970	9.70	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.70	208.930	9.23	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.90	239.883	8.12	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.10	275.423	6.57	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.27	316.228	4.78	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.40	363.078	3.02	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.50	416.869	1.59	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.61	478.630	0.36	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.80	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	2.14	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.72	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.60	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	4.74	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.09	104.713	6.10	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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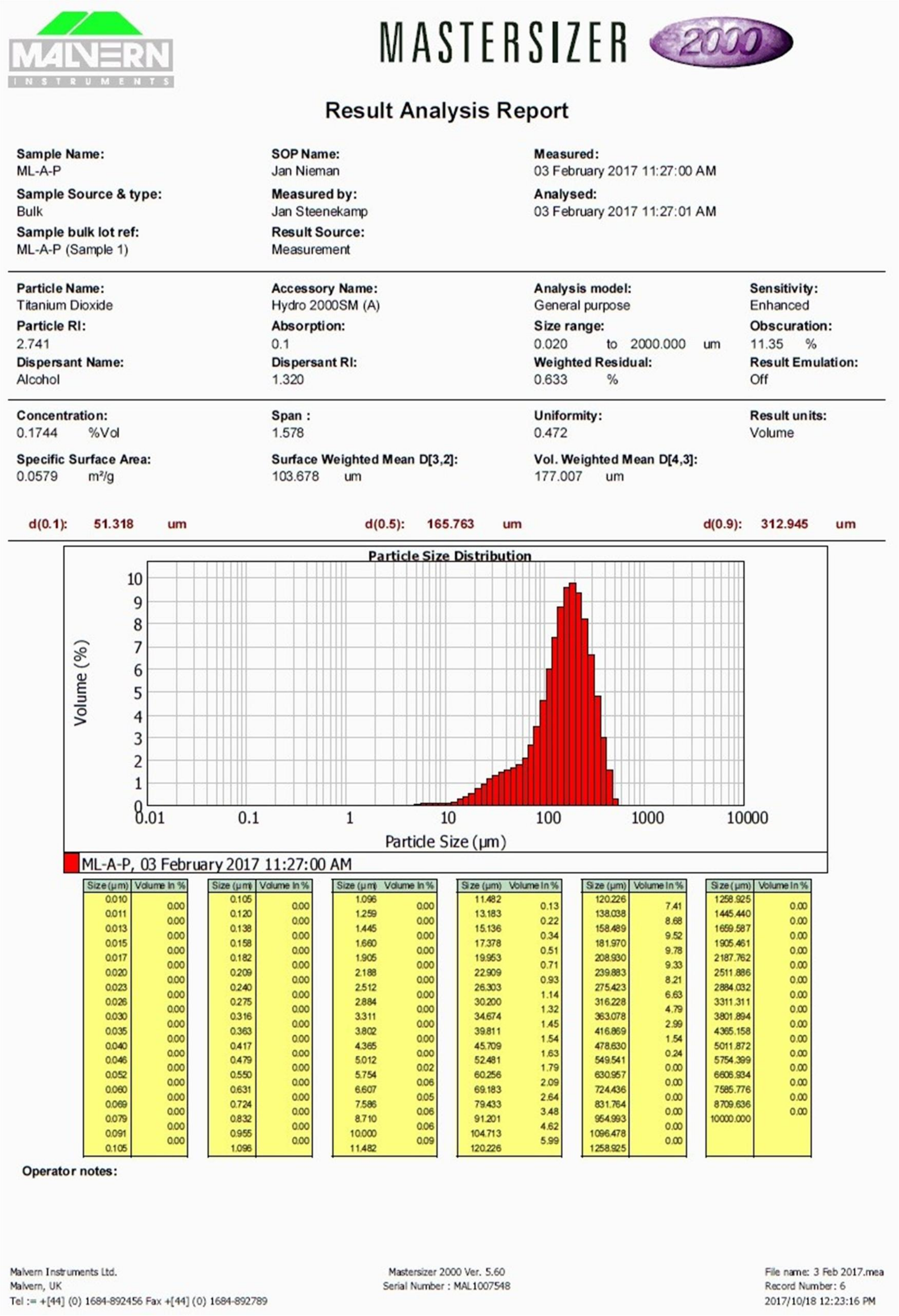
Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 3 Feb 2017.mea
Record Number: 5
2017/10/18 12:22:55 PM

Annexure B16: Malvern® Mastersizer Data Sheets (MicroceLac® 100 API Powder Sample 2)



Result Analysis Report

Sample Name:
ML-A-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:27:00 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:27:01 AM

Sample bulk lot ref:
ML-A-P (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:
11.35 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
0.633 %

Result Emulation:
Off

Concentration:
0.1744 %Vol

Span :
1.578

Uniformity:
0.472

Result units:
Volume

Specific Surface Area:
0.0579 m²/g

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

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

d(0.1): 51.318 um   **d(0.5): 165.763 um**   **d(0.9): 312.945 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	0.13	120.226	7.41	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.22	138.038	8.68	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.34	158.489	9.52	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.51	181.970	9.78	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.71	208.930	9.33	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.93	239.883	8.21	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.14	275.423	6.63	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.32	316.228	4.79	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.45	363.078	2.99	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.54	416.869	1.54	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.63	478.630	0.24	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.02	52.481	1.79	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.06	60.256	2.09	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.05	69.183	2.64	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.06	79.433	3.48	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.06	91.201	4.62	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.09	104.713	5.99	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

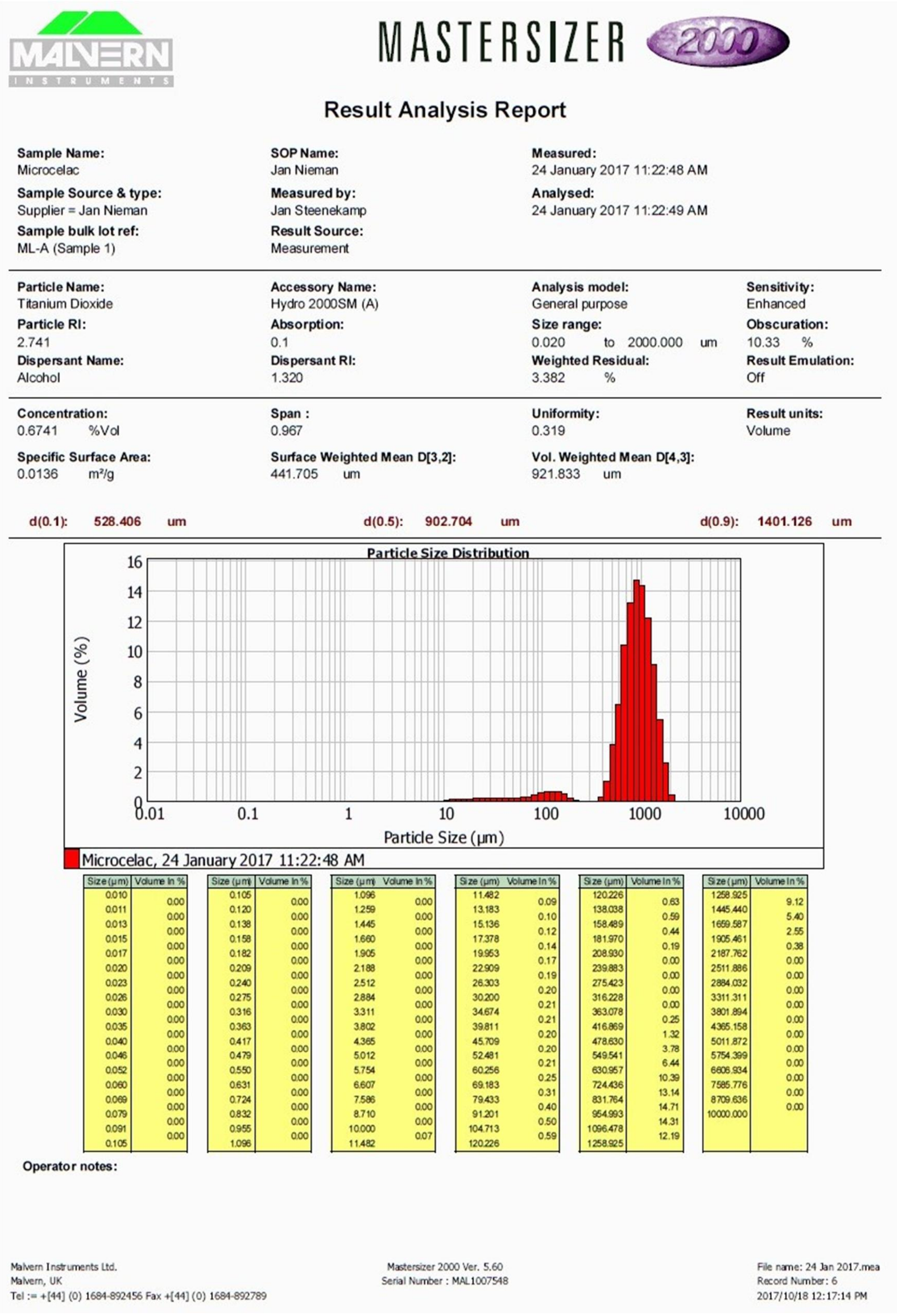
Operator notes:

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: 3 Feb 2017.mea
Record Number: 6
2017/10/18 12:23:16 PM

Annexure B17: Malvern® Mastersizer Data Sheets (MicroceLac® 100 API Beads Sample 1)



Result Analysis Report

Sample Name: Microcelac	**SOP Name:** Jan Nieman	**Measured:** 24 January 2017 11:22:48 AM
Sample Source & type: Supplier = Jan Nieman	**Measured by:** Jan Steenekamp	**Analysed:** 24 January 2017 11:22:49 AM
Sample bulk lot ref: ML-A (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:** 10.33 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 3.382 %	**Result Emulation:** Off

Concentration: 0.6741 %Vol	**Span :** 0.967	**Uniformity:** 0.319	**Result units:** Volume
Specific Surface Area: 0.0136 m²/g	**Surface Weighted Mean D[3,2]:** 441.705 um	**Vol. Weighted Mean D[4,3]:** 921.833 um	

d(0.1): 528.406 um **d(0.5):** 902.704 um **d(0.9):** 1401.126 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	0.09	120.226	0.63	1258.925	9.12
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.10	138.038	0.59	1445.440	5.40
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.12	158.489	0.44	1659.587	2.55
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.14	181.970	0.19	1905.461	0.38
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.17	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.19	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.20	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.21	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.21	363.078	0.25	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.20	416.869	1.32	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.20	478.630	3.78	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.21	549.541	6.44	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.25	630.957	10.39	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.31	724.436	13.14	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.40	831.764	14.71	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.50	954.993	14.31	10000.000	
0.091	0.00	0.955	0.00	10.000	0.07	104.713	0.59	1096.478	12.19		
0.105		1.096		11.482		120.226		1258.925			

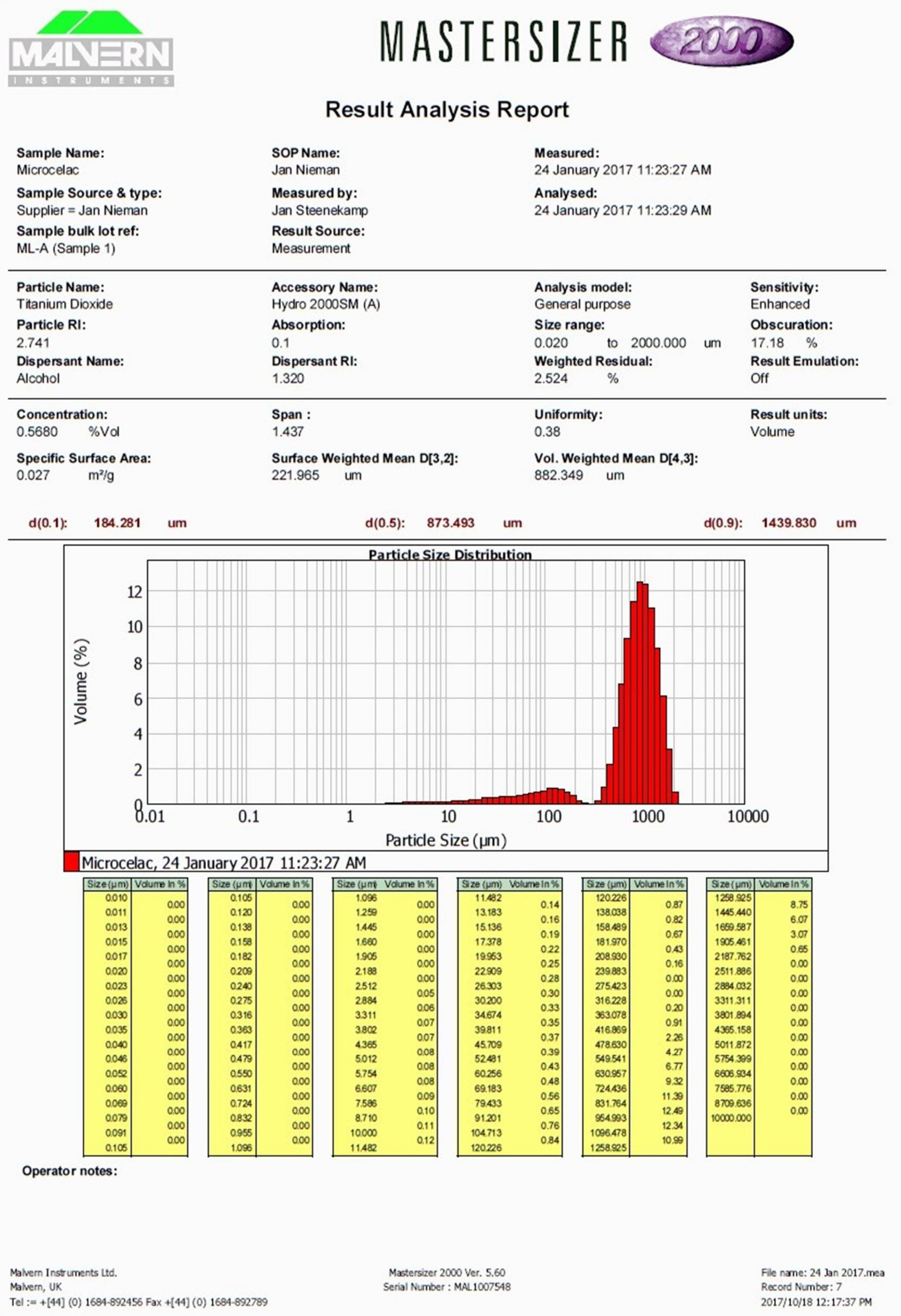
Operator notes:

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: 24 Jan 2017.mea
Record Number: 6
2017/10/18 12:17:14 PM

Annexure B18: Malvern® Mastersizer Data Sheets (MicroceLac® 100 API Beads Sample 2)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Microcelac	**SOP Name:** Jan Nieman	**Measured:** 24 January 2017 11:23:27 AM
Sample Source & type: Supplier = Jan Nieman	**Measured by:** Jan Steenekamp	**Analysed:** 24 January 2017 11:23:29 AM
Sample bulk lot ref: ML-A (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:** 17.18 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 2.524 %	**Result Emulation:** Off

Concentration: 0.5680 %Vol	**Span :** 1.437	**Uniformity:** 0.38	**Result units:** Volume
Specific Surface Area: 0.027 m²/g	**Surface Weighted Mean D[3,2]:** 221.965 um	**Vol. Weighted Mean D[4,3]:** 882.349 um	

d(0.1): 184.281 um   d(0.5): 873.493 um   d(0.9): 1439.830 um

🟥 Microcelac, 24 January 2017 11:23:27 AM

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	0.14	120.226	0.87	1258.925	8.75
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.16	138.038	0.82	1445.440	6.07
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.19	158.489	0.67	1659.587	3.07
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.22	181.970	0.43	1905.461	0.65
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.25	208.930	0.16	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.28	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.05	26.303	0.30	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.06	30.200	0.33	316.228	0.20	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.07	34.674	0.35	363.078	0.91	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.07	39.811	0.37	416.869	2.26	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.08	45.709	0.39	478.630	4.27	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.08	52.481	0.43	549.541	6.77	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.08	60.256	0.48	630.957	9.32	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.09	69.183	0.56	724.436	11.39	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	0.65	831.764	12.49	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.11	91.201	0.76	954.993	12.34	10000.000	
0.091	0.00	0.955	0.00	10.000	0.12	104.713	0.84	1096.478	10.99		
0.105		1.096		11.482		120.226		1258.925			

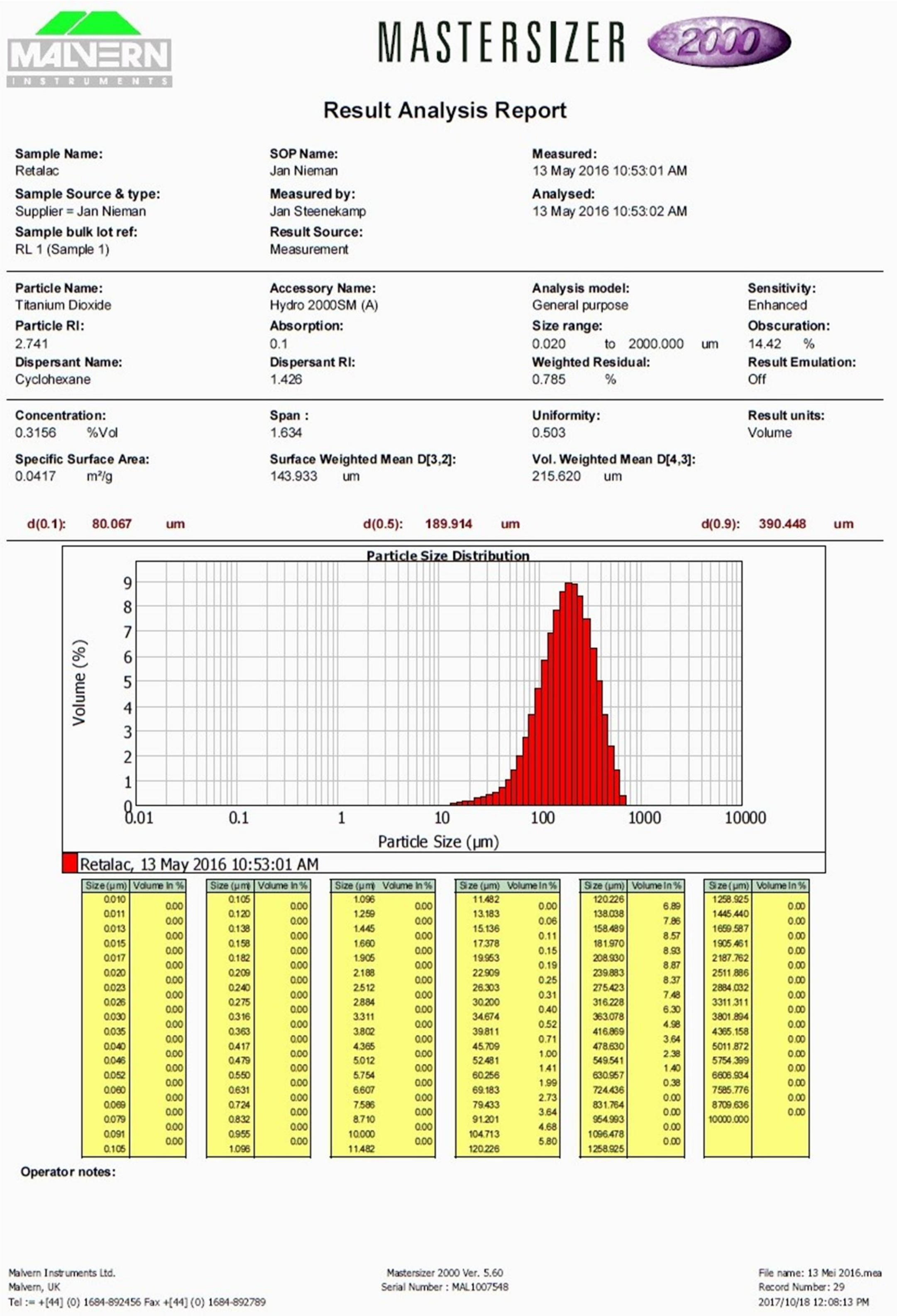
Operator notes:

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: 24 Jan 2017.mea
Record Number: 7
2017/10/18 12:17:37 PM

Annexure B19: Malvern® Mastersizer Data Sheets (RetaLac® Powder Sample 1)



Result Analysis Report

Sample Name:
Retalac

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
RL 1 (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
13 May 2016 10:53:01 AM

Analysed:
13 May 2016 10:53:02 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:
0.785 %

Sensitivity:
Enhanced

Obscuration:
14.42 %

Result Emulation:
Off

Concentration:
0.3156 %Vol

Specific Surface Area:
0.0417 m²/g

Span :
1.634

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

Uniformity:
0.503

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

Result units:
Volume

d(0.1): 80.067 um **d(0.5):** 189.914 um **d(0.9):** 390.448 um

🟥 Retalac, 13 May 2016 10:53:01 AM

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	6.89	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.06	138.038	7.86	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.11	158.489	8.57	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.15	181.970	8.93	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.19	208.930	8.87	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.25	239.883	8.37	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.31	275.423	7.48	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.40	316.228	6.30	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.52	363.078	4.98	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.71	416.869	3.64	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.00	478.630	2.38	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.41	549.541	1.40	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.99	630.957	0.38	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.73	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.64	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.68	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	5.80	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

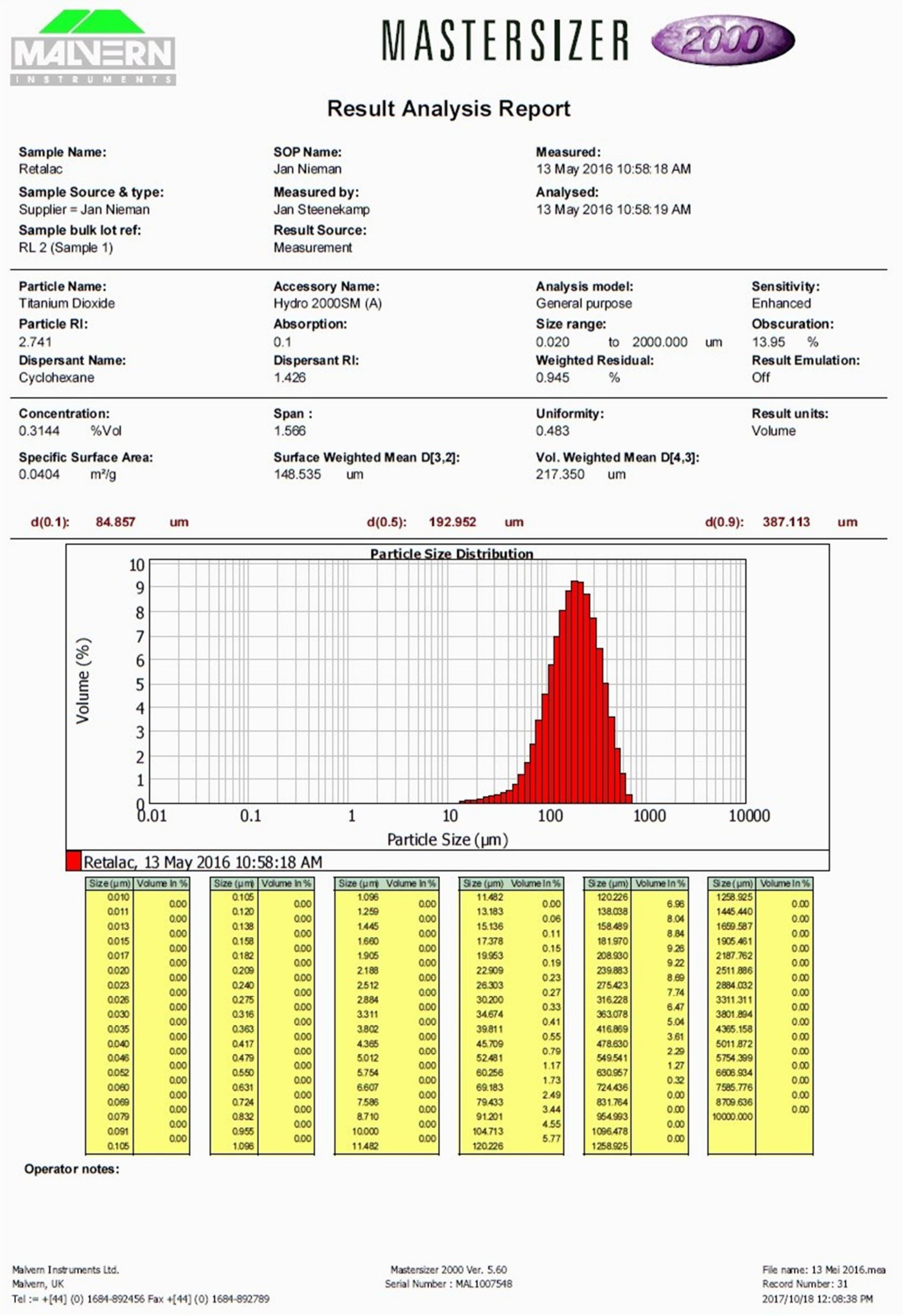
Operator notes:

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: 13 Mei 2016.mea
Record Number: 29
2017/10/18 12:08:13 PM

Annexure B20: Malvern® Mastersizer Data Sheets (RetaLac® Powder Sample 2)



Result Analysis Report

Sample Name:
Retalac

SOP Name:
Jan Nieman

Measured:
13 May 2016 10:58:18 AM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
13 May 2016 10:58:19 AM

Sample bulk lot ref:
RL 2 (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:
13.95 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
0.945 %

Result Emulation:
Off

Concentration:
0.3144 %Vol

Span :
1.566

Uniformity:
0.483

Result units:
Volume

Specific Surface Area:
0.0404 m²/g

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

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

d(0.1): 84.857 um **d(0.5): 192.952 um** **d(0.9): 387.113 um**

🟥 Retalac, 13 May 2016 10:58:18 AM

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	6.96	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.06	138.038	8.04	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.11	158.489	8.84	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.15	181.970	9.26	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.19	208.930	9.22	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.23	239.883	8.69	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.27	275.423	7.74	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.33	316.228	6.47	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.41	363.078	5.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.55	416.869	3.61	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.79	478.630	2.29	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.17	549.541	1.27	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.73	630.957	0.32	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.49	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.44	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.55	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	5.77	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

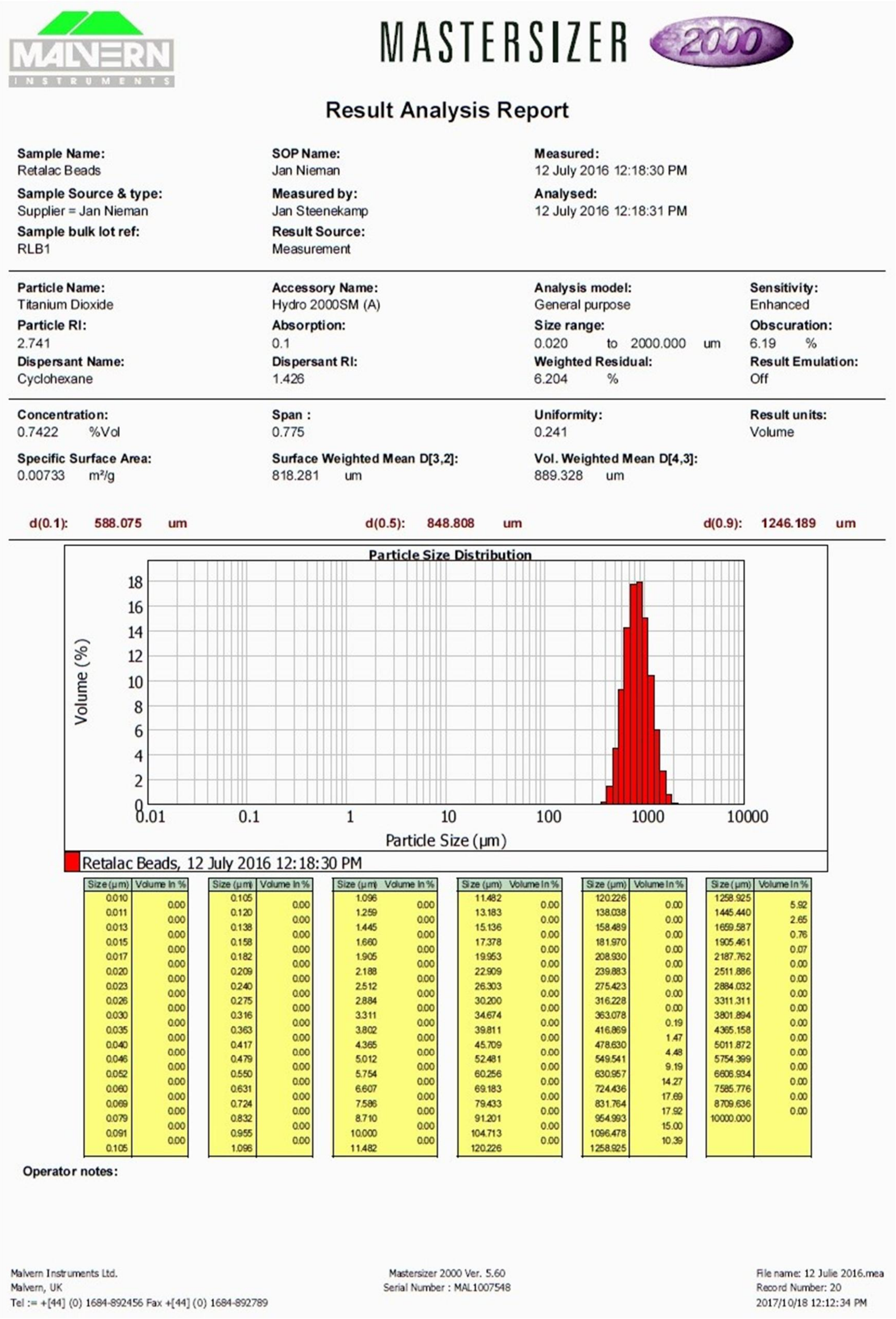
Operator notes:

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: 13 Mei 2016.mea
Record Number: 31
2017/10/18 12:08:38 PM

Annexure B21: Malvern® Mastersizer Data Sheets (RetaLac® Beads Sample 1)



Result Analysis Report

Sample Name:
Retalac Beads

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
RLB1

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
12 July 2016 12:18:30 PM

Analysed:
12 July 2016 12:18:31 PM

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:
6.204 %

Sensitivity:
Enhanced

Obscuration:
6.19 %

Result Emulation:
Off

Concentration:
0.7422 %Vol

Specific Surface Area:
0.00733 m²/g

Span :
0.775

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

Uniformity:
0.241

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

Result units:
Volume

d(0.1): **588.075** **um** **d(0.5):** **848.808** **um** **d(0.9):** **1246.189** **um**

Particle Size Distribution

🟥 Retalac Beads, 12 July 2016 12:18:30 PM

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	5.92
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	2.65
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	0.76
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.07
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	0.19	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	1.47	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	9.19	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	14.27	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	17.69	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	17.92	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	15.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	10.39		
0.105		1.096		11.482		120.226		1258.925			

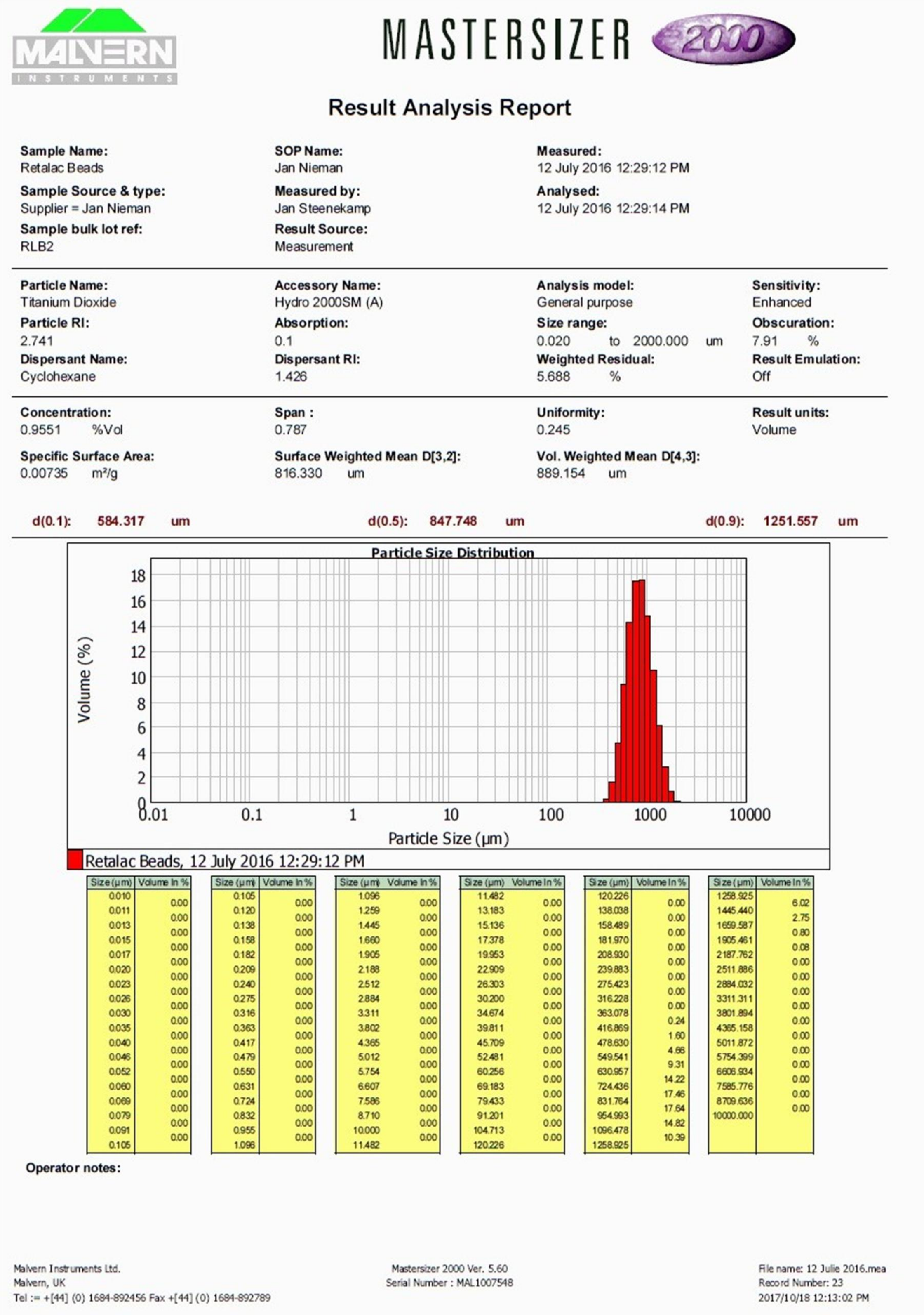
Operator notes:

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: 12 Julie 2016.mea
Record Number: 20
2017/10/18 12:12:34 PM

Annexure B22: Malvern® Mastersizer Data Sheets (RetaLac® Beads Sample 2)



Result Analysis Report

Sample Name:
Retalac Beads

SOP Name:
Jan Nieman

Measured:
12 July 2016 12:29:12 PM

Sample Source & type:
Supplier = Jan Nieman

Measured by:
Jan Steenekamp

Analysed:
12 July 2016 12:29:14 PM

Sample bulk lot ref:
RLB2

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:
7.91 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
5.688 %

Result Emulation:
Off

Concentration:
0.9551 %Vol

Span :
0.787

Uniformity:
0.245

Result units:
Volume

Specific Surface Area:
0.00735 m²/g

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

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

d(0.1): 584.317 um **d(0.5): 847.748 um** **d(0.9): 1251.557 um**

🟥 Retalac Beads, 12 July 2016 12:29:12 PM

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	6.02
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	2.75
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	0.80
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	0.24	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	1.60	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.66	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	9.31	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	14.22	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	17.46	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	17.64	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	14.82	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	10.39		
0.105		1.096		11.482		120.226		1258.925			

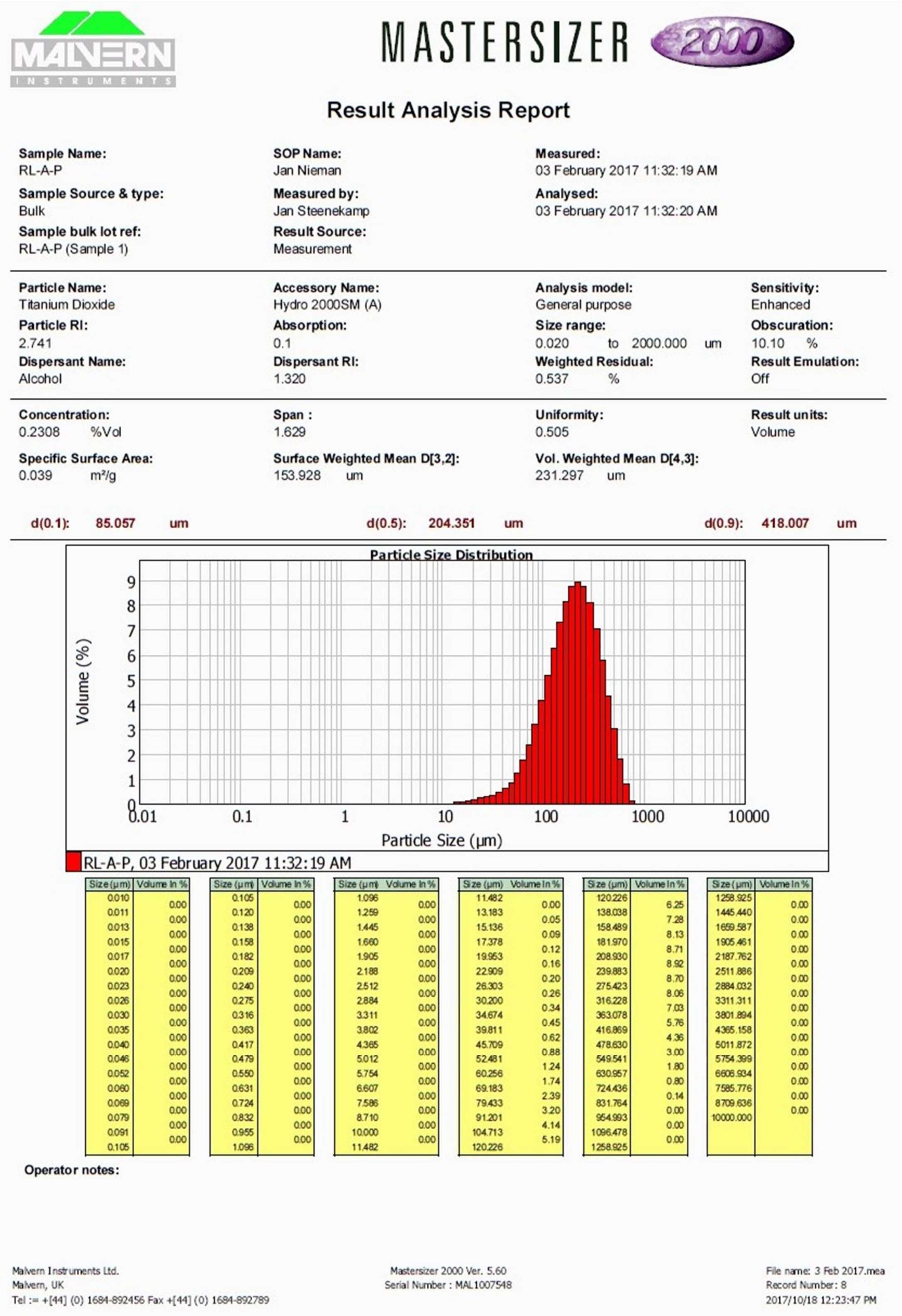
Operator notes:

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: 12 Julie 2016.mea
Record Number: 23
2017/10/18 12:13:02 PM

Annexure B23: Malvern® Mastersizer Data Sheets (RetaLac® API Powder Sample 1)



Result Analysis Report

Sample Name: RL-A-P
Sample Source & type: Bulk
Sample bulk lot ref: RL-A-P (Sample 1)

SOP Name: Jan Nieman
Measured by: Jan Steenekamp
Result Source: Measurement

Measured: 03 February 2017 11:32:19 AM
Analysed: 03 February 2017 11:32:20 AM

Particle Name: Titanium Dioxide
Particle RI: 2.741
Dispersant Name: Alcohol

Accessory Name: Hydro 2000SM (A)
Absorption: 0.1
Dispersant RI: 1.320

Analysis model: General purpose
Size range: 0.020 to 2000.000 um
Weighted Residual: 0.537 %

Sensitivity: Enhanced
Obscuration: 10.10 %
Result Emulation: Off

Concentration: 0.2308 %Vol
Specific Surface Area: 0.039 m²/g

Span : 1.629
Surface Weighted Mean D[3,2]: 153.928 um

Uniformity: 0.505
Vol. Weighted Mean D[4,3]: 231.297 um

Result units: Volume

d(0.1): 85.057 um **d(0.5):** 204.351 um **d(0.9):** 418.007 um

---

🟥 RL-A-P, 03 February 2017 11:32:19 AM

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	

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	

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	

Size (μm)	Volume In %
11.482	0.00
13.183	0.05
15.136	0.09
17.378	0.12
19.953	0.16
22.909	0.20
26.303	0.26
30.200	0.34
34.674	0.45
39.811	0.62
45.709	0.88
52.481	1.24
60.256	1.74
69.183	2.39
79.433	3.20
91.201	4.14
104.713	5.19
120.226	

Size (μm)	Volume In %
120.226	6.25
138.038	7.28
158.489	8.13
181.970	8.71
208.930	8.92
239.883	8.70
275.423	8.06
316.228	7.03
363.078	5.76
416.869	4.36
478.630	3.00
549.541	1.80
630.957	0.80
724.436	0.14
831.764	0.00
954.993	0.00
1096.478	0.00
1258.925	

Size (μm)	Volume In %
1258.925	0.00
1445.440	0.00
1659.587	0.00
1905.461	0.00
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	

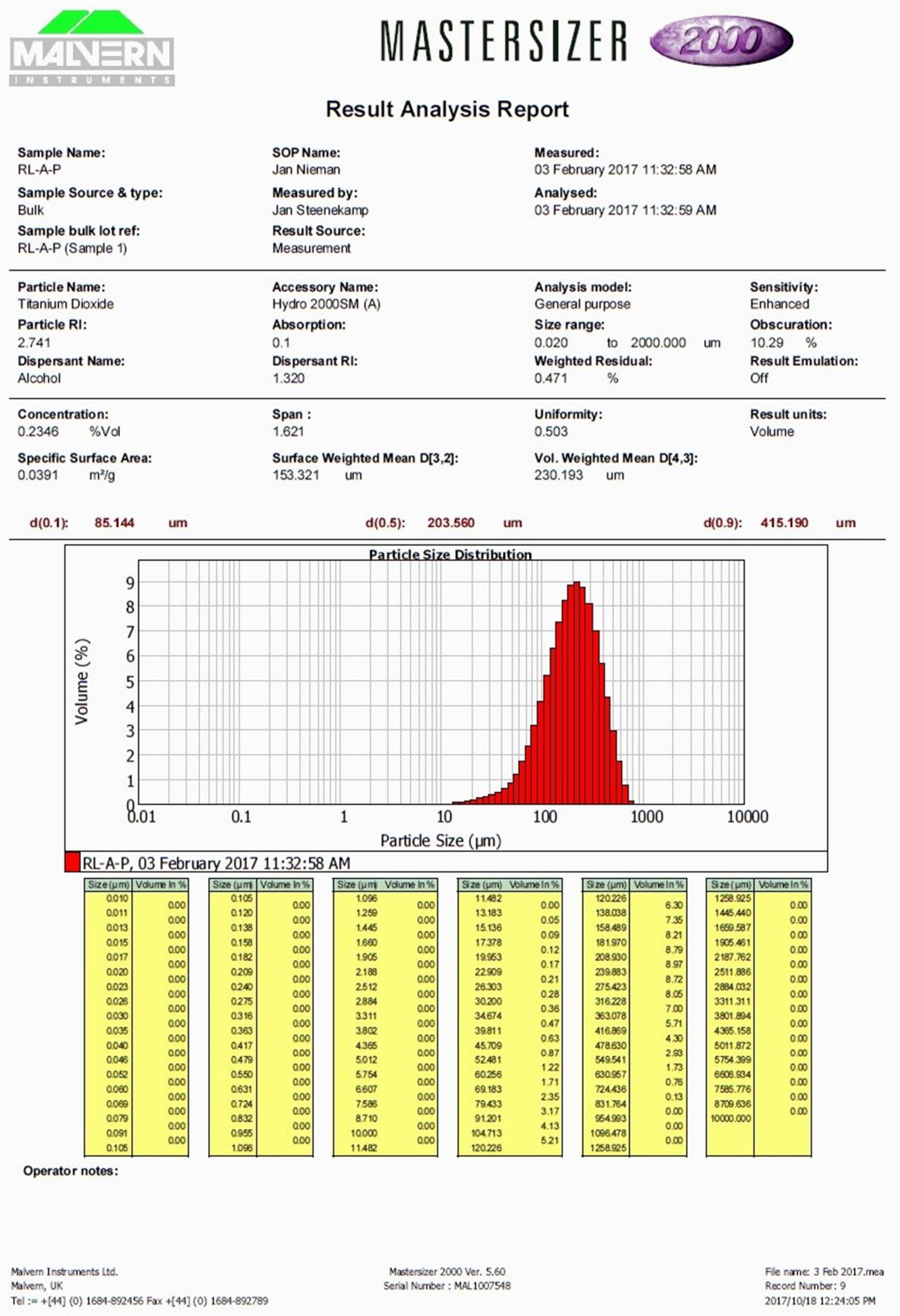
Operator notes:

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: 3 Feb 2017.mea
Record Number: 8
2017/10/18 12:23:47 PM

Annexure B24: Malvern® Mastersizer Data Sheets (RetaLac® API Powder Sample 2)



Result Analysis Report

Sample Name:
RL-A-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:32:58 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:32:59 AM

Sample bulk lot ref:
RL-A-P (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:
10.29 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
0.471 %

Result Emulation:
Off

Concentration:
0.2346 %Vol

Span :
1.621

Uniformity:
0.503

Result units:
Volume

Specific Surface Area:
0.0391 m²/g

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

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

d(0.1): **85.144** **um** **d(0.5):** **203.560** **um** **d(0.9):** **415.190** **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	6.30	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.05	138.038	7.35	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.09	158.489	8.21	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.12	181.970	8.79	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.17	208.930	8.97	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.21	239.883	8.72	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.28	275.423	8.05	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.36	316.228	7.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.47	363.078	5.71	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.63	416.869	4.30	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.87	478.630	2.93	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.22	549.541	1.73	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.71	630.957	0.76	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.35	724.436	0.13	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.17	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.13	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	5.21	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

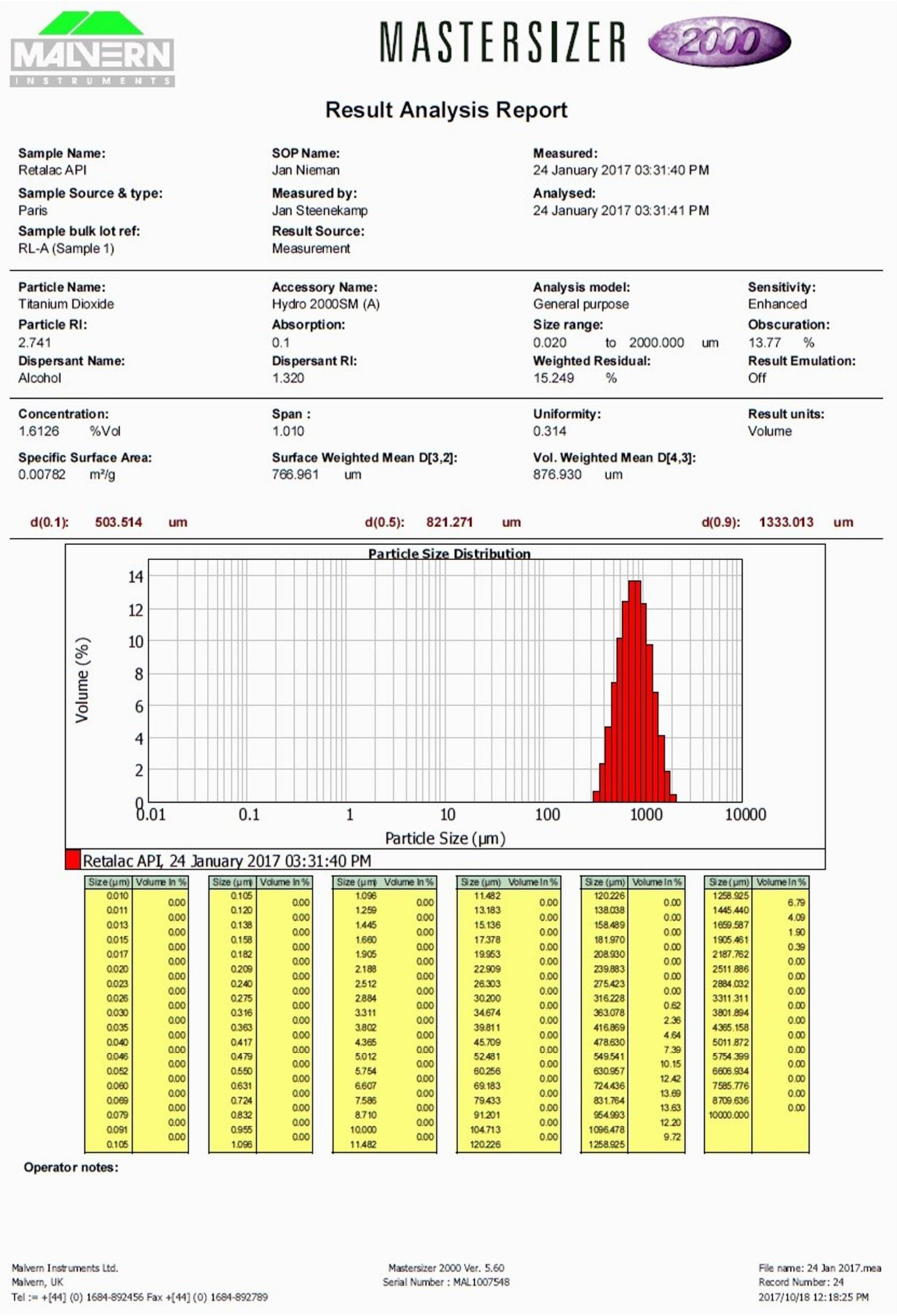
Operator notes:

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: 3 Feb 2017.mea
Record Number: 9
2017/10/18 12:24:05 PM

Annexure B25: Malvern® Mastersizer Data Sheets (RetaLac® API Beads Sample 1)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
Retalac API

Sample Source & type:
Paris

Sample bulk lot ref:
RL-A (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
24 January 2017 03:31:40 PM

Analysed:
24 January 2017 03:31:41 PM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
15.249 %

Sensitivity:
Enhanced

Obscuration:
13.77 %

Result Emulation:
Off

Concentration:
1.6126 %Vol

Specific Surface Area:
0.00782 m²/g

Span :
1.010

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

Uniformity:
0.314

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

Result units:
Volume

d(0.1): 503.514 um **d(0.5):** 821.271 um **d(0.9):** 1333.013 um

🟥 Retalac API, 24 January 2017 03:31:40 PM

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	6.79
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	4.09
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.90
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	0.62	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	2.36	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	4.64	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	7.39	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	10.15	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	12.42	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.69	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	13.63	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	12.20	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	9.72		
0.105		1.096		11.482		120.226		1258.925			

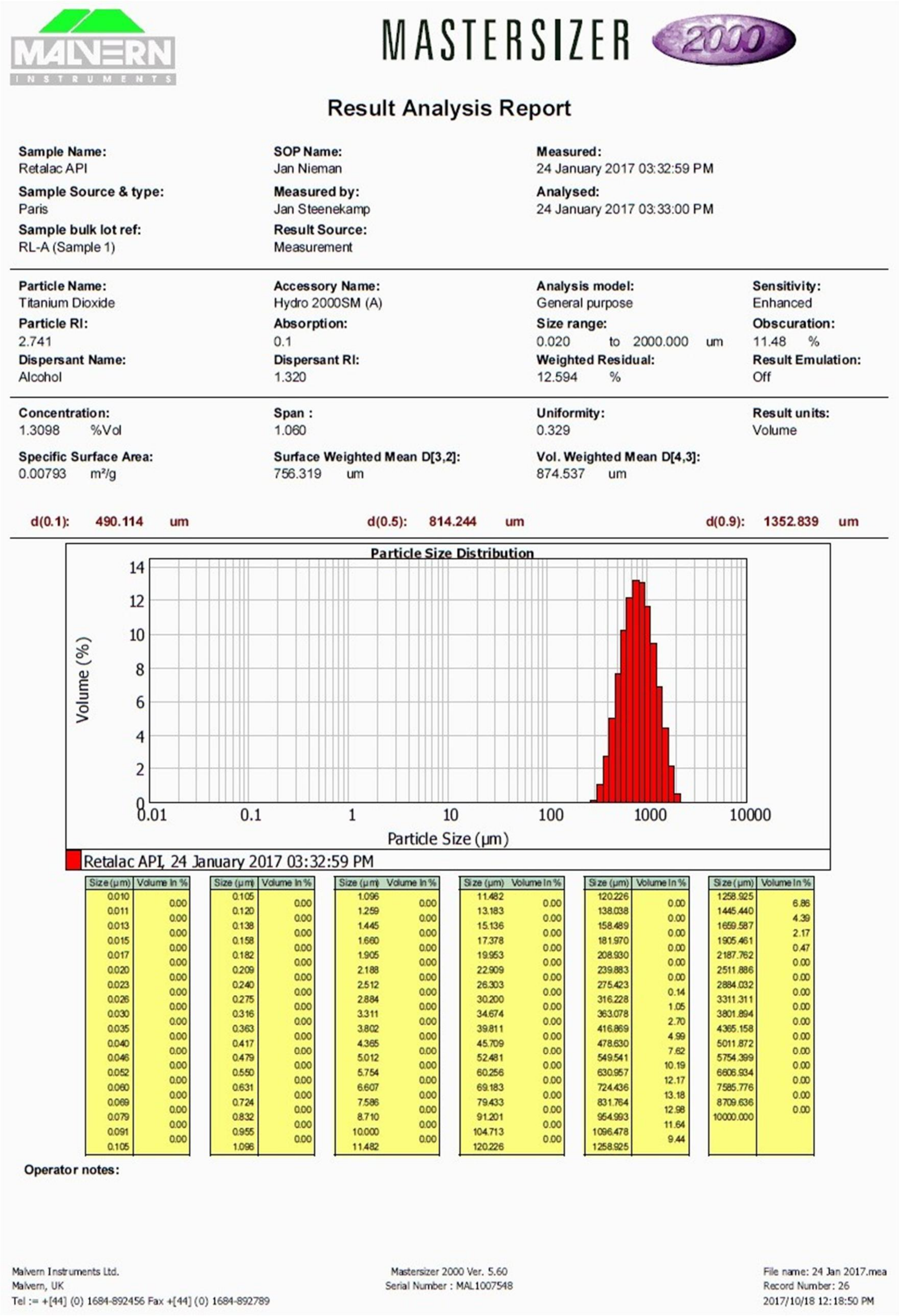
Operator notes:

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: 24 Jan 2017.mea
Record Number: 24
2017/10/18 12:18:25 PM

Annexure B26: Malvern® Mastersizer Data Sheets (RetaLac® API Beads Sample 2)



Result Analysis Report

Sample Name:
Retalac API

SOP Name:
Jan Nieman

Measured:
24 January 2017 03:32:59 PM

Sample Source & type:
Paris

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 03:33:00 PM

Sample bulk lot ref:
RL-A (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:
11.48 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
12.594 %

Result Emulation:
Off

Concentration:
1.3098 %Vol

Span :
1.060

Uniformity:
0.329

Result units:
Volume

Specific Surface Area:
0.00793 m²/g

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

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

d(0.1): 490.114 um **d(0.5): 814.244 um** **d(0.9): 1352.839 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	6.86
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	4.39
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.17
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.47
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	0.14	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	1.05	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	2.70	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	4.99	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	7.62	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	10.19	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	12.17	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.18	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	12.98	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	11.64	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	9.44		
0.105		1.096		11.482		120.226		1258.925			

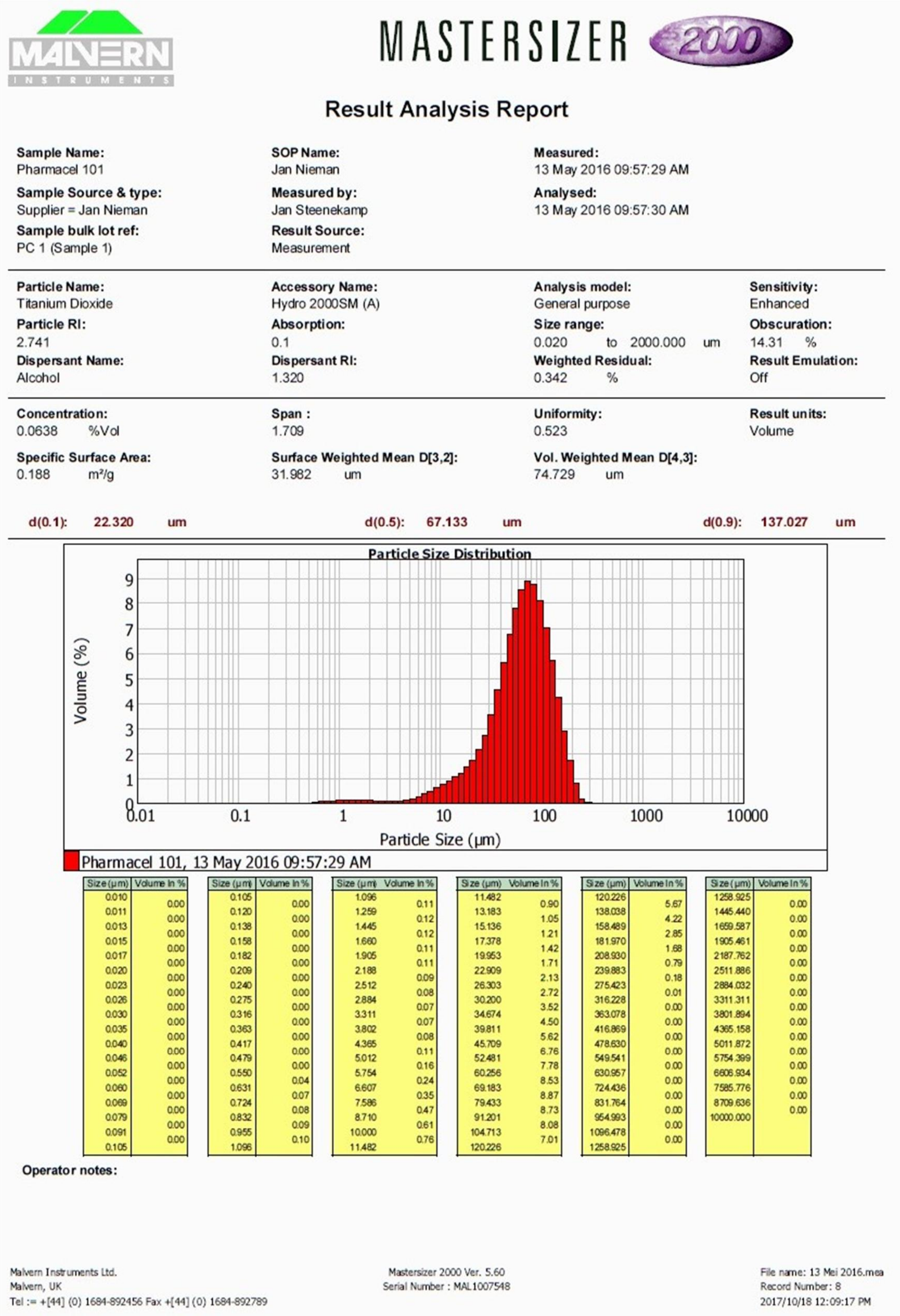
Operator notes:

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: 24 Jan 2017.mea
Record Number: 26
2017/10/18 12:18:50 PM

Annexure B27: Malvern® Mastersizer Data Sheets (Pharmacel® 101 Powder Sample 1)



Result Analysis Report

Sample Name: Pharmacel 101

Sample Source & type: Supplier = Jan Nieman

Sample bulk lot ref: PC 1 (Sample 1)

SOP Name: Jan Nieman

Measured by: Jan Steenekamp

Result Source: Measurement

Measured: 13 May 2016 09:57:29 AM

Analysed: 13 May 2016 09:57:30 AM

Particle Name: Titanium Dioxide

Particle RI: 2.741

Dispersant Name: Alcohol

Accessory Name: Hydro 2000SM (A)

Absorption: 0.1

Dispersant RI: 1.320

Analysis model: General purpose

Size range: 0.020 to 2000.000 um

Weighted Residual: 0.342 %

Sensitivity: Enhanced

Obscuration: 14.31 %

Result Emulation: Off

Concentration: 0.0638 %Vol

Specific Surface Area: 0.188 m²/g

Span : 1.709

Surface Weighted Mean D[3,2]: 31.982 um

Uniformity: 0.523

Vol. Weighted Mean D[4,3]: 74.729 um

Result units: Volume

d(0.1): 22.320 um **d(0.5):** 67.133 um **d(0.9):** 137.027 um

🟥 Pharmacel 101, 13 May 2016 09:57:29 AM

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	0.11	11.482	0.90	120.226	5.67	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.12	13.183	1.05	138.038	4.22	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.12	15.136	1.21	158.489	2.85	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.11	17.378	1.42	181.970	1.68	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.11	19.953	1.71	208.930	0.79	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.09	22.909	2.13	239.883	0.18	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.08	26.303	2.72	275.423	0.01	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	3.52	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.07	34.674	4.50	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.08	39.811	5.62	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.11	45.709	6.76	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.16	52.481	7.78	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.04	5.754	0.24	60.256	8.53	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.07	6.607	0.35	69.183	8.87	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.08	7.586	0.47	79.433	8.73	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.09	8.710	0.61	91.201	8.08	954.993	0.00	10000.000	
0.091	0.00	0.955	0.10	10.000	0.76	104.713	7.01	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

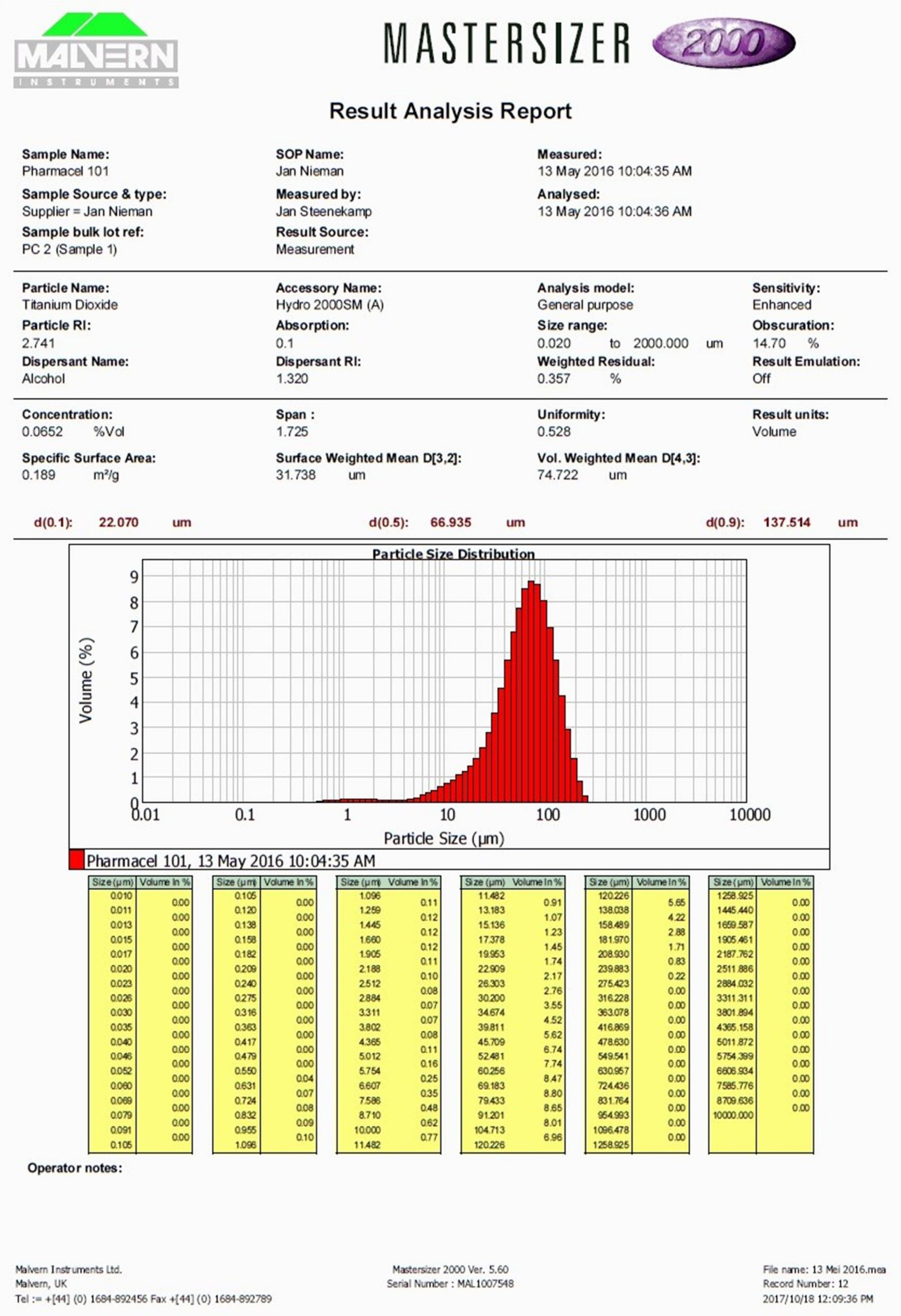
Operator notes:

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: 13 Mei 2016.mea
Record Number: 8
2017/10/18 12:09:17 PM

Annexure B28: Malvern® Mastersizer Data Sheets (Pharmacel® 101 Powder Sample 2)



Result Analysis Report

Sample Name: Pharmacel 101
SOP Name: Jan Nieman
Measured: 13 May 2016 10:04:35 AM
Sample Source & type: Supplier = Jan Nieman
Measured by: Jan Steenekamp
Analysed: 13 May 2016 10:04:36 AM
Sample bulk lot ref: PC 2 (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: 14.70 %
Dispersant Name: Alcohol
Dispersant RI: 1.320
Weighted Residual: 0.357 %
Result Emulation: Off

Concentration: 0.0652 %Vol
Span : 1.725
Uniformity: 0.528
Result units: Volume
Specific Surface Area: 0.189 m²/g
Surface Weighted Mean D[3,2]: 31.738 um
Vol. Weighted Mean D[4,3]: 74.722 um

d(0.1): 22.070 um
d(0.5): 66.935 um
d(0.9): 137.514 um

🟥 Pharmacel 101, 13 May 2016 10:04:35 AM

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	0.11	11.482	0.91	120.226	5.65	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.12	13.183	1.07	138.038	4.22	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.12	15.136	1.23	158.489	2.88	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.12	17.378	1.45	181.970	1.71	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.11	19.953	1.74	208.930	0.83	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.10	22.909	2.17	239.883	0.22	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.08	26.303	2.76	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	3.55	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.07	34.674	4.52	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.08	39.811	5.62	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.11	45.709	6.74	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.16	52.481	7.74	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.04	5.754	0.25	60.256	8.47	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.07	6.607	0.35	69.183	8.80	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.08	7.586	0.48	79.433	8.65	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.09	8.710	0.62	91.201	8.01	954.993	0.00	10000.000	
0.091	0.00	0.955	0.10	10.000	0.77	104.713	6.96	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

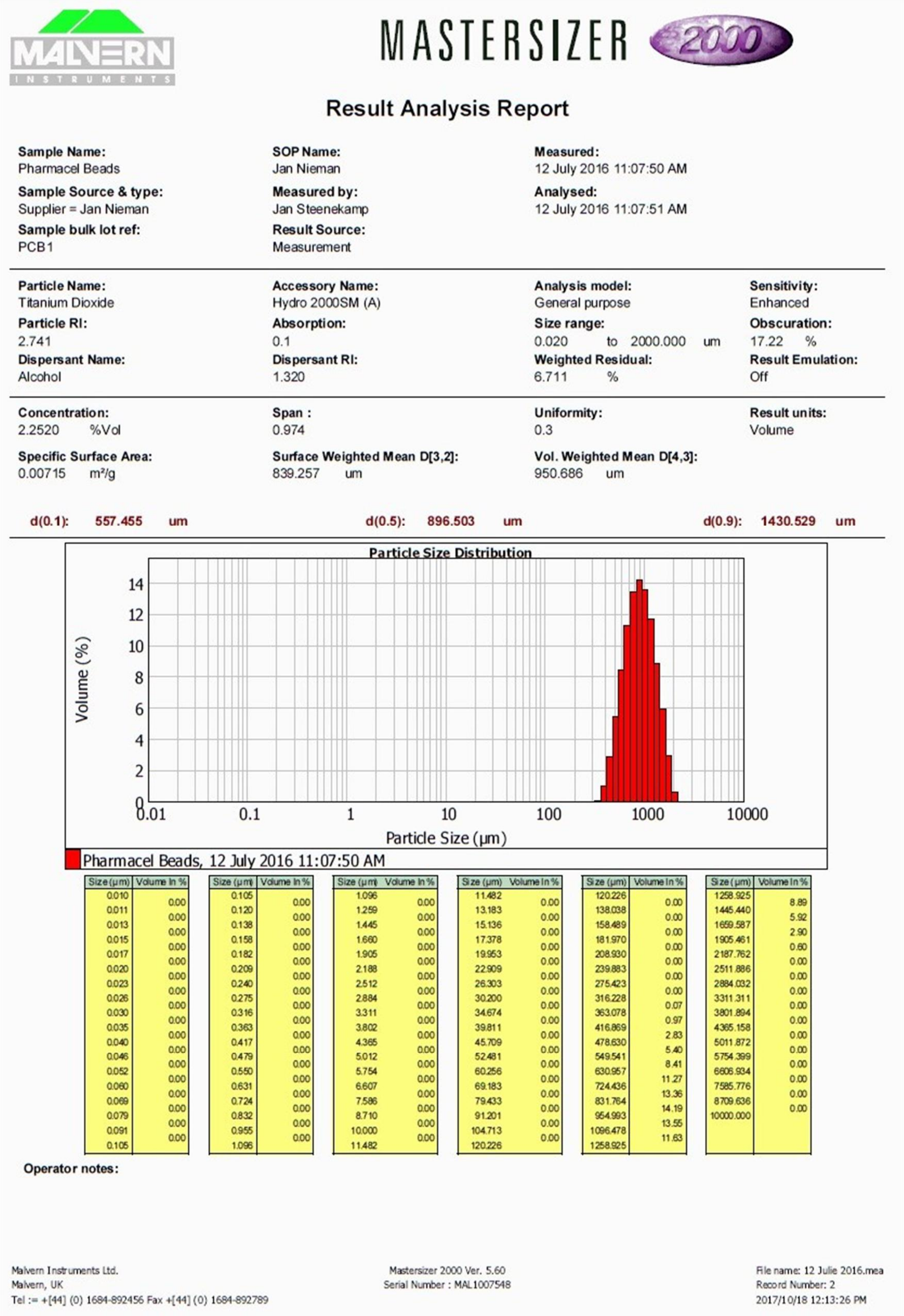
Operator notes:

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: 13 Mei 2016.mea
Record Number: 12
2017/10/18 12:09:36 PM

Annexure B29: Malvern® Mastersizer Data Sheets (Pharmacel® 101 Beads Sample 1)



MASTERSIZER 2000

Result Analysis Report

Sample Name:
Pharmacel Beads

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
PCB1

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
12 July 2016 11:07:50 AM

Analysed:
12 July 2016 11:07:51 AM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
6.711 %

Sensitivity:
Enhanced

Obscuration:
17.22 %

Result Emulation:
Off

Concentration:
2.2520 %Vol

Specific Surface Area:
0.00715 m²/g

Span :
0.974

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

Uniformity:
0.3

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

Result units:
Volume

d(0.1): 557.455 um **d(0.5):** 896.503 um **d(0.9):** 1430.529 um

🟥 Pharmacel Beads, 12 July 2016 11:07:50 AM

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	8.89
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.92
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	2.90
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.60
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	0.07	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.97	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	2.83	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	5.40	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	8.41	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	11.27	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.36	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	14.19	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	13.55	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	11.63		
0.105		1.096		11.482		120.226		1258.925			

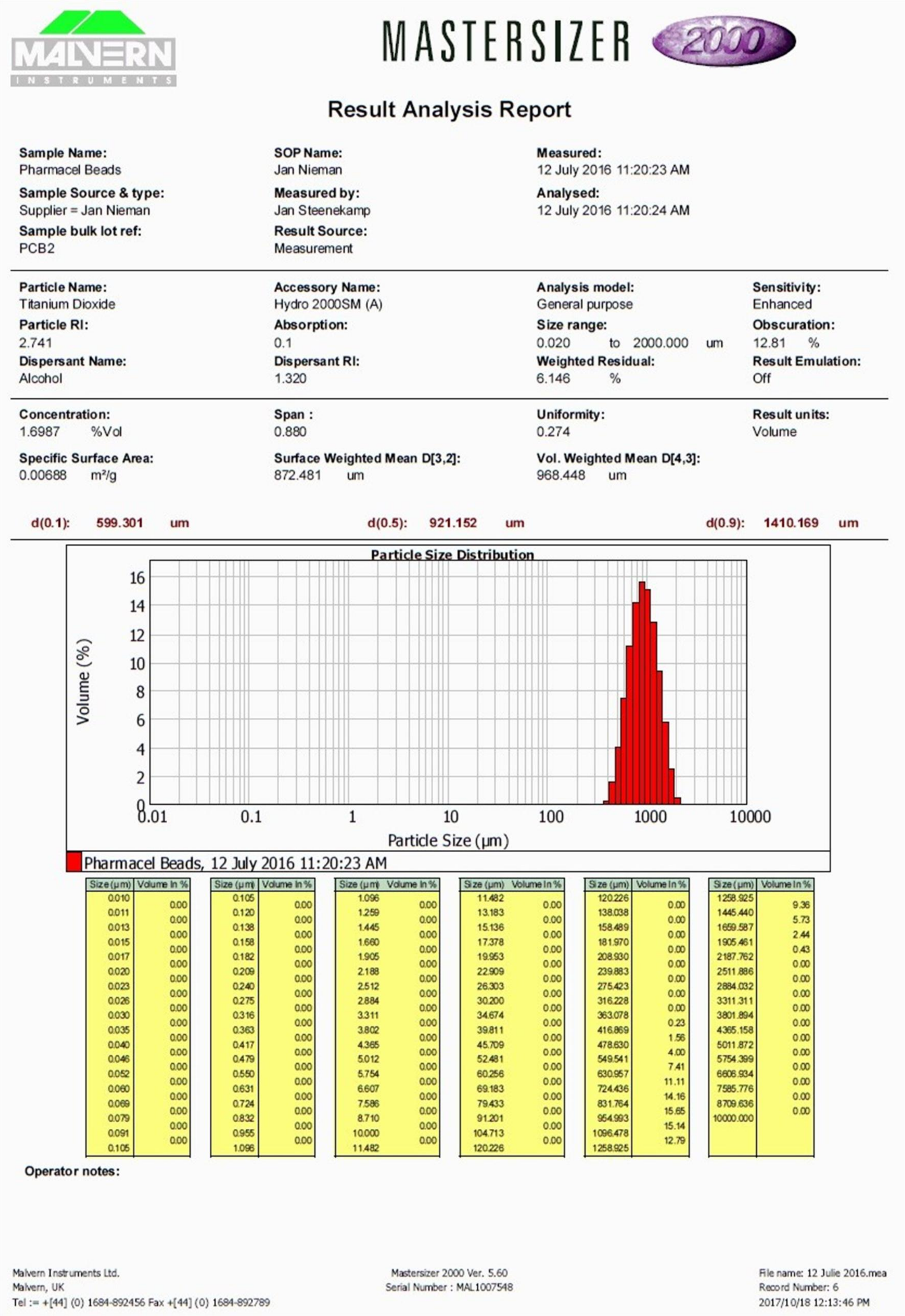
Operator notes:

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: 12 Julie 2016.mea
Record Number: 2
2017/10/18 12:13:26 PM

Annexure B30: Malvern® Mastersizer Data Sheets (Pharmacel® 101 Beads Sample 2)



Result Analysis Report

Sample Name:
Pharmacel Beads

Sample Source & type:
Supplier = Jan Nieman

Sample bulk lot ref:
PCB2

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
12 July 2016 11:20:23 AM

Analysed:
12 July 2016 11:20:24 AM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
6.146 %

Sensitivity:
Enhanced

Obscuration:
12.81 %

Result Emulation:
Off

Concentration:
1.6987 %Vol

Specific Surface Area:
0.00688 m²/g

Span :
0.880

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

Uniformity:
0.274

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

Result units:
Volume

d(0.1): 599.301 um **d(0.5):** 921.152 um **d(0.9):** 1410.169 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	

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	

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	

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	

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	0.23
416.869	1.56
478.630	4.00
549.541	7.41
630.957	11.11
724.436	14.16
831.764	15.65
954.993	15.14
1096.478	12.79
1258.925	

Size (µm)	Volume In %
1258.925	9.36
1445.440	5.73
1659.587	2.44
1905.461	0.43
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	

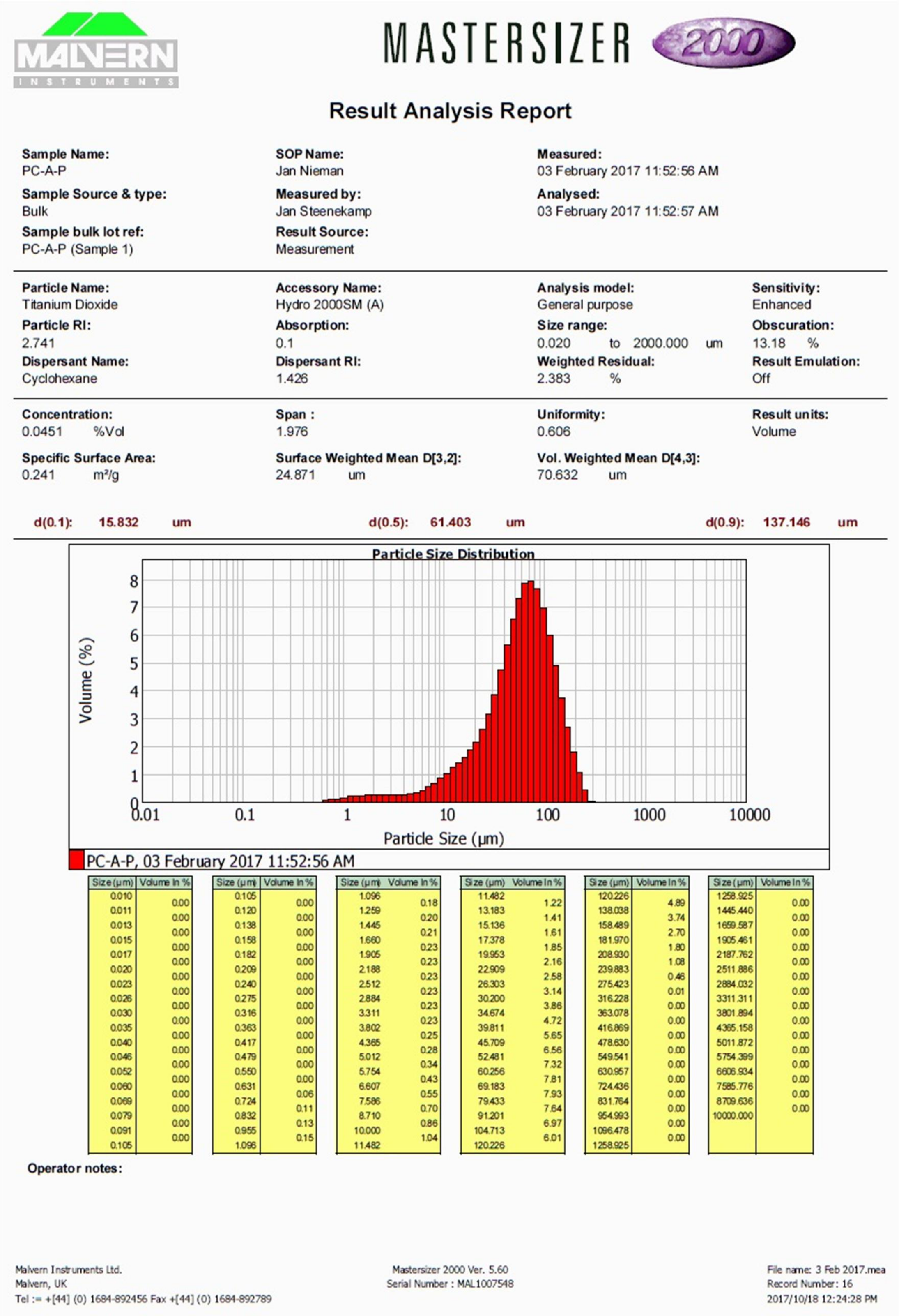
Operator notes:

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: 12 Julie 2016.mea
Record Number: 6
2017/10/18 12:13:46 PM

Annexure B31: Malvern® Mastersizer Data Sheets (Pharmacel® 101 API Powder Sample 1)



Result Analysis Report

Sample Name:
PC-A-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:52:56 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:52:57 AM

Sample bulk lot ref:
PC-A-P (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:
13.18 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
2.383 %

Result Emulation:
Off

Concentration:
0.0451 %Vol

Span :
1.976

Uniformity:
0.606

Result units:
Volume

Specific Surface Area:
0.241 m²/g

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

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

d(0.1): 15.832 um **d(0.5): 61.403 um** **d(0.9): 137.146 um**

🟥 PC-A-P, 03 February 2017 11:52:56 AM

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	

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	0.06
0.724	0.11
0.832	0.13
0.955	0.15
1.096	

Size (µm)	Volume In %
1.096	0.18
1.259	0.20
1.445	0.21
1.660	0.23
1.905	0.23
2.188	0.23
2.512	0.23
2.884	0.23
3.311	0.23
3.802	0.25
4.365	0.28
5.012	0.34
5.754	0.43
6.607	0.55
7.586	0.70
8.710	0.86
10.000	1.04
11.482	

Size (µm)	Volume In %
11.482	1.22
13.183	1.41
15.136	1.61
17.378	1.85
19.953	2.16
22.909	2.58
26.303	3.14
30.200	3.86
34.674	4.72
39.811	5.65
45.709	6.56
52.481	7.32
60.256	7.81
69.183	7.93
79.433	7.64
91.201	6.97
104.713	6.01
120.226	

Size (µm)	Volume In %
120.226	4.89
138.038	3.74
158.489	2.70
181.970	1.80
208.930	1.08
239.883	0.46
275.423	0.01
316.228	0.00
363.078	0.00
416.869	0.00
478.630	0.00
549.541	0.00
630.957	0.00
724.436	0.00
831.764	0.00
954.993	0.00
1096.478	0.00
1258.925	

Size (µm)	Volume In %
1258.925	0.00
1445.440	0.00
1659.587	0.00
1905.461	0.00
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	

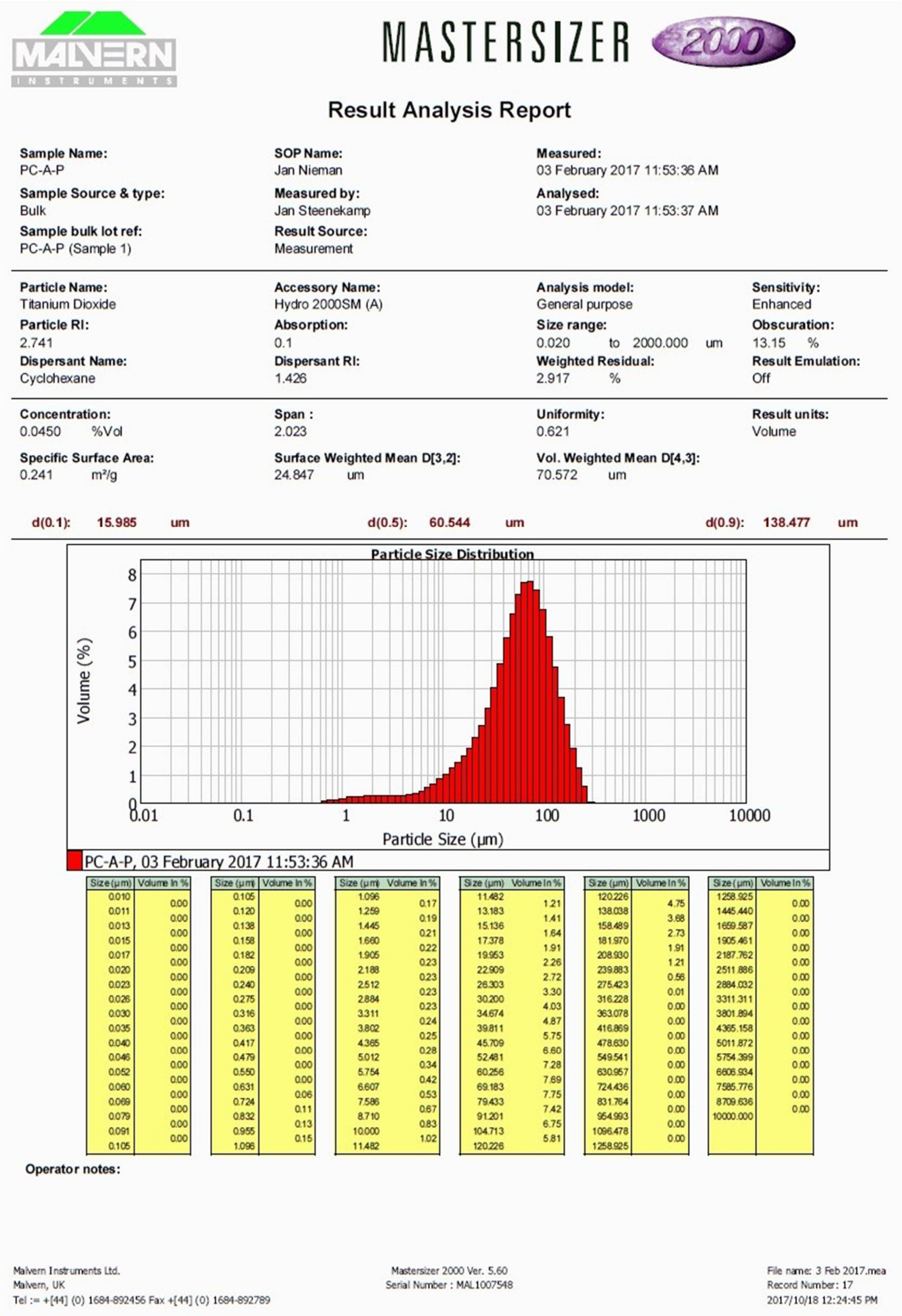
Operator notes:

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: 3 Feb 2017.mea
Record Number: 16
2017/10/18 12:24:28 PM

Annexure B32: Malvern® Mastersizer Data Sheets (Pharmacel® 101 API Powder Sample 2)



MASTERSIZER 2000

Result Analysis Report

Sample Name:
PC-A-P

Sample Source & type:
Bulk

Sample bulk lot ref:
PC-A-P (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
03 February 2017 11:53:36 AM

Analysed:
03 February 2017 11:53:37 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:
2.917 %

Sensitivity:
Enhanced

Obscuration:
13.15 %

Result Emulation:
Off

Concentration:
0.0450 %Vol

Specific Surface Area:
0.241 m²/g

Span :
2.023

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

Uniformity:
0.621

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

Result units:
Volume

d(0.1): 15.985 um **d(0.5):** 60.544 um **d(0.9):** 138.477 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	0.17	11.482	1.21	120.226	4.75	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.19	13.183	1.41	138.038	3.68	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.21	15.136	1.64	158.489	2.73	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.22	17.378	1.91	181.970	1.91	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.23	19.953	2.26	208.930	1.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.23	22.909	2.72	239.883	0.56	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.23	26.303	3.30	275.423	0.01	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.23	30.200	4.03	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.24	34.674	4.87	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.25	39.811	5.75	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.28	45.709	6.60	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.34	52.481	7.28	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.42	60.256	7.69	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.06	6.607	0.53	69.183	7.75	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.11	7.586	0.67	79.433	7.42	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.13	8.710	0.83	91.201	6.75	954.993	0.00	10000.000	
0.091	0.00	0.955	0.15	10.000	1.02	104.713	5.81	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

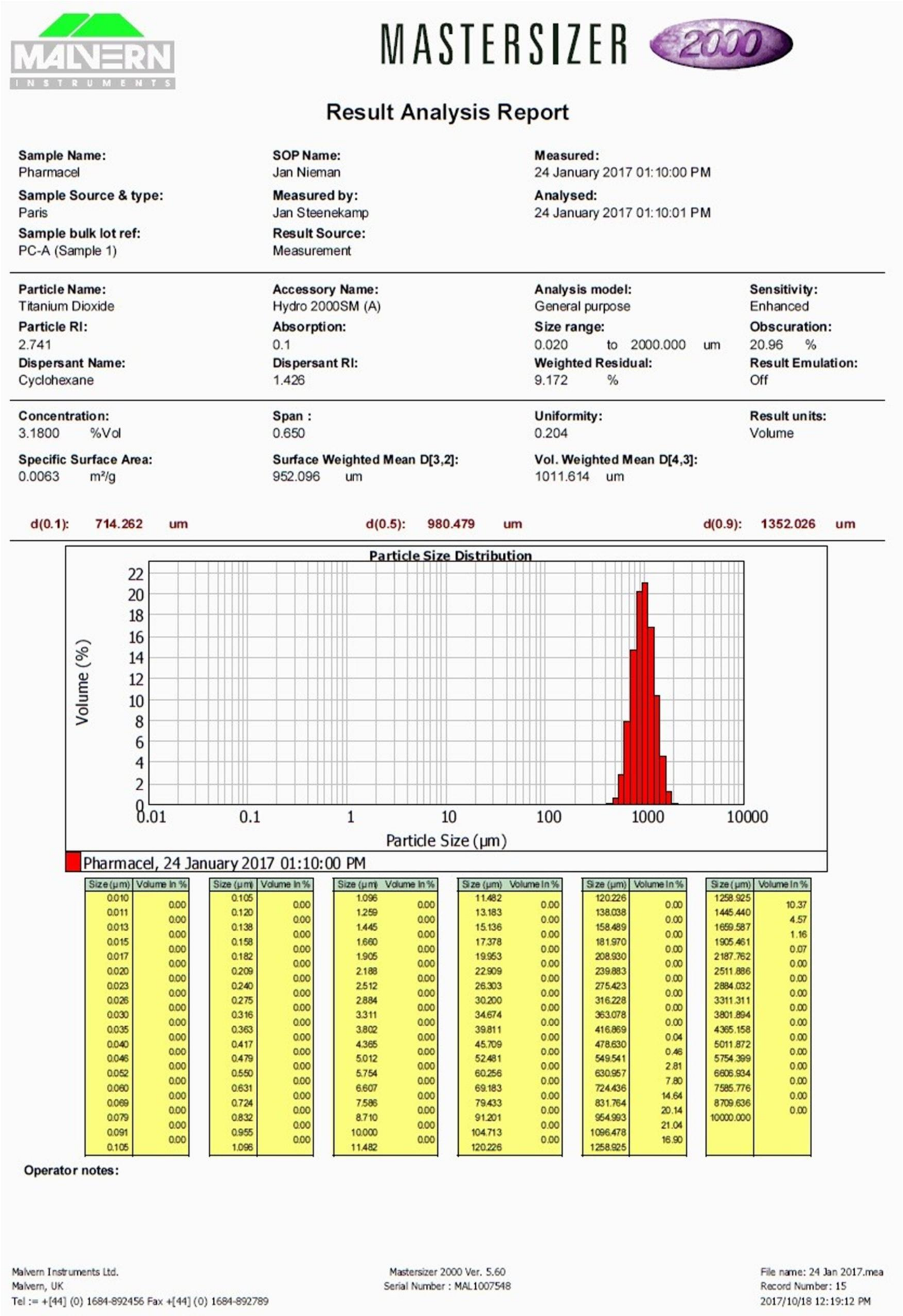
Operator notes:

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: 3 Feb 2017.mea
Record Number: 17
2017/10/18 12:24:45 PM

Annexure B33: Malvern® Mastersizer Data Sheets (Pharmacel® 101 API Beads Sample 1)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
Pharmacel

SOP Name:
Jan Nieman

Measured:
24 January 2017 01:10:00 PM

Sample Source & type:
Paris

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 01:10:01 PM

Sample bulk lot ref:
PC-A (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:
20.96 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
9.172 %

Result Emulation:
Off

Concentration:
3.1800 %Vol

Span :
0.650

Uniformity:
0.204

Result units:
Volume

Specific Surface Area:
0.0063 m²/g

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

Vol. Weighted Mean D[4,3]:
1011.614 um

d(0.1): 714.262 um   d(0.5): 980.479 um   d(0.9): 1352.026 um

🟥 Pharmacel, 24 January 2017 01:10:00 PM

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	

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	

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	

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	

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	0.04
478.630	0.46
549.541	2.81
630.957	7.80
724.436	14.64
831.764	20.14
954.993	21.04
1096.478	16.90
1258.925	

Size (μm)	Volume In %
1258.925	10.37
1445.440	4.57
1659.587	1.16
1905.461	0.07
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	

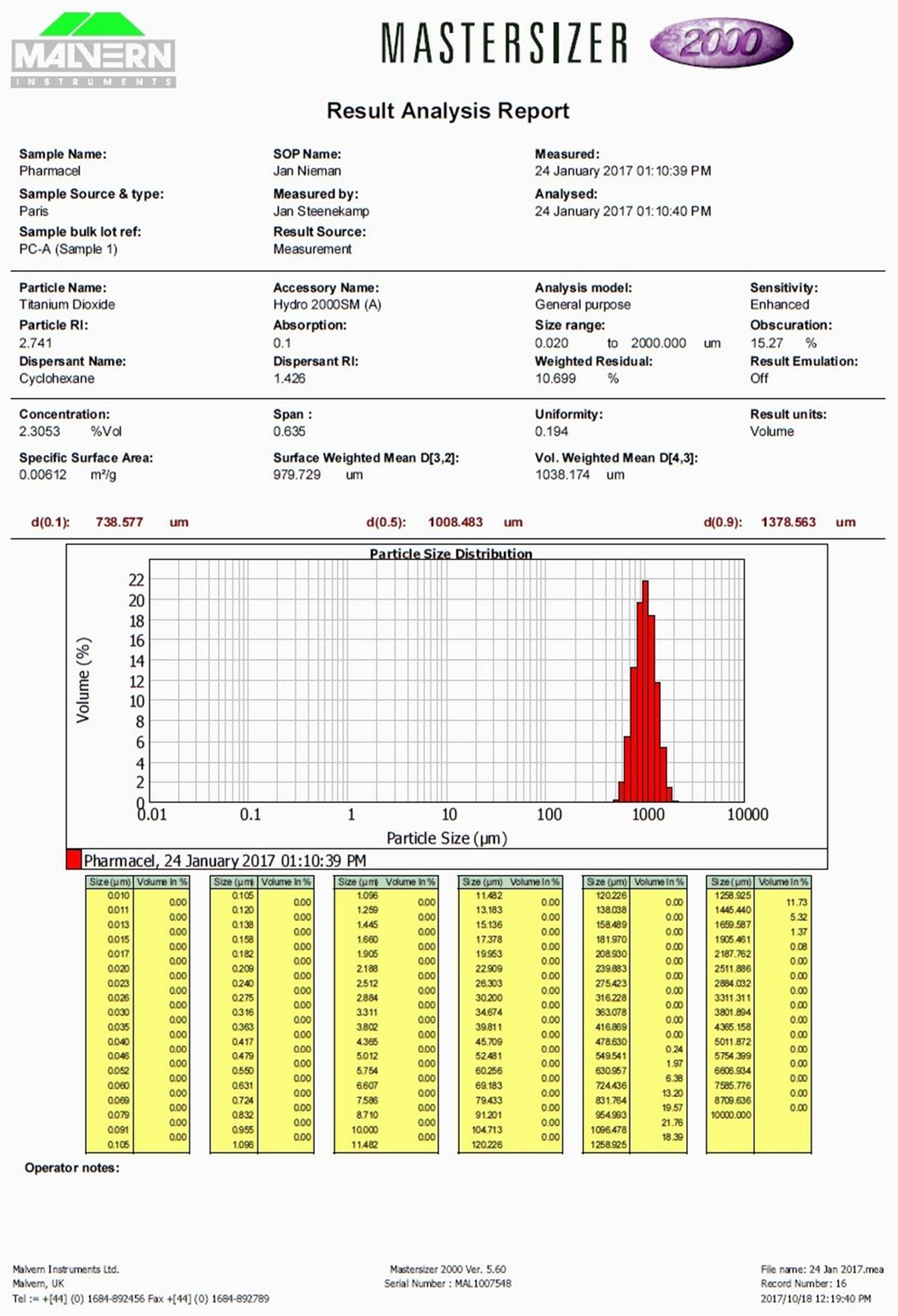
Operator notes:

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: 24 Jan 2017.mea
Record Number: 15
2017/10/18 12:19:12 PM

Annexure B34: Malvern® Mastersizer Data Sheets (Pharmacel® 101 API Beads Sample 2)



Result Analysis Report

Sample Name:
Pharmacel

SOP Name:
Jan Nieman

Measured:
24 January 2017 01:10:39 PM

Sample Source & type:
Paris

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 01:10:40 PM

Sample bulk lot ref:
PC-A (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:
15.27 %

Dispersant Name:
Cyclohexane

Dispersant RI:
1.426

Weighted Residual:
10.699 %

Result Emulation:
Off

Concentration:
2.3053 %Vol

Span :
0.635

Uniformity:
0.194

Result units:
Volume

Specific Surface Area:
0.00612 m²/g

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

Vol. Weighted Mean D[4,3]:
1038.174 um

d(0.1): 738.577 um **d(0.5): 1008.483 um** **d(0.9): 1378.563 um**

Pharmacel, 24 January 2017 01:10:39 PM

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	

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	

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	

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	

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	0.00
478.630	0.24
549.541	1.97
630.957	6.38
724.436	13.20
831.764	19.57
954.993	21.76
1096.478	18.39
1258.925	

Size (µm)	Volume In %
1258.925	11.73
1445.440	5.32
1659.587	1.37
1905.461	0.08
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	

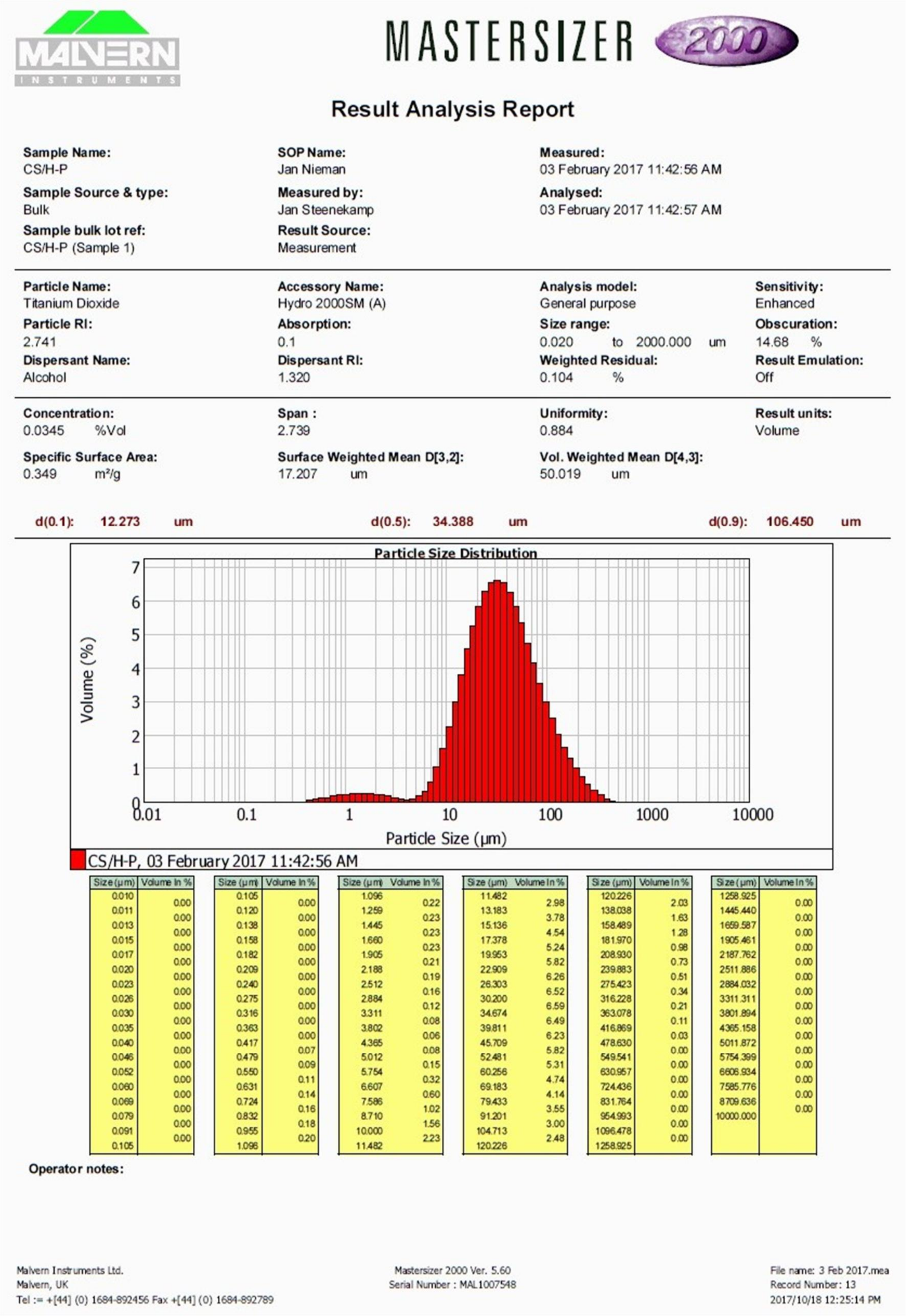
Operator notes:

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: 24 Jan 2017.mea
Record Number: 16
2017/10/18 12:19:40 PM

Annexure B35: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC Powder Sample 1)



Result Analysis Report

Sample Name: CS/H-P	**SOP Name:** Jan Nieman	**Measured:** 03 February 2017 11:42:56 AM
Sample Source & type: Bulk	**Measured by:** Jan Steenekamp	**Analysed:** 03 February 2017 11:42:57 AM
Sample bulk lot ref: CS/H-P (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:** 14.68 %
Dispersant Name: Alcohol	**Dispersant RI:** 1.320	**Weighted Residual:** 0.104 %	**Result Emulation:** Off

Concentration: 0.0345 %Vol	**Span :** 2.739	**Uniformity:** 0.884	**Result units:** Volume
Specific Surface Area: 0.349 m²/g	**Surface Weighted Mean D[3,2]:** 17.207 um	**Vol. Weighted Mean D[4,3]:** 50.019 um	

d(0.1): 12.273 um **d(0.5):** 34.388 um **d(0.9):** 106.450 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	0.22	11.482	2.98	120.226	2.03	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.23	13.183	3.78	138.038	1.63	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.23	15.136	4.54	158.489	1.28	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.23	17.378	5.24	181.970	0.98	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.21	19.953	5.82	208.930	0.73	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	6.26	239.883	0.51	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.16	26.303	6.52	275.423	0.34	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.12	30.200	6.59	316.228	0.21	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	6.49	363.078	0.11	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.06	39.811	6.23	416.869	0.03	4365.158	0.00
0.040	0.00	0.417	0.07	4.365	0.08	45.709	5.82	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.09	5.012	0.15	52.481	5.31	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.11	5.754	0.32	60.256	4.74	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.60	69.183	4.14	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.16	7.586	1.02	79.433	3.55	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.18	8.710	1.56	91.201	3.00	954.993	0.00	10000.000	
0.091	0.00	0.955	0.20	10.000	2.23	104.713	2.48	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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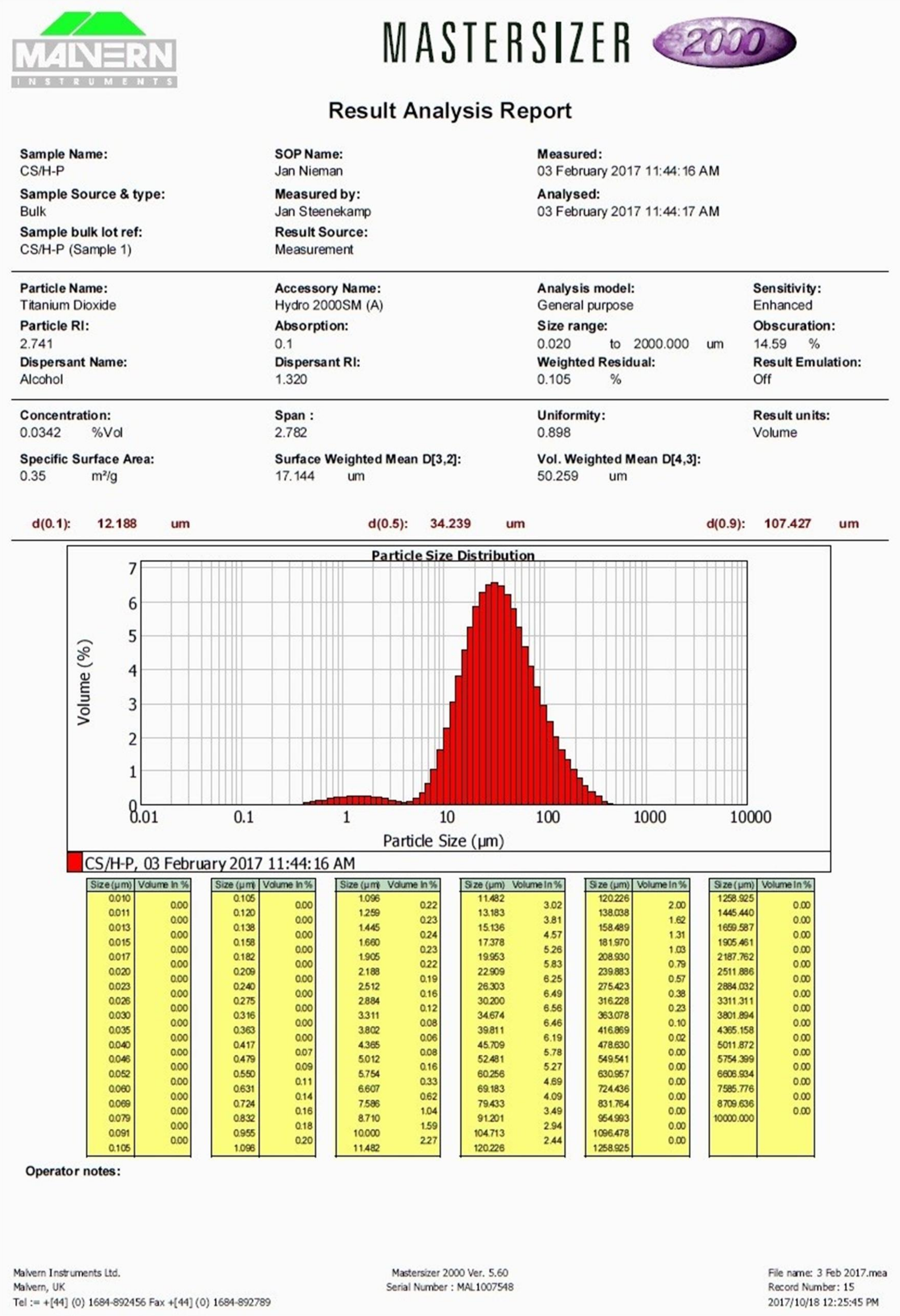
Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 3 Feb 2017.mea
Record Number: 13
2017/10/18 12:25:14 PM

Annexure B36: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC Powder Sample 2)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
CS/H-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:44:16 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:44:17 AM

Sample bulk lot ref:
CS/H-P (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:
14.59 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
0.105 %

Result Emulation:
Off

Concentration:
0.0342 %Vol

Span :
2.782

Uniformity:
0.898

Result units:
Volume

Specific Surface Area:
0.35 m²/g

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

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

d(0.1): 12.188 um **d(0.5): 34.239 um** **d(0.9): 107.427 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	0.22	11.482	3.02	120.226	2.00	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.23	13.183	3.81	138.038	1.62	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.24	15.136	4.57	158.489	1.31	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.23	17.378	5.26	181.970	1.03	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.22	19.953	5.83	208.930	0.79	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	6.25	239.883	0.57	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.16	26.303	6.49	275.423	0.38	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.12	30.200	6.56	316.228	0.23	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	6.46	363.078	0.10	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.06	39.811	6.19	416.869	0.02	4365.158	0.00
0.040	0.00	0.417	0.07	4.365	0.08	45.709	5.78	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.09	5.012	0.16	52.481	5.27	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.11	5.754	0.33	60.256	4.69	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.62	69.183	4.09	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.16	7.586	1.04	79.433	3.49	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.18	8.710	1.59	91.201	2.94	954.993	0.00	10000.000	
0.091	0.00	0.955	0.20	10.000	2.27	104.713	2.44	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

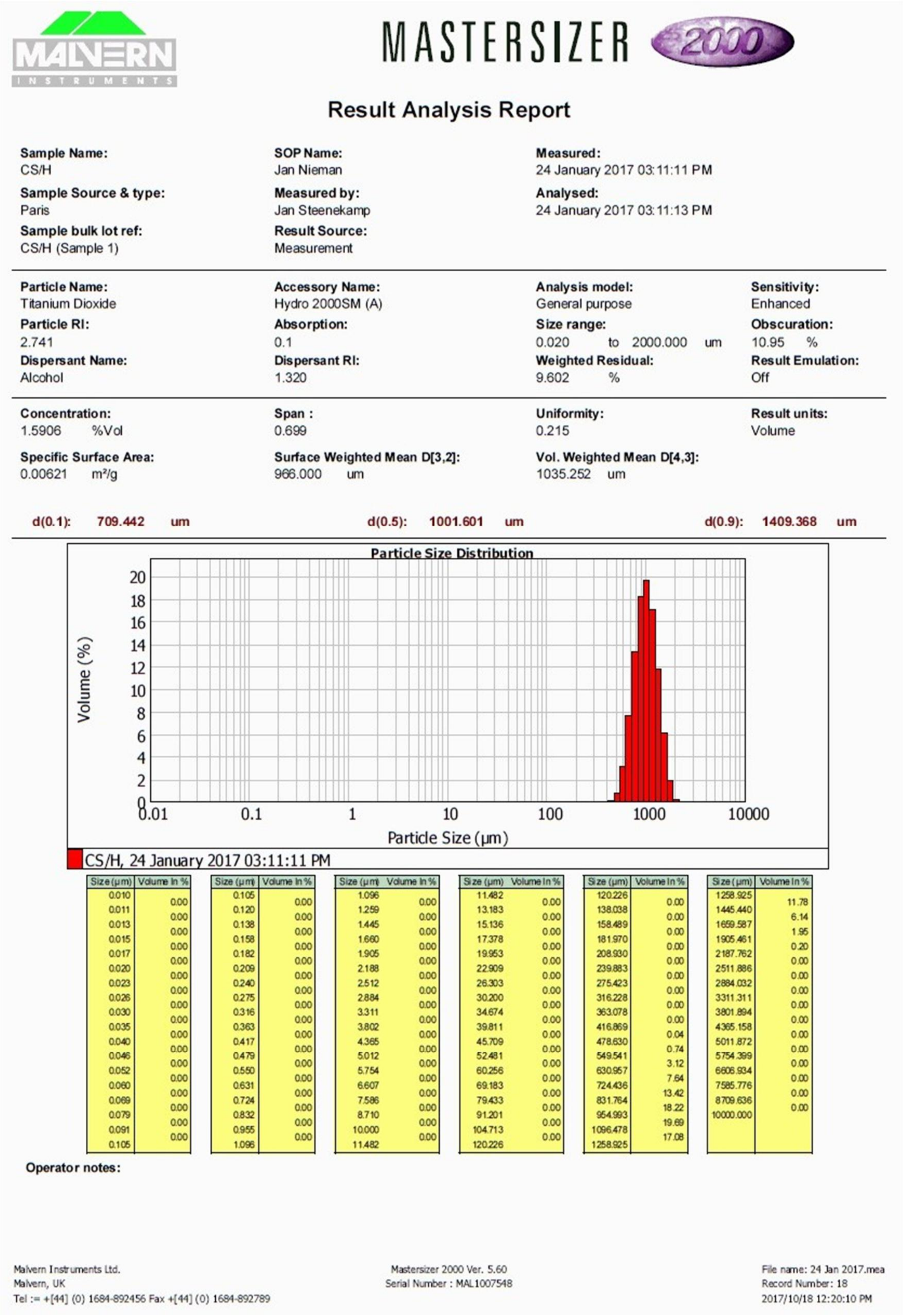
Operator notes:

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: 3 Feb 2017.mea
Record Number: 15
2017/10/18 12:25:45 PM

Annexure B37: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC Beads Sample 1)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
CS/H

SOP Name:
Jan Nieman

Measured:
24 January 2017 03:11:11 PM

Sample Source & type:
Paris

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 03:11:13 PM

Sample bulk lot ref:
CS/H (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:
10.95 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
9.602 %

Result Emulation:
Off

Concentration:
1.5906 %Vol

Span :
0.699

Uniformity:
0.215

Result units:
Volume

Specific Surface Area:
0.00621 m²/g

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

Vol. Weighted Mean D[4,3]:
1035.252 um

d(0.1): 709.442 um **d(0.5): 1001.601 um** **d(0.9): 1409.368 um**

Particle Size Distribution

🟥 CS/H, 24 January 2017 03:11:11 PM

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	11.78
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	6.14
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.95
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.20
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	0.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.74	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	3.12	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	7.64	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.42	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	18.22	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	19.69	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	17.08		
0.105		1.096		11.482		120.226		1258.925			

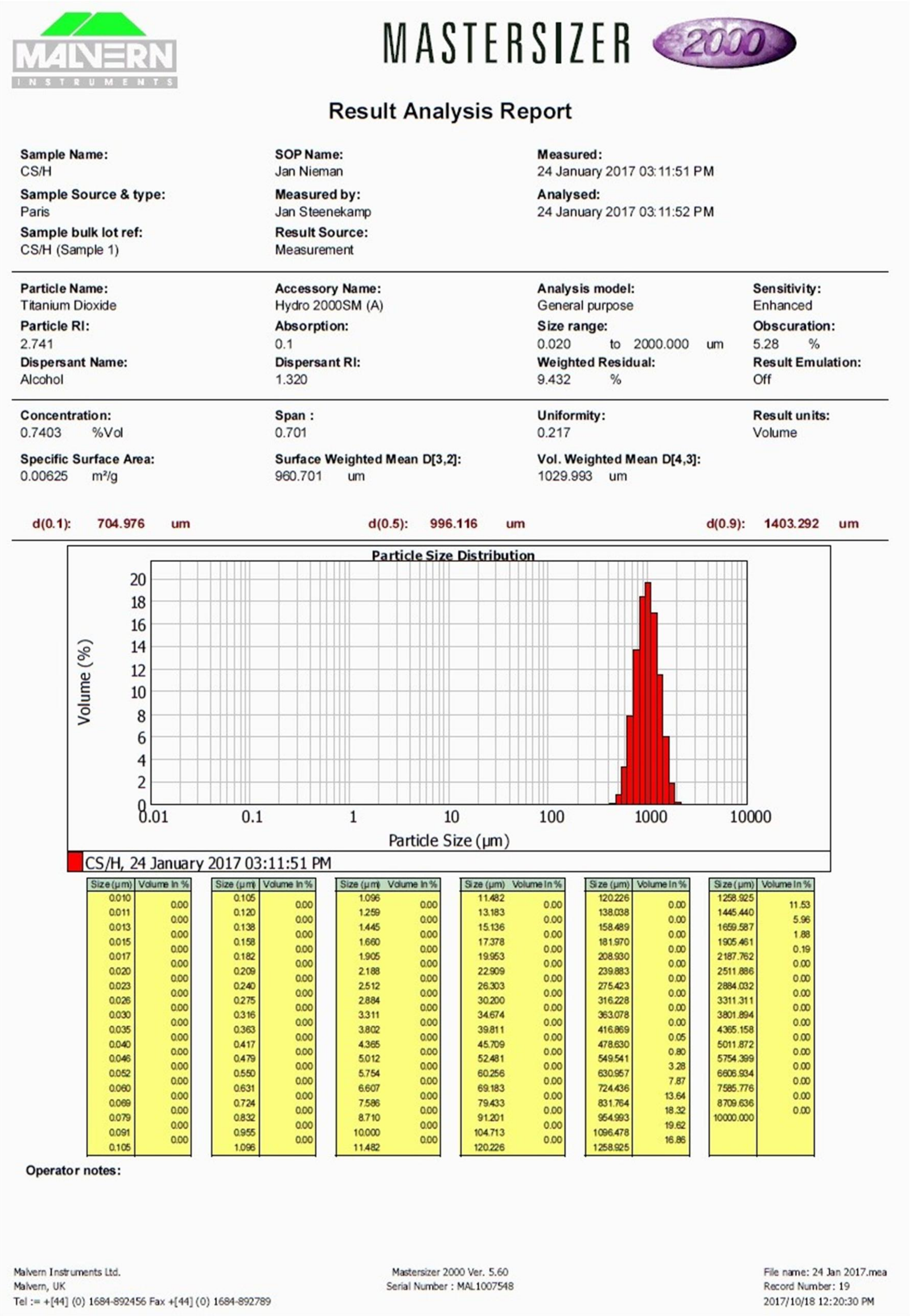
Operator notes:

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: 24 Jan 2017.mea
Record Number: 18
2017/10/18 12:20:10 PM

Annexure B38: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC Beads Sample 2)



Result Analysis Report

Sample Name: CS/H
SOP Name: Jan Nieman
Measured: 24 January 2017 03:11:51 PM
Sample Source & type: Paris
Measured by: Jan Steenekamp
Analysed: 24 January 2017 03:11:52 PM
Sample bulk lot ref: CS/H (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: 5.28 %
Dispersant Name: Alcohol
Dispersant RI: 1.320
Weighted Residual: 9.432 %
Result Emulation: Off

Concentration: 0.7403 %Vol
Span : 0.701
Uniformity: 0.217
Result units: Volume
Specific Surface Area: 0.00625 m²/g
Surface Weighted Mean D[3,2]: 960.701 um
Vol. Weighted Mean D[4,3]: 1029.993 um

d(0.1): 704.976 um
d(0.5): 996.116 um
d(0.9): 1403.292 um

🟥 CS/H, 24 January 2017 03:11:51 PM

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	11.53
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.96
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.489	0.00	1659.587	1.88
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	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.05	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	0.80	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	3.28	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	7.87	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	13.64	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	18.32	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	19.62	10000.000	
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	16.86		
0.105		1.096		11.482		120.226		1258.925			

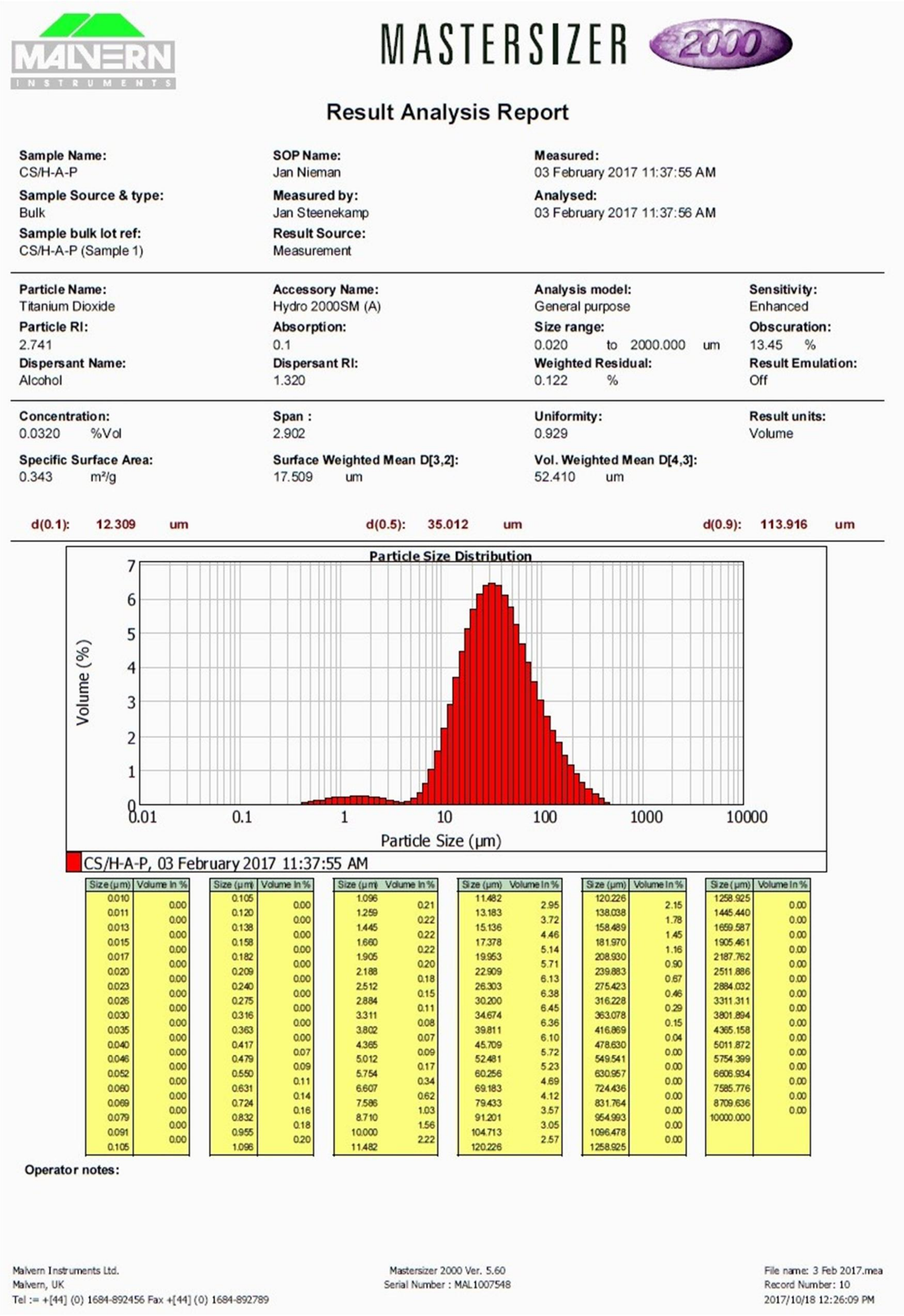
Operator notes:

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: 24 Jan 2017.mea
Record Number: 19
2017/10/18 12:20:30 PM

Annexure B39: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC API Powder Sample 1)



Result Analysis Report

Sample Name:
CS/H-A-P

SOP Name:
Jan Nieman

Measured:
03 February 2017 11:37:55 AM

Sample Source & type:
Bulk

Measured by:
Jan Steenekamp

Analysed:
03 February 2017 11:37:56 AM

Sample bulk lot ref:
CS/H-A-P (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:
13.45 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
0.122 %

Result Emulation:
Off

Concentration:
0.0320 %Vol

Span :
2.902

Uniformity:
0.929

Result units:
Volume

Specific Surface Area:
0.343 m²/g

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

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

d(0.1): 12.309 um **d(0.5):** 35.012 um **d(0.9):** 113.916 um

🟥 CS/H-A-P, 03 February 2017 11:37:55 AM

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	0.21	11.482	2.95	120.226	2.15	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.22	13.183	3.72	138.038	1.78	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.22	15.136	4.46	158.489	1.45	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.22	17.378	5.14	181.970	1.16	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.20	19.953	5.71	208.930	0.90	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.18	22.909	6.13	239.883	0.67	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.15	26.303	6.38	275.423	0.46	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	6.45	316.228	0.29	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	6.36	363.078	0.15	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.07	39.811	6.10	416.869	0.04	4365.158	0.00
0.040	0.00	0.417	0.07	4.365	0.09	45.709	5.72	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.09	5.012	0.17	52.481	5.23	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.11	5.754	0.34	60.256	4.69	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.62	69.183	4.12	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.16	7.586	1.03	79.433	3.57	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.18	8.710	1.56	91.201	3.05	954.993	0.00	10000.000	
0.091	0.00	0.955	0.20	10.000	2.22	104.713	2.57	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

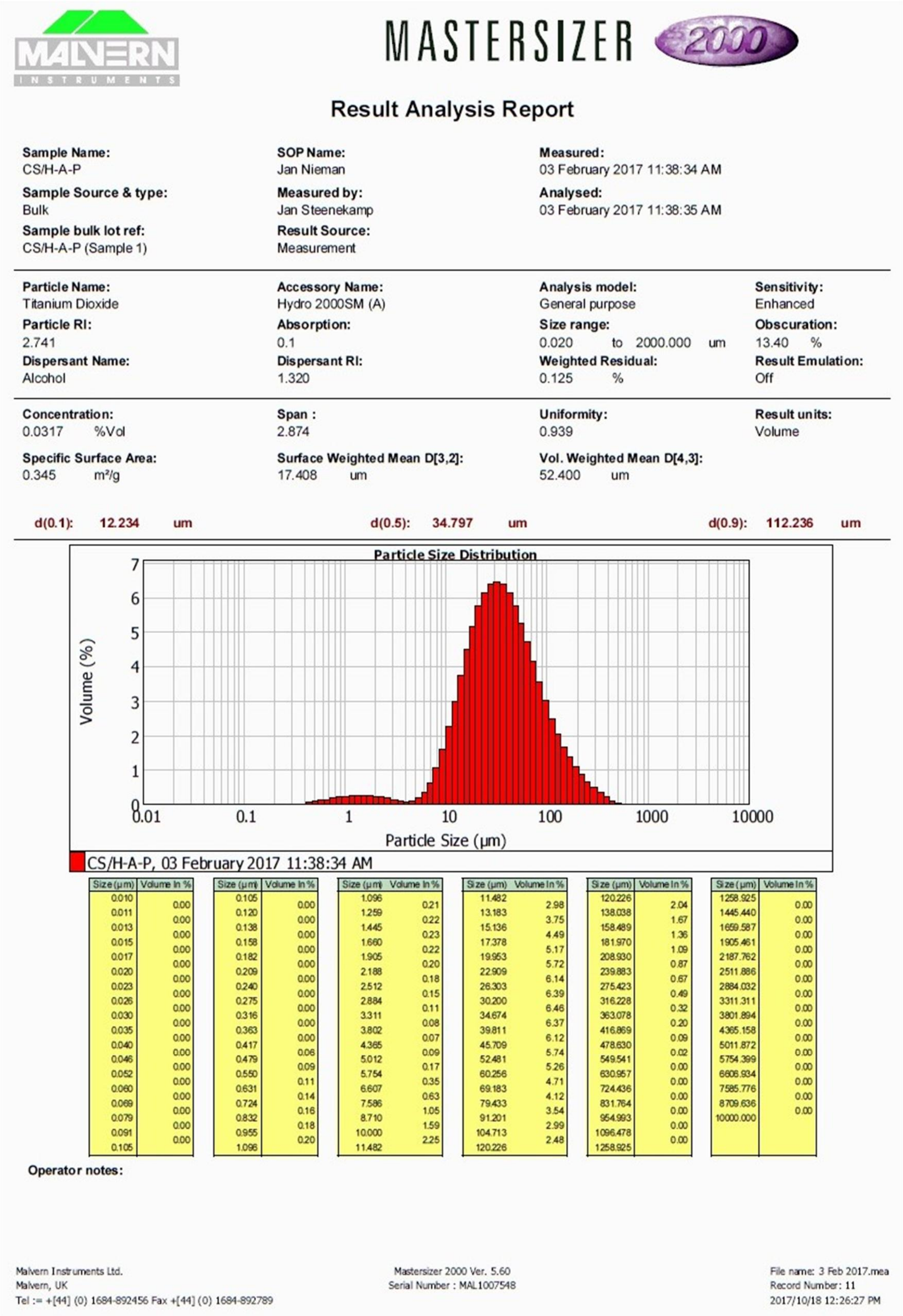
Operator notes:

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: 3 Feb 2017.mea
Record Number: 10
2017/10/18 12:26:09 PM

Annexure B40: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC API Powder Sample 2)



Result Analysis Report

Sample Name:
CS/H-A-P

Sample Source & type:
Bulk

Sample bulk lot ref:
CS/H-A-P (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
03 February 2017 11:38:34 AM

Analysed:
03 February 2017 11:38:35 AM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
0.125 %

Sensitivity:
Enhanced

Obscuration:
13.40 %

Result Emulation:
Off

Concentration:
0.0317 %Vol

Specific Surface Area:
0.345 m²/g

Span :
2.874

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

Uniformity:
0.939

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

Result units:
Volume

d(0.1): 12.234 um **d(0.5): 34.797 um** **d(0.9): 112.236 um**

🟥 CS/H-A-P, 03 February 2017 11:38:34 AM

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	

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	0.06
0.479	0.09
0.550	0.11
0.631	0.14
0.724	0.16
0.832	0.18
0.955	0.20
1.096	

Size (µm)	Volume In %
1.096	0.21
1.259	0.22
1.445	0.23
1.660	0.22
1.905	0.20
2.188	0.18
2.512	0.15
2.884	0.11
3.311	0.08
3.802	0.07
4.365	0.09
5.012	0.17
5.754	0.35
6.607	0.63
7.586	1.05
8.710	1.59
10.000	2.25
11.482	

Size (µm)	Volume In %
11.482	2.98
13.183	3.75
15.136	4.49
17.378	5.17
19.953	5.72
22.909	6.14
26.303	6.39
30.200	6.46
34.674	6.37
39.811	6.12
45.709	5.74
52.481	5.26
60.256	4.71
69.183	4.12
79.433	3.54
91.201	2.99
104.713	2.48
120.226	

Size (µm)	Volume In %
120.226	2.04
138.038	1.67
158.489	1.36
181.970	1.09
208.930	0.87
239.883	0.67
275.423	0.49
316.228	0.32
363.078	0.20
416.869	0.09
478.630	0.02
549.541	0.00
630.957	0.00
724.436	0.00
831.764	0.00
954.993	0.00
1096.478	0.00
1258.925	

Size (µm)	Volume In %
1258.925	0.00
1445.440	0.00
1659.587	0.00
1905.461	0.00
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	

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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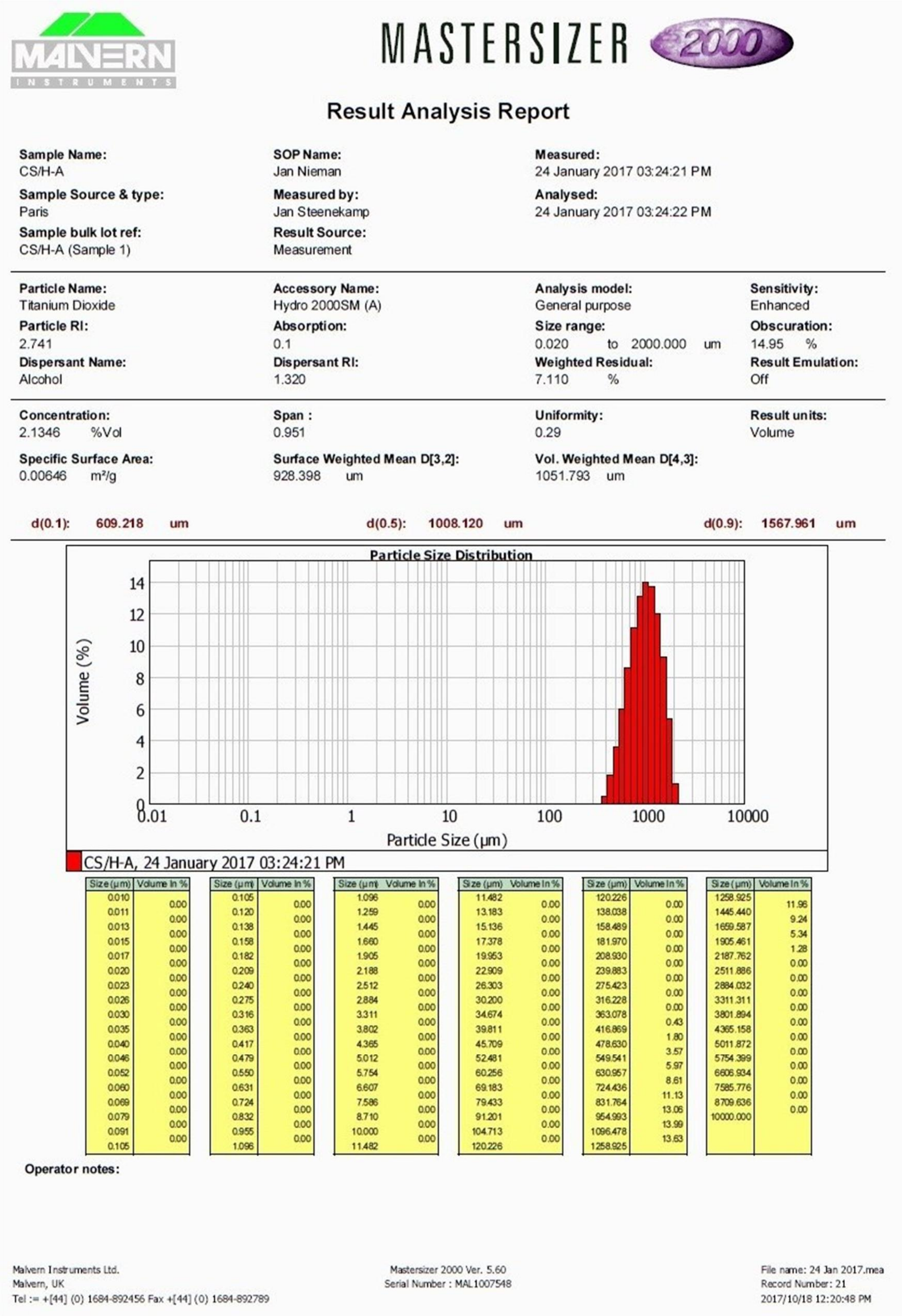
Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 3 Feb 2017.mea
Record Number: 11
2017/10/18 12:26:27 PM

Annexure B41: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC API Beads Sample 1)



Result Analysis Report

Sample Name:
CS/H-A

SOP Name:
Jan Nieman

Measured:
24 January 2017 03:24:21 PM

Sample Source & type:
Paris

Measured by:
Jan Steenekamp

Analysed:
24 January 2017 03:24:22 PM

Sample bulk lot ref:
CS/H-A (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:
14.95 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
7.110 %

Result Emulation:
Off

Concentration:
2.1346 %Vol

Span :
0.951

Uniformity:
0.29

Result units:
Volume

Specific Surface Area:
0.00646 m²/g

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

Vol. Weighted Mean D[4,3]:
1051.793 um

d(0.1): **609.218** **um**   **d(0.5):** **1008.120** **um**   **d(0.9):** **1567.961** **um**

🟥 CS/H-A, 24 January 2017 03:24:21 PM

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	

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	

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	

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	

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	0.43
416.869	1.80
478.630	3.57
549.541	5.97
630.957	8.61
724.436	11.13
831.764	13.06
954.993	13.99
1096.478	13.63
1258.925	

Size (μm)	Volume In %
1258.925	11.96
1445.440	9.24
1659.587	5.34
1905.461	1.28
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	

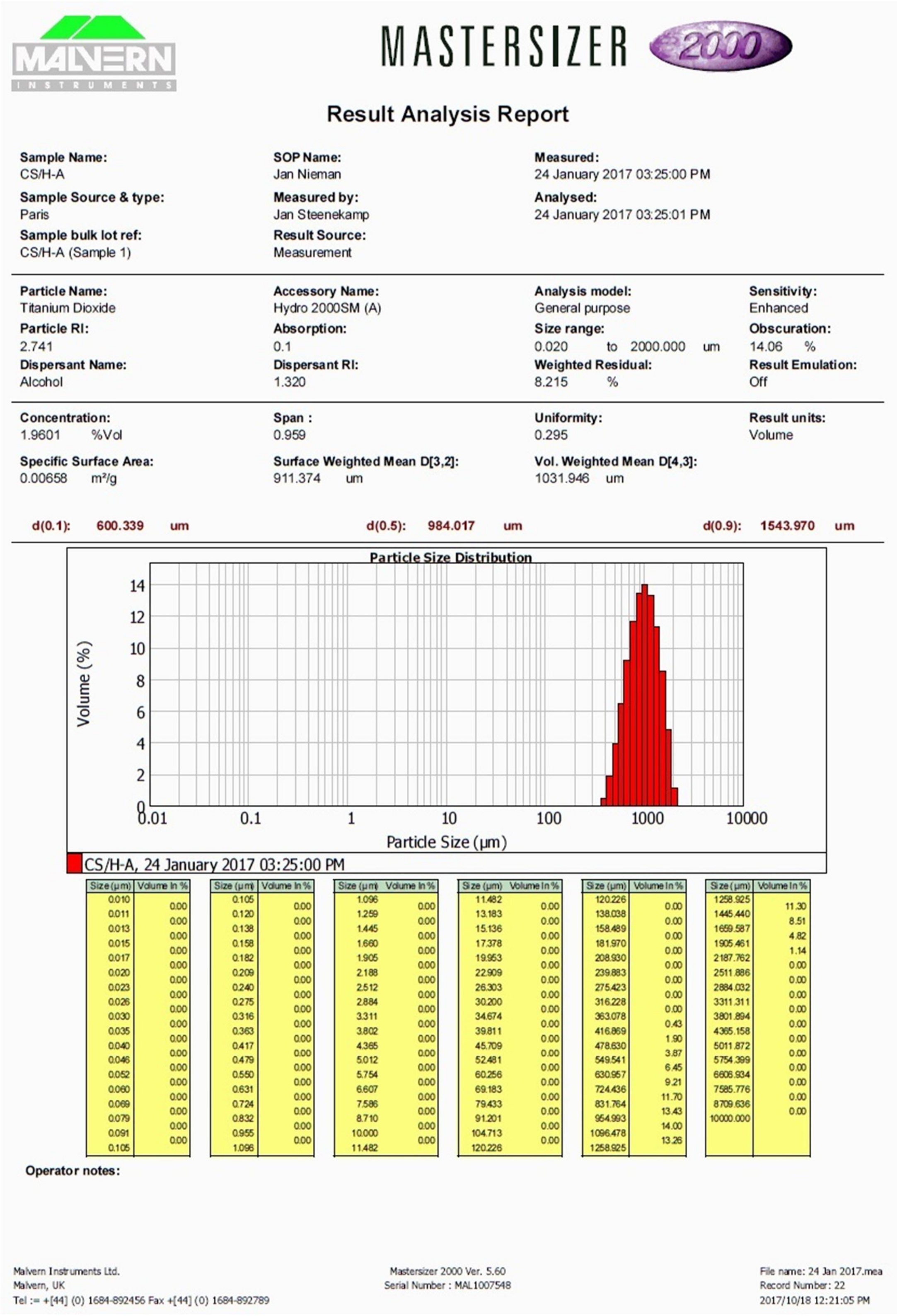
Operator notes:

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: 24 Jan 2017.mea
Record Number: 21
2017/10/18 12:20:48 PM

Annexure B42: Malvern® Mastersizer Data Sheets (Cassava starch/HPMC API Beads Sample 2)



MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name:
CS/H-A

Sample Source & type:
Paris

Sample bulk lot ref:
CS/H-A (Sample 1)

SOP Name:
Jan Nieman

Measured by:
Jan Steenekamp

Result Source:
Measurement

Measured:
24 January 2017 03:25:00 PM

Analysed:
24 January 2017 03:25:01 PM

Particle Name:
Titanium Dioxide

Particle RI:
2.741

Dispersant Name:
Alcohol

Accessory Name:
Hydro 2000SM (A)

Absorption:
0.1

Dispersant RI:
1.320

Analysis model:
General purpose

Size range:
0.020 to 2000.000 um

Weighted Residual:
8.215 %

Sensitivity:
Enhanced

Obscuration:
14.06 %

Result Emulation:
Off

Concentration:
1.9601 %Vol

Specific Surface Area:
0.00658 m²/g

Span :
0.959

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

Uniformity:
0.295

Vol. Weighted Mean D[4,3]:
1031.946 um

Result units:
Volume

d(0.1): 600.339 um **d(0.5):** 984.017 um **d(0.9):** 1543.970 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	

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	

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	

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	

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	0.43
416.869	1.90
478.630	3.87
549.541	6.45
630.957	9.21
724.436	11.70
831.764	13.43
954.993	14.00
1096.478	13.26
1258.925	

Size (μm)	Volume In %
1258.925	11.30
1445.440	8.51
1659.587	4.82
1905.461	1.14
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	

Operator notes:

Malvern Instruments Ltd.
Malvern, UK
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Mastersizer 2000 Ver. 5.60
Serial Number : MAL1007548

File name: 24 Jan 2017.mea
Record Number: 22
2017/10/18 12:21:05 PM

Annexure C:

SeDeM Expert Diagram System Raw Data

Annexure C1: SeDeM Diagram Expert System Raw Data (Gliclazide)

	Loss on Drying				Flowability		
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)		
Sample 1	50	3	52.92	2.667	-		
Sample 2	50	3.01	52.93	2.658	-		
Sample 3	50	3.02	52.9	3.974	-		
	Hygroscopicity				Cohesion Index		
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)		
Sample 1	50	1	51.01	1	35		
Sample 2	50	1.01	51.025	1.485148515	35		
Sample 3	50	1.05	51.07	1.904761905	35		
	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	250	0.4	4	11.4	35.06
	Tapped	100	156	0.641025641			
Sample 2	Bulk	100	246	0.406504065	4.1	11.2	36.21
	Tapped	100	152	0.657894737			
Sample 3	Bulk	100	248	0.403225806	4.3	11	38.02
	Tapped	100	155	0.64516129			

Particle Size Analysis	
Particles <50εm	69.22
Homogeneity Index	0.028468

Annexure C2: SeDeM Diagram Expert System Raw Data (*CombiLac® Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	147.66	3.01	150.55	3.987	1.9
Sample 2	145.75	3.06	148.65	5.22	1.69
Sample 3	145.95	3.01	148.87	2.990	1.72

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	1.08	51.11	2.777777778	210
Sample 2	50	1.05	51.08	2.857142857	210
Sample 3	50	1.04	51.09	4.807692308	210

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	210	0.47619048	2.7	15.1	19.68
	Tapped	100	172	0.58139535			
Sample 2	Bulk	100	214	0.46728972	2.6	14.8	19.36
	Tapped	100	174	0.57471264			
Sample 3	Bulk	100	212	0.47169811	2.6	15.2	18.89
	Tapped	100	176	0.56818182			

Particle Size Analysis	
Particles <50εm	2.26
Homogeneity Index	0.006

Annexure C3: SeDeM Diagram Expert System Raw Data (*CombiLac® API Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	197.36	2.03	199.28	6.241	1.95
Sample 2	197.36	2.05	199.28	6.341	2.13
Sample 3	197.36	2.07	199.28	6.441	2.05

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.06	52.11	2.427184466	150
Sample 2	50	2.06	52.11	2.427184466	150
Sample 3	50	2.06	52.11	2.427184466	150

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	210	0.47619048	3.5	13.5	27.41
	Tapped	100	160	0.625			
Sample 2	Bulk	100	208	0.48076923	3.4	13.3	27.08
	Tapped	100	158	0.63291139			
Sample 3	Bulk	100	212	0.47169811	3.5	13.4	27.58
	Tapped	100	162	0.61728395			

Particle Size Analysis	
Particles <50εm	7.15
Homogeneity Index	0.00605

Annexure C4: SeDeM Diagram Expert System Raw Data (*CombiLac® Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	46.13	3.07	49.11	2.931596091	1.01
Sample 2	47.22	3.06	50.18	3.267973856	1.24
Sample 3	46.8	3.1	49.81	2.903225806	1.19

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.05	52.08	1.463414634	157
Sample 2	50	2.02	52.07	2.475247525	157
Sample 3	50	2.02	52.06	1.98019802	157

		Bulk/Tapped Density			Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	110	0.90909091	2	11.8	18.73
	Tapped	100	105	0.95238095			
Sample 2	Bulk	100	108	0.92592593	2.4	12.2	21.48
	Tapped	100	102	0.98039216			
Sample 3	Bulk	100	105	0.95238095	2.1	12.2	19.00
	Tapped	100	99	1.01010101			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	0.232588

Annexure C5: SeDeM Diagram Expert System Raw Data (*CombiLac® API Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	203.67	2.09	205.35	19.61722488	1.68
Sample 2	211.12	2.04	212.75	20.09803922	1.64
Sample 3	197.36	2.08	199.02	20.19230769	1.71

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.09	52.1	0.4784689	110
Sample 2	50	2.04	52.06	0.980392157	110
Sample 3	50	2.08	52.09	0.480769231	110

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	157	0.63694268	2.5	12.5	21.80
	Tapped	100	140	0.71428571			
Sample 2	Bulk	100	154	0.64935065	2.3	12.6	20.06
	Tapped	100	138	0.72463768			
Sample 3	Bulk	100	158	0.63291139	2.6	12.5	22.59
	Tapped	100	140	0.71428571			

Particle Size Analysis	
Particles <50εm	1.11
Homogeneity Index	0.047702

Annexure C6: SeDeM Diagram Expert System Raw Data (*MicroceLac® 100 Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	147.02	3.01	150.02	0.332225914	1.5
Sample 2	147.85	3.03	150.87	0.330033003	1.38
Sample 3	146.06	3.04	149.08	0.657894737	1.45

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	1.02	51.09	6.862745098	220
Sample 2	50	1.02	51.07	4.901960784	220
Sample 3	50	1	51.05	5	220

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	196	0.51020408	2.2	14.9	16.45
	Tapped	100	156	0.64102564			
Sample 2	Bulk	100	200	0.5	2.3	15	17.05
	Tapped	100	164	0.6097561			
Sample 3	Bulk	100	192	0.52083333	2.3	14.9	17.16
	Tapped	100	160	0.625			

Particle Size Analysis	
Particles <50εm	4.44
Homogeneity Index	0.005753

Annexure C7: SeDeM Diagram Expert System Raw Data (*MicroceLac® 100 API Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	203.45	2.07	205.44	4.574688995	2.48
Sample 2	203.45	2.09	205.44	4.784688995	2.52
Sample 3	203.45	2.011	205.44	4.994688995	2.6

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.01	52.04	1.492537313	180
Sample 2	50	2.01	52.04	1.492537313	180
Sample 3	50	2.01	52.04	1.492537313	180

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	198	0.50505051	3.5	13.3	27.76
	Tapped	100	158	0.63291139			
Sample 2	Bulk	100	196	0.51020408	3.4	13.3	27.08
	Tapped	100	160	0.625			
Sample 3	Bulk	100	200	0.5	3.4	13.4	26.91
	Tapped	100	155	0.64516129			

Particle Size Analysis	
Particles <50εm	0.695
Homogeneity Index	0.045295

Annexure C8: SeDeM Diagram Expert System Raw Data (*MicroceLac*$^{®}$ *100 Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	43.43	3.32	46.55	6.024096386	1.14
Sample 2	47.3	3.24	50.47	2.160493827	1.04
Sample 3	46.54	3.27	49.74	2.140672783	1

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.05	52.06	0.487804878	212
Sample 2	50	2.1	52.11	0.476190476	212
Sample 3	50	2.11	52.13	0.947867299	212

		Bulk/Tapped Density			Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	108	0.92592593	1.9	13	16.29
	Tapped	100	105	0.95238095			
Sample 2	Bulk	100	118	0.84745763	2	12.8	17.35
	Tapped	100	112	0.89285714			
Sample 3	Bulk	100	118	0.84745763	1.9	12.8	16.53
	Tapped	100	114	0.87719298			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	0.99995

Annexure C9: SeDeM Diagram Expert System Raw Data (*MicroceLac$^{®}$ 100 API Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	197.73	2.01	199.3	21.89054726	1.38
Sample 2	211.23	2.01	212.81	21.39303483	1.42
Sample 3	197.2	2.04	198.85	19.11764706	1.37
	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.01	52.02	0.497512438	197
Sample 2	50	2.01	52.02	0.497512438	197
Sample 3	50	2.06	52.07	0.485436893	197

		Bulk/Tapped Density			Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	130	0.76923077	2	12.3	18.01
	Tapped	100	124	0.80645161			
Sample 2	Bulk	100	132	0.75757576	2.1	12.5	18.57
	Tapped	100	124	0.80645161			
Sample 3	Bulk	100	131	0.76335878	2	12.1	18.29
	Tapped	100	125	0.8			

Particle Size Analysis	
Particles <50εm	0.695
Homogeneity Index	0.045295

Annexure C10: SeDeM Diagram Expert System Raw Data (*RetaLac*$^{®}$ *Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	146.15	3.04	149.03	5.263157895	2.12
Sample 2	147.07	3.03	149.97	4.290429043	2.25
Sample 3	149.31	3.03	152.22	3.96039604	2.2

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	1.01	51.04	2.97029703	135
Sample 2	50	1.04	51.07	2.884615385	135
Sample 3	50	1.01	51.03	1.98019802	135

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	292	0.34246575	4	15.2	27.76
	Tapped	100	230	0.43478261			
Sample 2	Bulk	100	290	0.34482759	4.1	16	27.14
	Tapped	100	228	0.43859649			
Sample 3	Bulk	100	296	0.33783784	3.9	16.2	25.71
	Tapped	100	230	0.43478261			

Particle Size Analysis	
Particles <50εm	1.77
Homogeneity Index	0.004356

Annexure C11: SeDeM Diagram Expert System Raw Data (*RetaLac® API Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	195.84	2.06	197.74	7.766990291	2.58
Sample 2	195.84	2.06	197.74	7.766990291	2.54
Sample 3	195.84	2.06	197.74	7.766990291	2.61

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.02	52.13	5.445544554	121
Sample 2	50	2.02	52.13	5.445544554	121
Sample 3	50	2.02	52.13	5.445544554	121

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	280	0.35714286	4.1	15	28.66
	Tapped	100	210	0.47619048			
Sample 2	Bulk	100	278	0.35971223	4.1	15.2	28.35
	Tapped	100	209	0.4784689			
Sample 3	Bulk	100	281	0.35587189	4	14.8	28.39
	Tapped	100	216	0.46296296			

Particle Size Analysis	
Particles <50εm	3.285
Homogeneity Index	0.003613

Annexure C12: SeDeM Diagram Expert System Raw Data (*RetaLac® Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	59.07	3.13	61.4	25.55910543	2.5
Sample 2	25.17	3.03	27.45	24.75247525	2.42
Sample 3	33.24	3.07	35.55	24.75570033	2.38
	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.05	52.11	2.926829268	26
Sample 2	50	1.99	52.06	3.51758794	26
Sample 3	50	2.04	52.08	1.960784314	26

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	204	0.49019608	4	14.7	28.56
	Tapped	100	190	0.52631579			
Sample 2	Bulk	100	210	0.47619048	4	14.9	28.23
	Tapped	100	196	0.51020408			
Sample 3	Bulk	100	204	0.49019608	4	15	28.07
	Tapped	100	194	0.51546392			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	1

Annexure C13: SeDeM Diagram Expert System Raw Data (*RetaLac® API Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	197.2	2.04	198.63	29.90196078	13.92
Sample 2	203.48	2.05	204.88	31.70731707	14.13
Sample 3	203.19	2.01	204.59	30.34825871	14.05
	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.07	52.08	0.483091787	18
Sample 2	50	2.01	52.03	0.995024876	18
Sample 3	50	2.08	52.1	0.961538462	18

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume(ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	240	0.41666667	5	13	37.57
	Tapped	100	210	0.47619048			
Sample 2	Bulk	100	246	0.40650407	4.8	13.4	35.62
	Tapped	100	214	0.46728972			
Sample 3	Bulk	100	244	0.40983607	5.1	13.5	37.07
	Tapped	100	210	0.47619048			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	1

Annexure C14: SeDeM Diagram Expert System Raw Data (*Pharmacel® 101 Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	146.03	3.04	148.89	5.921052632	4.01
Sample 2	147.2	3	150.02	6	4.4
Sample 3	148.17	3.04	151.02	6.25	4.3

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	1.01	51.11	9.900990099	212
Sample 2	50	1.02	51.08	5.882352941	212
Sample 3	50	1.04	51.09	4.807692308	212

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	296	0.33783784	4.4	17.6	26.57
	Tapped	100	214	0.46728972			
Sample 2	Bulk	100	286	0.34965035	4.9	18.2	28.30
	Tapped	100	218	0.4587156			
Sample 3	Bulk	100	288	0.34722222	4.5	18	26.57
	Tapped	100	220	0.45454545			

Particle Size Analysis	
Particles <50εm	36.245
Homogeneity Index	0.011109

Annexure C15: SeDeM Diagram Expert System Raw Data (*Pharmacel® 101 API Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	195.84	2.06	197.74	7.766990291	2.58
Sample 2	195.84	2.06	197.74	7.766990291	2.54
Sample 3	195.84	2.06	197.74	7.766990291	2.61

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.02	52.13	5.445544554	121
Sample 2	50	2.02	52.13	5.445544554	121
Sample 3	50	2.02	52.13	5.445544554	121

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	280	0.35714286	4.1	15	28.66
	Tapped	100	210	0.47619048			
Sample 2	Bulk	100	278	0.35971223	4.1	15.2	28.35
	Tapped	100	209	0.4784689			
Sample 3	Bulk	100	281	0.35587189	4	14.8	28.39
	Tapped	100	216	0.46296296			

Particle Size Analysis	
Particles <50εm	3.285
Homogeneity Index	0.003613

Annexure C16: SeDeM Diagram Expert System Raw Data (*Pharmacel® 101 Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	46.68	3.44	48.79	38.6627907	1.29
Sample 2	47.54	3.01	49.4	38.20598007	1.16
Sample 3	36.33	3.12	38.27	37.82051282	1.19

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.07	52.17	4.830917874	25
Sample 2	50	2.09	52.18	4.306220096	25
Sample 3	50	2.01	52.13	5.970149254	25

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	136	0.73529412	1.7	13.2	14.44
	Tapped	100	132	0.75757576			
Sample 2	Bulk	100	140	0.71428571	1.9	12.7	16.66
	Tapped	100	136	0.73529412			
Sample 3	Bulk	100	140	0.71428571	2	13	17.10
	Tapped	100	136	0.73529412			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	0.97871

Annexure C17: SeDeM Diagram Expert System Raw Data (*Pharmacel*$^{®}$ *101 API Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	196.58	2.05	198.07	27.31707317	1.71
Sample 2	203.45	2.06	204.98	25.72815534	1.76
Sample 3	206.4	2.05	207.89	27.31707317	1.68
	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.07	52.09	0.966183575	23
Sample 2	50	2.01	52.03	0.995024876	23
Sample 3	50	2.08	52.1	0.961538462	23

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	140	0.71428571	2	12.4	17.88
	Tapped	100	132	0.75757576			
Sample 2	Bulk	100	142	0.70422535	2.2	12.7	19.11
	Tapped	100	132	0.75757576			
Sample 3	Bulk	100	140	0.71428571	2.1	12.8	18.17
	Tapped	100	134	0.74626866			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	1

Annexure C18: SeDeM Diagram Expert System Raw Data (*Cassava starch/HPMC Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	206.81	2.01	208.7	5.970149254	-
Sample 2	206.81	2.01	208.7	5.970149254	-
Sample 3	206.81	2.01	208.7	5.970149254	-

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.01	52.12	5.472636816	154
Sample 2	50	2.02	52.1	3.96039604	154
Sample 3	50	2	52.09	4.5	154

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	202	0.4950495	5	12	39.81
	Tapped	100	162	0.61728395			
Sample 2	Bulk	100	204	0.49019608	4.9	11.8	39.71
	Tapped	100	160	0.625			
Sample 3	Bulk	100	200	0.5	5.1	12.5	39.21
	Tapped	100	164	0.6097561			

Particle Size Analysis	
Particles <50εm	69.39
Homogeneity Index	0.025556

Annexure C19: SeDeM Diagram Expert System Raw Data (*Cassava starch/HPMC API Powder*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	196.58	2.01	198.3	14.4278607	-
Sample 2	196.58	2.01	198.3	14.4278607	-
Sample 3	196.58	2.01	198.3	14.4278607	-

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	1.97	52.07	5.076142132	148
Sample 2	50	1.97	52.07	5.076142132	148
Sample 3	50	1.97	52.07	5.076142132	148

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	208	0.48076923	5.2	11.6	41.88
	Tapped	100	168	0.5952381			
Sample 2	Bulk	100	208	0.48076923	5.3	12	41.46
	Tapped	100	166	0.60240964			
Sample 3	Bulk	100	206	0.48543689	5.4	12	41.99
	Tapped	100	167	0.5988024			

Particle Size Analysis	
Particles <50εm	68.295
Homogeneity Index	0.02314

Annexure C20: SeDeM Diagram Expert System Raw Data (*Cassava starch/HPMC Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass(g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	48.35	3.13	50.85	20.12779553	1.33
Sample 2	45.47	3.11	47.96	19.93569132	1.32
Sample 3	53.66	3.24	56.27	19.44444444	1.34

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.05	52.07	0.975609756	20
Sample 2	50	2.06	52.08	0.970873786	20
Sample 3	50	2.08	52.1	0.961538462	20

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	150	0.66666667	2.1	12.8	18.17
	Tapped	100	140	0.71428571			
Sample 2	Bulk	100	152	0.65789474	2.1	12.5	18.57
	Tapped	100	144	0.69444444			
Sample 3	Bulk	100	150	0.66666667	2.2	12.6	19.25
	Tapped	100	142	0.70422535			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	1

Annexure C21: SeDeM Diagram Expert System Raw Data (*Cassava starch/HPMC Beads*)

	Loss on Drying				Flowability
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Lost	Flow Time (s)
Sample 1	195.84	2.05	197.38	24.87804878	2.14
Sample 2	211.05	2.09	212.59	26.31578947	2.28
Sample 3	201.71	2.01	203.23	24.37810945	2.09

	Hygroscopicity				Cohesion Index
	Beaker Mass (g)	Initial Powder Mass (g)	End Mass (g)	% Mass Gained	Hardness (N)
Sample 1	50	2.05	52.06	0.487804878	14
Sample 2	50	2.09	52.1	0.4784689	14
Sample 3	50	2.01	52.02	0.497512438	14

	Bulk/Tapped Density				Angle of Repose		
		Weight (g)	Volume (ml)	Density (g/ml)	Height (cm)	Diameter (cm)	Angle of Repose (°)
Sample 1	Bulk	100	160	0.625	3.1	12.5	26.38
	Tapped	100	150	0.66666667			
Sample 2	Bulk	100	164	0.6097561	3	12.8	25.11
	Tapped	100	150	0.66666667			
Sample 3	Bulk	100	158	0.63291139	3.1	12.8	25.84
	Tapped	100	153	0.65359477			

Particle Size Analysis	
Particles <50εm	0
Homogeneity Index	1

Annexure D:

Tablet Evaluation Raw Data

Annexure D1: Tablet Evaluation Raw Data (CombiLac® Powder Tablets)

	Mass Variation (g)			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1	339	335	345	359	349	330
2	342	334	349	357	348	334
3	338	330	342	358	351	335
4	339	331	347	357	348	339
5	339	331	342	362	350	337
6	337	336	341	358	350	341
7	336	332	342	357	351	342
8	336	337	344	356	344	338
9	340	331	343	358	349	343
10	338	337	346	357	348	341
11	338	334	341	359	348	342
12	340	334	343	361	348	342
13	336	336	343	360	349	340
14	341	333	346	358	348	344
15	338	335	342	361	352	344
16	342	336	343	357	351	342
17	341	333	342	358	350	345
18	341	329	350	358	348	341
19	343	331	342	361	351	344
20	340	334	349	363	348	343
Average	339.2	333.45	344.1	358.75	349.05	340.35
STD DEV	2.092593	2.394621	2.807884	1.943275	1.79106	3.8563
%RSD	0.61692	0.718135	0.816008	0.541679	0.513124	1.13304

	Friability			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
Initial Mass (g)	3.39	3.34	3.4	3.57	3.48	3.31
End Mass (g)	3.38	3.33	3.39	3.56	3.46	3.28
% Mass Lost	0.294985	0.299401	0.294118	0.280112	0.574713	0.906344

	Hardness (N)			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1	45	156	161	167	159	145
2	49	152	161	161	162	146
3	44	138	161	165	158	138
4	55	138	158	159	163	104
5	49	149	163	159	157	144
6	49	152	148	164	159	148
7	45	142	155	158	159	98
8	43	154	152	158	156	141
9	45	139	163	157	149	144
10	37	150	168	156	164	149
Average	46.1	147	159	160.4	158.6	135.7
STD DEV	4.526588	6.663332	5.585696	3.527038	4.029888	17.65814
%RSD	9.819063	4.532879	3.513016	2.198902	2.540913	13.01263

	Disintegration (s)			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1	615	450	480	900	900	900
2	615	450	480	900	900	900
3	615	450	480	900	900	900
4	615	450	480	900	900	900
5	615	450	480	900	900	900
6	615	450	480	900	900	900
7	660	300	470	900	900	900
8	660	300	470	900	900	900
9	660	300	470	900	900	900
10	660	300	470	900	900	900
11	660	300	470	900	900	900
12	660	300	470	900	900	900
13	580	360	360	900	900	900
14	580	360	360	900	900	900
15	580	360	360	900	900	900
16	580	360	360	900	900	900
17	580	360	360	900	900	900
18	580	360	360	900	900	900
Average	618.3333	370	436.6667	900	900	900

Annexure D2: Tablet Evaluation Raw Data (CombiLac$^{®}$ Bead Tablets)

	Mass Variation (g)			CombiLac$^{®}$		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1		300	284		285	288
2		282	255		268	300
3		300	250		267	298
4		301	268		278	305
5		290	277		268	301
6		302	257		285	293
7		296	264		277	306
8		295	283		274	297
9		297	271		269	303
10		280	284		266	300
11		282	259		269	298
12		305	260		281	299
13		272	281		288	311
14		272	270		277	304
15		275	278		264	297
16		293	271		278	302
17		270	278		268	293
18		282	274		269	298
19		303	275		281	303
20		288	268		277	287
Average	-	289.25	270.35	-	274.45	299.15
STD DEV	-	11.55251	10.15291	-	7.20727	5.842449
%RSD	-	3.993954	3.755469	-	2.626078	1.953017

	Friability			CombiLac$^{®}$		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
Initial Mass (g)		2.86	2.68		2.74	2.96
End Mass (g)		2.78	2.64		2.7	2.93
% Mass Lost	-	2.797203	1.492537	-	1.459854	1.013514

	Hardness (N)			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1		20	25		21	36
2		18	33		20	34
3		14	27		18	37
4		20	27		18	35
5		18	26		20	37
6		18	30		20	41
7		16	28		21	35
8		17	27		20	39
9		18	34		21	35
10		13	27		20	35
Average	-	17.2	28.4	-	19.9	36.4
STD DEV	-	2.181742	2.835489	-	1.044031	2.059126
%RSD	-	12.68455	9.984118	-	5.246385	5.65694

	Disintegration (s)			CombiLac®		
	0.5CL0	0.5CL2	0.5CL5	1CL0	1CL2	1CL5
1		900	900		900	900
2		900	900		900	900
3		900	900		900	900
4		900	900		900	900
5		900	900		900	900
6		900	900		900	900
7		900	900		900	900
8		900	900		900	900
9		900	900		900	900
10		900	900		900	900
11		900	900		900	900
12		900	900		900	900
13		900	900		900	900
14		900	900		900	900
15		900	900		900	900
16		900	900		900	900
17		900	900		900	900
18		900	900		900	900
Average	-	900	900	-	900	900

Annexure D3: Tablet Evaluation Raw Data (MicroceLac® Powder Tablets)

	Mass Variation (g)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	316	306	301	277	306	301
2	311	303	294	278	304	301
3	315	303	295	268	305	310
4	314	303	291	279	307	298
5	316	313	300	274	305	307
6	315	308	291	278	305	307
7	318	299	296	268	309	301
8	317	312	296	280	312	298
9	314	304	292	267	303	299
10	315	308	299	269	305	296
11	316	299	292	278	305	301
12	316	305	298	276	303	299
13	313	311	291	277	305	306
14	316	309	297	275	302	312
15	318	309	292	268	304	300
16	319	311	292	277	301	304
17	319	306	297	269	295	298
18	318	309	294	280	306	298
19	314	305	294	279	301	299
20	314	308	293	278	305	300
Average	315.7	306.55	294.75	274.75	304.4	301.75
STD DEV	2.07998	3.966637	3.12671	4.66651	3.36233	4.423323
%RSD	0.658847	1.293961	1.060801	1.698457	1.104576	1.46589

	Friability			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
Initial Mass (g)	3.16	3.06	2.76	2.74	3.05	2.96
End Mass(g)	3.15	3.02	2.76	2.72	3.03	2.95
% Mass Lost	0.316456	1.30719	0	0.729927	0.655738	0.337838

	Hardness (N)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	60	92	137	132	132	94
2	59	96	132	137	115	98
3	58	64	135	132	108	103
4	78	93	135	138	121	97
5	65	109	58	131	114	103
6	64	92	67	130	113	96
7	65	96	66	137	116	96
8	60	96	137	113	115	101
9	58	93	145	106	117	95
10	55	99	69	135	112	106
Average	62.2	93	108.1	129.1	116.3	98.9
STD DEV	6.128621	10.77961	35.42725	10.26109	6.132699	3.858756
%RSD	9.853089	11.59098	32.77266	7.948173	5.273172	3.901675

	Disintegration (s)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	195	900	900	900	900	900
2	195	900	900	900	900	900
3	195	900	900	900	900	900
4	195	900	900	900	900	900
5	195	900	900	900	900	900
6	195	900	900	900	900	900
7	300	900	900	900	900	900
8	300	900	900	900	900	900
9	300	900	900	900	900	900
10	300	900	900	900	900	900
11	300	900	900	900	900	900
12	300	900	900	900	900	900
13	330	900	900	900	900	900
14	330	900	900	900	900	900
15	330	900	900	900	900	900
16	330	900	900	900	900	900
17	330	900	900	900	900	900
18	330	900	900	900	900	900
Average	275	900	900	900	900	900

Annexure D4: Tablet Evaluation Raw Data (MicroceLac® Bead Tablets)

	Mass Variation (g)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	320	331	329	272	337	323
2	302	323	313	291	342	294
3	301	350	339	282	346	293
4	320	332	310	292	326	312
5	329	329	325	279	314	289
6	329	353	338	295	316	291
7	319	329	315	291	318	318
8	322	325	337	297	319	313
9	325	336	328	291	339	289
10	325	326	316	285	327	320
11	326	320	329	299	337	286
12	326	309	335	295	331	310
13	321	327	330	296	341	288
14	327	324	318	285	328	326
15	327	333	315	292	331	312
16	314	352	319	298	316	318
17	325	332	330	287	314	306
18	328	337	318	299	343	312
19	328	352	323	304	341	304
20	327	326	326	288	333	316
Average	322.05	332.3	324.65	290.9	329.95	306
STD DEV	8.035939	11.67138	8.845308	7.690733	10.75798	13.15895
%RSD	2.495246	3.512301	2.724567	2.643772	3.260489	4.30031

	Friability			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
Initial Mass (g)	3.24	3.39	3.12	2.91	3.21	3.18
End Mass (g)	3.18	3.37	3.11	2.72	3.14	3
% Mass Lost	1.851852	0.589971	0.320513	6.52921	2.180685	5.660377

	Hardness (N)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	21	88	80	22	70	53
2	23	67	78	21	72	62
3	20	91	75	20	81	69
4	25	84	89	21	68	64
5	21	98	80	21	69	63
6	23	100	87	23	50	66
7	22	73	73	23	73	66
8	23	95	77	22	67	54
9	22	95	88	21	74	64
10	22	89	80	23	93	70
Average	22.2	88	80.7	21.7	71.7	63.1
STD DEV	1.32665	10.16858	5.254522	1.004988	10.31552	5.356305
%RSD	5.975901	11.5552	6.51118	4.631279	14.38706	8.488597

	Disintegration (s)			MicroceLac®		
	0.5ML0	0.5ML2	0.5ML5	1ML0	1ML2	1ML5
1	900	900	900	900	900	900
2	900	900	900	900	900	900
3	900	900	900	900	900	900
4	900	900	900	900	900	900
5	900	900	900	900	900	900
6	900	900	900	900	900	900
7	900	900	900	900	900	900
8	900	900	900	900	900	900
9	900	900	900	900	900	900
10	900	900	900	900	900	900
11	900	900	900	900	900	900
12	900	900	900	900	900	900
13	900	900	900	900	900	900
14	900	900	900	900	900	900
15	900	900	900	900	900	900
16	900	900	900	900	900	900
17	900	900	900	900	900	900
18	900	900	900	900	900	900
Average	900	900	900	900	900	900

Annexure D5: Tablet Evaluation Raw Data (RetaLac® Powder Tablets)

	Mass Variation (g)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	336	353	358	347	361	346
2	340	351	353	340	357	345
3	341	353	357	346	355	344
4	337	350	354	346	353	354
5	337	357	356	348	359	344
6	333	352	357	346	356	347
7	338	356	358	338	354	352
8	337	354	359	346	355	344
9	341	352	352	349	357	344
10	334	352	354	348	351	348
11	335	360	356	348	355	346
12	335	354	354	342	356	345
13	334	352	355	349	353	347
14	340	358	348	345	357	348
15	334	353	357	348	353	349
16	337	352	357	350	357	351
17	337	360	356	348	349	346
18	338	361	356	346	359	345
19	334	359	351	346	349	346
20	340	351	357	349	353	349
Average	336.9	354.5	355.25	346.25	354.95	347
STD DEV	2.531902	3.456497	2.692582	3.075797	3.170173	2.828427
%RSD	0.751529	0.975034	0.75794	0.888317	0.893132	0.815109

	Friability			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
Initial Mass (g)	3.41	3.54	3.45	3.48	3.56	3.43
End Mass (g)	3.37	3.52	3.45	3.47	3.56	3.42
% Mass Lost	1.173021	0.564972	0	0.287356	0	0.291545

	Hardness (N)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	88	102	102	93	106	93
2	85	104	98	98	99	105
3	84	98	100	99	96	95
4	90	81	104	95	102	106
5	85	95	100	98	102	104
6	82	99	105	94	102	103
7	87	98	97	95	104	97
8	88	99	96	103	104	103
9	85	101	94	98	104	106
10	88	101	85	93	95	103
Average	86.2	97.8	98.1	96.6	101.4	101.5
STD DEV	2.271563	6.079474	5.467175	3.006659	3.44093	4.477723
%RSD	2.635224	6.216231	5.573063	3.112484	3.393422	4.411549

	Disintegration (s)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	900	900	900	900	900	900
2	900	900	900	900	900	900
3	900	900	900	900	900	900
4	900	900	900	900	900	900
5	900	900	900	900	900	900
6	900	900	900	900	900	900
7	900	900	900	900	900	900
8	900	900	900	900	900	900
9	900	900	900	900	900	900
10	900	900	900	900	900	900
11	900	900	900	900	900	900
12	900	900	900	900	900	900
13	900	900	900	900	900	900
14	900	900	900	900	900	900
15	900	900	900	900	900	900
16	900	900	900	900	900	900
17	900	900	900	900	900	900
18	900	900	900	900	900	900
Average	900	900	900	900	900	900

Annexure D6: Tablet Evaluation Raw Data (RetaLac® Bead Tablets)

	Mass Variation (g)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	306	356	388	315	350	393
2	311	339	383	318	322	379
3	294	327	405	323	346	368
4	293	345	375	315	316	387
5	304	340	416	314	346	389
6	318	355	411	317	310	386
7	305	350	409	310	318	396
8	301	352	408	315	343	370
9	304	332	386	331	319	386
10	299	352	389	317	320	395
11	307	353	398	317	345	389
12	300	340	381	324	324	399
13	296	340	378	315	315	370
14	308	341	415	317	339	367
15	315	350	404	312	337	402
16	311	343	420	305	321	399
17	314	342	400	326	346	403
18	310	351	410	320	336	372
19	310	335	407	331	342	399
20	306	348	407	311	325	388
Average	305.6	344.55	399.5	317.65	331	386.85
STD DEV	6.900801	7.970175	13.7745	6.643358	13.06663	11.99243
%RSD	2.258115	2.313213	3.447935	2.091408	3.947623	3.100021

	Friability			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
Initial Mass (g)	3.11	3.44	4	3.16	3.26	3.92
End Mass (g)	2.95	3.44	0	2.99	3.21	0
% Mass Lost	5.144695	0	100	5.379747	1.533742	100

	Hardness (N)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	0	89	47	0	77	47
2	0	91	49	0	71	53
3	0	87	38	0	68	40
4	0	86	50	0	71	42
5	0	73	49	0	53	41
6	0	95	52	0	74	38
7	0	86	47	0	80	38
8	0	93	44	0	77	38
9	0	92	46	0	81	44
10	0	96	54	0	75	45
Average	0	88.8	47.6	0	72.7	42.6
STD DEV	0	6.257795	4.223742	0	7.629548	4.565085
%RSD	-	7.047067	8.873408	-	10.49456	10.71616

	Disintegration (s)			RetaLac®		
	0.5RL0	0.5RL2	0.5RL5	1RL0	1RL2	1RL5
1	900	900	900	900	900	900
2	900	900	900	900	900	900
3	900	900	900	900	900	900
4	900	900	900	900	900	900
5	900	900	900	900	900	900
6	900	900	900	900	900	900
7	900	900	900	900	900	900
8	900	900	900	900	900	900
9	900	900	900	900	900	900
10	900	900	900	900	900	900
11	900	900	900	900	900	900
12	900	900	900	900	900	900
13	900	900	900	900	900	900
14	900	900	900	900	900	900
15	900	900	900	900	900	900
16	900	900	900	900	900	900
17	900	900	900	900	900	900
18	900	900	900	900	900	900
Average	900	900	900	900	900	900

Annexure D7: Tablet Evaluation Raw Data (Pharmacel® Powder Tablets)

	Mass Variation (g)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1	306	293	289	303	304	306
2	294	289	288	307	295	307
3	297	282	284	307	296	302
4	293	298	279	298	304	308
5	300	290	276	306	290	309
6	303	291	286	308	300	303
7	298	303	290	311	308	302
8	300	289	289	312	299	309
9	291	289	284	302	301	311
10	296	284	290	312	303	309
11	303	294	286	313	301	298
12	303	302	286	305	290	310
13	303	290	285	309	303	311
14	295	301	284	316	303	301
15	304	290	289	307	306	314
16	302	291	288	317	296	308
17	308	292	280	318	304	305
18	307	298	281	296	304	305
19	300	301	290	310	304	301
20	301	282	279	305	301	305
Average	300.2	292.45	285.15	308.1	300.6	306.2
STD DEV	4.730639	6.328507	4.233637	5.830049	4.924696	4.124382
%RSD	1.575829	2.163962	1.484705	1.892259	1.638289	1.346957

	Friability			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
Initial Mass (g)	3.04	3.04	2.93	3.13	3	3.12
End Mass (g)	3.02	3.03	2.92	3.13	2.99	3.07
% Mass Lost	0.657895	0.328947	0.341297	0	0.333333	1.602564

	Hardness (N)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1	103	292	244	289	192	165
2	65	269	267	286	183	167
3	87	264	264	284	181	164
4	81	264	285	279	162	172
5	86	260	262	290	181	163
6	79	248	255	260	177	170
7	79	239	262	285	184	167
8	87	284	264	289	178	175
9	68	248	261	285	173	166
10	74	269	259	276	178	166
Average	80.9	263.7	262.3	282.3	178.9	167.5
STD DEV	10.3097	15.44701	9.716481	8.532878	7.408779	3.556684
%RSD	12.74376	5.857795	3.704339	3.022628	4.141296	2.123393

	Disintegration (s)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1	900	900	900	900	900	900
2	900	900	900	900	900	900
3	900	900	900	900	900	900
4	900	900	900	900	900	900
5	900	900	900	900	900	900
6	900	900	900	900	900	900
7	900	900	900	900	900	900
8	900	900	900	900	900	900
9	900	900	900	900	900	900
10	900	900	900	900	900	900
11	900	900	900	900	900	900
12	900	900	900	900	900	900
13	900	900	900	900	900	900
14	900	900	900	900	900	900
15	900	900	900	900	900	900
16	900	900	900	900	900	900
17	900	900	900	900	900	900
18	900	900	900	900	900	900
Average	900	900	900	900	900	900

Annexure D8: Tablet Evaluation Raw Data (Pharmacel® Bead Tablets)

	Mass Variation (g)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1		264	269		301	288
2		252	289		290	265
3		266	284		300	288
4		248	273		309	275
5		266	275		305	272
6		259	271		304	295
7		245	277		297	261
8		266	270		313	300
9		247	286		299	276
10		256	285		295	288
11		264	276		298	283
12		255	270		308	275
13		248	262		308	278
14		246	285		295	284
15		256	276		305	289
16		251	284		300	273
17		255	271		302	285
18		245	286		295	286
19		246	265		304	279
20		252	286		304	276
Average	-	254.35	277	-	301.6	280.8
STD DEV	-	7.583049	8.072044	-	5.706875	9.616871
%RSD	-	2.981344	2.914095	-	1.8922	3.424812

	Friability			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
Initial Mass (g)		2.54	2.71		3.01	2.82
End Mass (g)		2.44	2.65		2.93	2.75
% Mass Lost	-	3.937008	2.214022	-	2.657807	2.48227

	Hardness (N)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1		0	0		0	0
2		0	0		0	0
3		0	0		0	0
4		0	0		0	0
5		0	0		0	0
6		0	0		0	0
7		0	0		0	0
8		0	0		0	0
9		0	0		0	0
10		0	0		0	0
Average	-	0	0	-	0	0
STD DEV	-	0	0	-	0	0
%RSD	-	-	-	-	-	-

	Disintegration (s)			Pharmacel®		
	0.5PC0	0.5PC2	0.5PC5	1PC0	1PC2	1PC5
1		900	900		900	900
2		900	900		900	900
3		900	900		900	900
4		900	900		900	900
5		900	900		900	900
6		900	900		900	900
7		900	900		900	900
8		900	900		900	900
9		900	900		900	900
10		900	900		900	900
11		900	900		900	900
12		900	900		900	900
13		900	900		900	900
14		900	900		900	900
15		900	900		900	900
16		900	900		900	900
17		900	900		900	900
18		900	900		900	900
Average	-	900	900	-	900	900

Annexure D9: Tablet Evaluation Raw Data (Cassava starch/HPMC Powder Tablets)

	Mass Variation (g)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1	317	287	319	297	339	362
2	316	299	323	303	350	371
3	306	285	335	293	349	357
4	304	280	331	307	339	369
5	312	284	329	308	349	367
6	313	295	328	298	339	373
7	313	287	335	302	348	366
8	319	287	322	312	350	387
9	298	294	327	315	347	372
10	308	293	332	308	363	379
11	294	299	328	311	354	374
12	302	286	325	298	354	381
13	312	301	331	301	348	384
14	293	296	329	301	329	376
15	295	295	334	298	333	383
16	300	283	341	294	346	380
17	310	298	339	302	347	376
18	307	293	324	311	361	377
19	316	283	318	308	367	367
20	321	285	335	315	349	384
Average	307.8	290.5	329.25	304.1	348.05	374.25
STD DEV	8.569223	6.444092	6.264982	6.750439	9.383496	7.979414
%RSD	2.784023	2.218276	1.902804	2.219809	2.69602	2.132108

	Friability			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
Initial Mass (g)	3.16	2.94	3.27	3.12	3.62	3.67
End Mass (g)	3.03	2.92	3.25	3.11	3.51	3.66
% Mass Lost	4.113924	0.680272	0.611621	0.320513	3.038674	0.27248

	Hardness (N)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1	67	121	95	95	85	108
2	55	119	99	91	79	116
3	43	118	100	99	74	117
4	70	108	102	93	78	109
5	37	139	107	99	83	107
6	22	142	94	92	84	113
7	60	96	109	92	96	98
8	67	129	135	80	85	106
9	77	115	89	81	70	93
10	58	74	96	83	89	103
Average	55.6	116.1	102.6	90.5	82.3	107
STD DEV	16.07607	19.08114	12.20819	6.576473	7.071775	7.183314
%RSD	28.91379	16.43509	11.89882	7.266821	8.592679	6.713378

	Disintegration (s)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1	900	900	900	900	900	900
2	900	900	900	900	900	900
3	900	900	900	900	900	900
4	900	900	900	900	900	900
5	900	900	900	900	900	900
6	900	900	900	900	900	900
7	900	900	900	900	900	900
8	900	900	900	900	900	900
9	900	900	900	900	900	900
10	900	900	900	900	900	900
11	900	900	900	900	900	900
12	900	900	900	900	900	900
13	900	900	900	900	900	900
14	900	900	900	900	900	900
15	900	900	900	900	900	900
16	900	900	900	900	900	900
17	900	900	900	900	900	900
18	900	900	900	900	900	900
Average	900	900	900	900	900	900

Annexure D10: Tablet Evaluation Raw Data (Cassava starch/HPMC Bead Tablets)

	Mass Variation (g)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1				366		
2				369		
3				352		
4				362		
5				368		
6				366		
7				356		
8				350		
9				362		
10				363		
11				368		
12				356		
13				355		
14				356		
15				355		
16				364		
17				365		
18				359		
19				370		
20				358		
Average	-	-	-	361	-	-
STD DEV	-	-	-	6.008766	-	-
%RSD	-	-	-	1.664478	-	-

	Friability			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
Initial Mass (g)				3.6		
End Mass (g)				3.52		
% Mass Lost	-	-	-	2.222222	-	-

	Hardness (N)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1				11		
2				12		
3				10		
4				11		
5				11		
6				11		
7				13		
8				11		
9				10		
10				10		
Average	-	-	-	11	-	-
STD DEV	-	-	-	0.894427	-	-
%RSD	-	-	-	8.131156	-	-

	Disintegration (s)			Cassava starch/HPMC		
	0.5CS0	0.5CS2	0.5CS5	1CS0	1CS2	1CS5
1				900		
2				900		
3				900		
4				900		
5				900		
6				900		
7				900		
8				900		
9				900		
10				900		
11				900		
12				900		
13				900		
14				900		
15				900		
16				900		
17				900		
18				900		
Average	-	-	-	900	-	-