

Effect of powder particle and punch type on the physical and compaction properties of tablets

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TABLE OF CONTENTS

1	CHAPTER 1: PROBLEM STATEMENT, AIM AND OBJECTIVES.....	1
1.1	BACKGROUND.....	1
1.1.1	PARTICLE SIZE AND SHAPE	2
1.1.2	TABLET PRESS PUNCH TYPE.....	2
1.2	RESEARCH QUESTION	2
1.3	AIM AND OBJECTIVES	3
1.4	OUTLINE OF CHAPTERS.....	3
2	CHAPTER 2: TABLETS AS SOLID ORAL DOSAGE FORMS.....	4
2.1	INTRODUCTION	4
2.2	TABLET MANUFACTURING TECHNIQUES	5
2.2.1	WET GRANULATION	5
2.2.2	DRY GRANULATION.....	6
2.2.3	DIRECT COMPRESSION.....	6
2.3	FACTORS INFLUENCING TABLET FORMULATION AND MANUFACTURING ..	7
2.3.1	COMPRESSION FORCE	7
2.3.2	COMPATIBILITY BETWEEN EXCIPIENTS AND ACTIVE INGREDIENTS	7
2.3.3	POWDER PROPERTIES.....	8
2.4	EXCIPIENTS IN TABLET FORMULATION	8
2.4.1	DILUENTS/FILLERS	8
2.4.2	DISINTEGRANTS	9
2.4.3	LUBRICANTS	9
2.4.4	BINDERS.....	10
2.4.5	GLIDANTS	10
2.5	BEADS AS SOLID ORAL DOSAGE FORMS	10
2.5.1	EXTRUSION SPHERONISATION	11
2.5.1.1	<i>The extrusion-spheronisation technique.....</i>	<i>11</i>
2.5.1.2	<i>Factors influencing the process of extrusion-spheronisation</i>	<i>12</i>

2.6	SINGLE-UNIT SOLID ORAL DOSAGE FORMS	14
2.6.1	IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS	14
2.6.2	MODIFIED RELEASE SOLID ORAL DOSAGE FORMS	15
2.7	MULTIPLE-UNIT DOSAGE FORMS	17
2.7.1	MULTIPLE-UNIT PELLET SYSTEM (MUPS) TABLETS.....	18
2.7.2	MULTIPLE-UNIT PELLET SYSTEM (MUPS) CAPSULES	19
2.8	SUMMARY	20
3	CHAPTER 3: EXPERIMENTAL METHODS	22
3.1	INTRODUCTION	22
3.2	MATERIALS.....	22
3.3	METHODS.....	23
3.3.1	SELECTION OF ACTIVE INGREDIENT.....	23
3.3.2	SELECTION OF FILLERS	23
3.3.3	SELECTION OF DISINTEGRANT.....	24
3.3.4	SELECTION OF BINDER	24
3.3.5	SELECTION OF LUBRICANT.....	24
3.4	COMPOSITION OF FORMULATIONS	24
3.5	THE MIXING PROCESS.....	28
3.6	POWDER, GRANULE AND BEAD FORMULATIONS	28
3.6.1	POWDER FORMULATION.....	28
3.6.2	THE GRANULATION PROCESS	29
3.6.3	THE PRODUCTION OF BEADS	29
3.7	SCANNING ELECTRON MICROSCOPY	31
3.8	PARTICLE SIZE ANALYSIS	32
3.9	FLOWABILITY CHARACTERISATION.....	32
3.9.1	ANGLE OF REPOSE (AOR)	32
3.9.2	CRITICAL ORIFICE DIAMETER (COD).....	33
3.9.3	POWDER DENSITY.....	35
3.9.3.1	<i>Hausner ratio</i>	35

3.9.3.2	<i>Carr's index</i>	35
3.9.4	FLOW RATE.....	36
3.10	COMPRESSION OF TABLETS.....	37
3.11	TABLET EVALUATION.....	37
3.11.1	WEIGHT VARIATION.....	37
3.11.2	DISINTEGRATION	38
3.11.3	CRUSHING STRENGTH, THICKNESS AND DIAMETER	39
3.11.4	FRIABILITY	40
3.11.5	DISSOLUTION.....	41
3.11.5.1	<i>Apparatus</i>	41
3.11.5.2	<i>Standard curve</i>	41
3.11.5.3	<i>Dissolution method</i>	42
3.12	STATISTICAL ANALYSIS.....	42
4	CHAPTER 4: SOLID PARTICLE FORMULATION FLOWABILITY AND TABLET EVALUATION RESULTS	43
4.1	INTRODUCTION	43
4.2	SCANNING ELECTRON MICROSCOPY	44
4.3	PARTICLE SIZE ANALYSIS	48
4.4	FLOWABILITY CHARACTERIZATION	50
4.4.1	ANGLE OF REPOSE (AOR).....	51
4.4.2	CRITICAL ORIFICE DIAMETER (COD).....	53
4.4.3	HAUSNER RATIO	56
4.4.4	CARR'S INDEX (% COMPRESSIBILITY)	57
4.4.5	FLOW RATE (10 MM AND 15 MM ORIFICE).....	59
4.4.6	FLOW CHARACTERISATION SUMMARY	61
4.5	TABLET EVALUATION.....	62
4.5.1	MASS VARIATION	64
4.5.2	DISINTEGRATION TIME	65
4.5.3	CRUSHING STRENGTH	67

4.5.4	TABLET DIAMETER AND THICKNESS.....	69
4.5.5	FRIABILITY	70
4.5.6	TABLET EVALUATION SUMMARY	71
4.6	DISSOLUTION BEHAVIOUR OF DIFFERENT TABLET FORMULATIONS	72
4.6.1	TABLETS COMPRESSED FROM DRY POWDER FORMULATIONS.....	77
4.6.2	TABLETS COMPRESSED FROM GRANULE FORMULATIONS	78
4.6.3	TABLET COMPRESSED FROM BEAD FORMULATIONS	79
4.6.4	INFLUENCE OF SPECIFIC FACTORS ON DISSOLUTION.....	80
4.6.4.1	<i>Effect of diluent (filler)</i>	80
4.6.4.2	<i>Particle type</i>	80
4.6.4.3	<i>Punch type</i>	81
4.7	SUMMARY	81
5	CHAPTER 5: SUMMARY AND FUTURE PROSPECTS.....	83
5.1	SUMMARY	83
5.2	FUTURE PROSPECTS	84
6	REFERENCES.....	86
7	ANNEXURE A: PARTICLE SIZE DATA.....	94
7.1	AVICEL [®] -CONTAINING FORMULATIONS	94
7.1.1	AVICEL [®] -CONTAINING DRY POWDER FORMULATIONS.....	94
7.1.1.1	<i>Formulation 1</i>	94
7.1.1.2	<i>Formulation 2</i>	97
7.1.1.3	<i>Formulation 3</i>	100
7.1.1.4	<i>Formulation 4</i>	103
7.1.2	AVICEL [®] -CONTAINING GRANULE FORMULATIONS.....	106
7.1.2.1	<i>Formulation 1</i>	106
7.1.2.2	<i>Formulation 2</i>	109
7.1.2.3	<i>Formulation 3</i>	112
7.1.2.4	<i>Formulation 4</i>	115
7.1.3	AVICEL [®] -CONTAINING BEADS FORMULATIONS.....	118

7.1.3.1	<i>Formulation 1</i>	118
7.1.3.2	<i>Formulation 2</i>	121
7.2	MICROCELAC[®]-CONTAINING FORMULATIONS	124
7.2.1	MICROCELAC[®]-CONTAINING DRY POWDER FORMULATIONS	124
7.2.1.1	<i>Formulation 1</i>	124
7.2.1.2	<i>Formulation 2</i>	127
7.2.1.3	<i>Formulation 3</i>	130
7.2.1.4	<i>Formulation 4</i>	133
7.2.2	MICROCELAC[®]-CONTAINING GRANULE FORMULATIONS	136
7.2.2.1	<i>Formulation 1</i>	136
7.2.2.2	<i>Formulation 2</i>	139
7.2.2.3	<i>Formulation 3</i>	142
7.2.2.4	<i>Formulation 4</i>	145
7.2.3	MICROCELAC[®]-CONTAINING BEAD FORMULATIONS	148
7.2.3.1	<i>Formulation 1</i>	148
7.2.3.2	<i>Formulation 2</i>	151
8	ANNEXURE B: FLOWABILITY DATA	154
8.1	AVICEL[®]-CONTAINING FORMULATIONS	154
8.1.1	AVICEL[®]-CONTAINING DRY POWDER FORMULATIONS	154
8.1.1.1	<i>Formulation 1</i>	154
8.1.1.2	<i>Formulation 2</i>	155
8.1.1.3	<i>Formulation 3</i>	156
8.1.1.4	<i>Formulation 4</i>	157
8.1.2	AVICEL[®]-CONTAINING GRANULE FORMULATIONS	158
8.1.2.1	<i>Formulation 1</i>	158
8.1.2.2	<i>Formulation 2</i>	159
8.1.2.3	<i>Formulation 3</i>	160
8.1.2.4	<i>Formulation 4</i>	161
8.1.3	AVICEL[®]-CONTAINING BEADS FORMULATIONS	162

8.1.3.1	<i>Formulation 1</i>	162
8.1.3.2	<i>Formulation 2</i>	163
8.2	MICROCELAC[®]-CONTAINING FORMULATIONS	164
8.2.1	MICROCELAC[®]-CONTAINING DRY POWDER FORMULATIONS	164
8.2.1.1	<i>Formulation 1</i>	164
8.2.1.2	<i>Formulation 2</i>	165
8.2.1.3	<i>Formulation 3</i>	166
8.2.1.4	<i>Formulation 4</i>	167
8.2.2	MICROCELAC[®]-CONTAINING GRANULE FORMULATIONS	168
8.2.2.1	<i>Formulation 1</i>	168
8.2.2.2	<i>Formulation 2</i>	169
8.2.2.3	<i>Formulation 3</i>	170
8.2.2.4	<i>Formulation 4</i>	171
8.2.3	MICROCELAC[®]-CONTAINING BEAD FORMULATIONS	172
8.2.3.1	<i>Formulation 1</i>	172
8.2.3.2	<i>Formulation 2</i>	173
9	ANNEXURE C: TABLET EVALUATION DATA	174
9.1	CRUSHING STRENGTH	174
9.1.1	AVICEL[®]-CONTAINING TABLET FORMULATIONS	174
9.1.1.1	<i>Dry powder-containing tablets</i>	174
9.1.1.2	<i>Granule-containing tablets</i>	174
9.1.1.3	<i>Bead-containing tablets</i>	175
9.1.2	MICROCELAC[®]-CONTAINING TABLET FORMULATIONS	175
9.1.2.1	<i>Dry powder-containing tablets</i>	175
9.1.2.2	<i>Granule-containing tablets</i>	176
9.1.2.3	<i>Bead-containing tablets</i>	176
9.2	TABLET THICKNESS	177
9.2.1	AVICEL[®]-CONTAINING TABLET FORMULATIONS	177
9.2.1.1	<i>Dry powder-containing tablets</i>	177

9.2.1.2	<i>Granule-containing tablets</i>	177
9.2.1.3	<i>Bead-containing</i>	178
9.2.2	MICROCELAC [®] -CONTAINING TABLET FORMULATIONS.....	178
9.2.2.1	<i>Dry powder-containing tablets</i>	178
9.2.2.2	<i>Granule-containing tablets</i>	179
9.2.2.3	<i>Bead-containing tablets</i>	179
9.3	TABLET DIAMETER	180
9.3.1	AVICEL [®] -CONTAINING FORMULATIONS.....	180
9.3.1.1	<i>Dry powder-containing tablets</i>	180
9.3.1.2	<i>Granule-containing tablets</i>	180
9.3.1.3	<i>Bead-containing tablets</i>	181
9.3.2	MICROCELAC [®] -CONTAINING FORMULATIONS.....	181
9.3.2.1	<i>Dry powder-containing tablets</i>	181
9.3.2.2	<i>Granule-containing tablets</i>	182
9.3.2.3	<i>Bead-containing tablets</i>	182
9.4	TABLET DISINTEGRATION TIME	183
9.4.1	AVICEL [®] -CONTAINING FORMULATIONS	183
9.4.1.1	<i>Dry powder-containing tablets</i>	183
9.4.1.2	<i>Granule-containing tablets</i>	183
9.4.1.3	<i>Bead-containing tablets</i>	184
9.4.2	MICROCELAC [®] -CONTAINING FORMULATIONS.....	184
9.4.2.1	<i>Dry powder-containing tablets</i>	184
9.4.2.2	<i>Granule-containing tablets</i>	185
9.4.2.3	<i>Bead-containing tablets</i>	185
9.5	TABLET FRIABILITY (%).....	186
9.5.1	AVICEL [®] -CONTAINING FORMULATIONS.....	186
9.5.1.1	<i>Dry powder-containing tablets</i>	186
9.5.1.2	<i>Granule-containing tablets</i>	186
9.5.1.3	<i>Bead-containing tablets</i>	186

9.5.2	MICROCELAC [®] -CONTAINING FORMULATIONS.....	187
9.5.2.1	<i>Dry powder-containing tablets</i>	<i>187</i>
9.5.2.2	<i>Granule-containing tablets</i>	<i>187</i>
9.5.2.3	<i>Bead-containing tablets</i>	<i>187</i>
9.6	TABLET MASS VARIATION	188
9.6.1	AVICEL [®] -CONTAINING FORMULATIONS.....	188
9.6.1.1	<i>Dry powder-containing tablets</i>	<i>188</i>
9.6.1.2	<i>Granule-containing tablets</i>	<i>189</i>
9.6.1.3	<i>Bead-containing tablets</i>	<i>190</i>
9.6.2	MICROCELAC [®] -CONTAINING FORMULATIONS.....	191
9.6.2.1	<i>Dry powder-containing tablets</i>	<i>191</i>
9.6.2.2	<i>Granule-containing tablets</i>	<i>192</i>
9.6.2.3	<i>Bead-containing tablets</i>	<i>193</i>
10	ANNEXURE D: DISSOLUTION DATA.....	194
10.1	DISSOLUTION DATA.....	194
10.1.1	AVICEL [®] -CONTAINING FORMULATIONS.....	194
10.1.1.1	<i>Dry powder-containing tablets</i>	<i>194</i>
10.1.1.2	<i>Granule-containing tablets</i>	<i>195</i>
10.1.1.3	<i>Bead-containing tablets</i>	<i>196</i>
10.1.2	MICROCELAC [®] -CONTAINING FORMULATIONS.....	197
10.1.2.1	<i>Dry powder-containing tablets</i>	<i>197</i>
10.1.2.2	<i>Granule-containing tablets</i>	<i>198</i>
10.1.2.3	<i>Bead-containing tablets</i>	<i>199</i>
10.1.3	CONCLUSIVE TABLE	199

LIST OF FIGURES

Figure 2.1:	Figure illustrating the controlled release mechanisms	17
Figure 3.1:	The averages of the most important parameters regarding tablet dissolution and tablet strength for all the tablet formulations	28
Figure 3.2a:	Image depicting the Caleva® Extruder	31
Figure 3.2b:	Image depicting the Caleva® Spheroniser	31
Figure 3.2c:	Image depicting the VirTis® bench top freeze drier	31
Figure 3.3:	Image depicting the angle of repose apparatus	33
Figure 3.4:	Image depicting the copper discs and the shutter used	34
Figure 3.5:	Image depicting the COD apparatus with funnel fitted to the top	34
Figure 3.6:	Image depicting the Erweka® density apparatus	36
Figure 3.7:	Image depicting the Erweka® granulate flow tester	36
Figure 3.8a:	Image depicting the Korsch XP1® tablet press	37
Figure 3.8b:	Image depicting the PharmaResearch® unit	37
Figure 3.9a:	Image depicting the six tube compartment of the disintegration apparatus	39
Figure 3.9b:	Image depicting the screen at the bottom of the glass tubes	39
Figure 3.10:	Image depicting the Erweka® Crushing strength apparatus	40
Figure 3.11:	Image depicting the Erweka® friabilitor	40
Figure 3.12:	Image depicting the Distek® dissolution apparatus	41
Figure 4.1:	Images depicting the a) filler, Avicel® PH200, b) filler MicroceLac® 200 c) API (active pharmaceutical ingredient), pyridoxine hydrochloride d) superdisintegrant, Ac-di-sol® e) lubricant, magnesium stearate f) binder, Kollidon® VA 64	45
Figure 4.2:	Micrographs depicting the a (I) Avicel®-containing dry powder formulation particles, a (II) MicroceLac®-containing dry powder formulation particles, b (I) Avicel®-containing granule formulation particles, b (II) MicroceLac®-containing granule formulation particles, c (I) Avicel®-containing bead formulation particle, c (II)	

	MicroceLac®-containing bead formulation particles.....	46
Figure 4.3:	Micrographs depicting the internal structure of an a) Avicel®-containing bead and, b) MicroceLac®-containing bead.....	48
Figure 4.4:	Angle of repose results for all formulas.....	52
Figure 4.5:	Critical orifice diameter results for all formulas.....	54
Figure 4.6:	Hausner ratio results for all formulas.....	56
Figure 4.7:	Image depicting the conclusive % compressibility results for all formulas.....	58
Figure 4.8:	Flow rate of the different formulations.....	59
Figure 4.9:	Average disintegration time of tablets prepared from the different Formulations.....	65
Figure 4.10:	Crushing strength results for all formulas.....	67
Figure 4.11:	Dissolution profiles of tablets prepared from formulation 1 of the dry powder and granule formulations.....	72
Figure 4.12:	Dissolution profiles of tablets prepared from formulation 2 of the dry powder and granule formulations.....	73
Figure 4.13:	Dissolution profiles of tablets prepared from formulation 3 of the dry powder and granule formulations.....	74
Figure 4.14:	Dissolution profiles of tablets prepared from formulation 4 of the dry powder and granule formulations.....	75
Figure 4.15:	Dissolution profiles of tablets prepared from formulation 1 and 2 of the bead formulations.....	76

LIST OF TABLES

Table 3.1:	List of materials used in the study.....	22
Table 3.2:	Factorial design indicating the different factors and levels employed in the formulations.....	25
Table 3.3:	Table of abbreviations used in figures 4.4 to 4.10 to identify the different formulations.....	26
Table 3.4:	Table of abbreviations identifying different formulations used in the figures and tables in chapter 4 to explain the results of powder flow and tablet evaluation tests.....	27
Table 4.1:	Summary of the particle size analyses results of the different MicroceLac®- and Avicel®-containing formulations used to compress the respective flat faced and concave tablets.....	49
Table 4.2:	Summary of the flowability results of the different formulations (dry powders, granules and beads) prepared with Avicel® and MicroceLac® dry powders, granules, and beads intended for compression of the respective flat faced and concave tablets.....	51
Table 4.3:	Description of the angle of repose classification.....	52
Table 4.4:	Description of the critical orifice diameter classification.....	54
Table 4.5:	Description of Hausner ratio classification.....	56
Table 4.6:	Description of %compressibility standards.....	58
Table 4.7:	Description of flow rate for a 10 mm diameter orifice.....	59
Table 4.8:	Description of flow rate for a 15 mm diameter orifice.....	59
Table 4.9:	Summary of the flow characterisation results of the different powder, granule and bead formulations.....	61
Table 4.10:	Table depicting the evaluation results for all Avicel® tablet formulations.....	62
Table 4.11:	Table depicting the evaluation results for all MicroceLac® tablet formulations.....	63
Table 4.12:	Average mass values as a function of filler, particle type and punch type	

		64
Table 4.13:	Average disintegration times as a function of filler, particle type and punch type.....	66
Table 4.14:	Average crushing strength values as a function of filler, particle type and punch type.....	68
Table 4.15:	Bulk and tapped densities of all Avicel®- and MicroceLac®-containing particle types.....	70
Table 4.16:	Average % friability as a function of filler, particle type and punch type.....	71
Table 4.17:	The average* MDT and I _{dr} values of the different formulations grouped by particle and punch type.....	77

ABSTRACT

The main purpose of developing a dosage form or improving on a current dosage form is to ensure that the active ingredient present in the dosage form reaches the site of pharmacologic action. A dosage form must ensure the stability of the active pharmaceutical ingredient (API) and contribute to the safe and effective treatment of a patient. To provide a suitable dosage form with the aforementioned properties, it is important that the active ingredient and excipients form a coherent unit that provides the necessary properties of an acceptable dosage form. In this study, tablets were compressed using three different particle types, namely dry powders, granules and beads (pellets). It is important to select the optimum particle type when formulating and compressing tablets, because the flow properties and compaction properties depend on the type of particles used to compress the tablets. Two different types of punches were also used to compress tablets, namely 9 mm diameter flat faced and concave punches. These tablets were evaluated with respect to physical properties as well as dissolution behaviour.

A fractional factorial design was used to formulate twenty different particle type mixtures (dry powders, granules or beads) differing with respect to filler, binder and disintegrant. The amount of active ingredient (pyridoxine hydrochloride) used in the tablets was kept constant at 20% w/w. The fillers used were Avicel® (microcrystalline cellulose (MCC)) and MicroceLac® (MCC-lactose). The lubricant was magnesium stearate and was kept constant at 0.5% w/w. The disintegrant used was Ac-di-sol® (super-disintegrant) at a concentration level of either 0.5 or 1% w/w. Kollidon® VA 64 was used as binder and at a 1.5% w/w concentration level for bead-containing tablets and either 3 or 5% w/w for granule and dry powder-containing tablet formulations. The particle type mixtures were characterised with respect to angle of repose (AOR), flow rate, critical orifice diameter (COD), % compressibility and Hausner ratio. Flowability was characterised as flow behaviour plays a significant role in tablet compression as well as during the general handling of powders (particulate mixtures).

Upon flowability characterisation, each formulation was compressed using both the flat faced and concave punch sets. During the compression process, the weight of the tablets compressed in this study was kept constant at 250 mg. The tablets were evaluated with respect to crushing strength, mass variation, diameter and thickness, friability, disintegration time and dissolution behaviour.

The flowability results indicated that the bead formulations exhibited the most promising flow properties of the three particle types used. The granules exhibited the weakest flow properties with inconsistencies observed especially during flow rate characterisation through both the 10 and 15 mm diameter orifices. Granules had irregular shapes with rough surface

textures, whereas the bead particles possessed spherical particles with smoother surfaces contributing to better flow properties and therefore would promote fast and effective compression of uniform tablets.

All tablet batches evaluated, complied with the specifications as set by the British Pharmacopoeia (BP) regarding mass variation, disintegration time, and friability. However, tablets compressed with dry powder and bead particles exhibited a lower variation in tablet mass than the tablets compressed with the granule particles. There was also a pronounced difference between the average crushing strength values of tablets formulated with Avicel® and those formulated with MicroceLac® as filler. The tablets formulated with MicroceLac® as filler, produced tablets with higher average crushing strength values than the tablets formulated with Avicel® as filler.

The dissolution profiles of the different formulations were characterised with regard to mean dissolution time (MDT) and the initial dissolution rate (I_{dr}). Analysis of the dissolution data indicated that all the Avicel®-containing particle type tablets exhibited a burst release with the shortest average MDT values and the fastest average I_{dr} values indicating faster release of the API from these tablet formulations in comparison to the MicroceLac®-containing formulations. All Avicel®-containing formulations showed an average MDT of 12.22 ± 9.406 min and the MicroceLac®-containing formulations showed an average MDT of 23.80 ± 11.441 min. Avicel®-containing formulations exhibited an average I_{dr} value of 4.59 ± 0.444 $\% \cdot \text{min}^{-1}$ and MicroceLac®-containing formulations an average I_{dr} value of 3.38 ± 1.305 $\% \cdot \text{min}^{-1}$. Regarding tablets containing different particle types, the MicroceLac®-containing granule formulations exhibited markedly longer average MDT values and slower average I_{dr} values. The punch type, however, used to compress the different tablet formulations in this study did not have a significant effect on the results that were obtained. Regardless of the differences, all the tablets exhibited profiles with a 90 – 100 % release of the API within 4 hours.

It is clear that the fillers used in this study had a pronounced effect on the physical tablet properties; it also significantly affected the release of the active ingredient from the dosage form significantly. The particle type used to compress the different formulations had an effect on the flowability of the different formulations. It is therefore clear that the particle type and excipients, although considered to be inert, have a prominent influence on the physical properties of tablets as well as an influence on the release of the active ingredient from tablets. It is thus very important to choose the particle type and excipients such as a filler with great thoroughness and care as it clearly influences the quality of the final dosage form.

Keywords: powders; granules; beads; flowability; Avicel®; MicroceLac®

UITTREKSEL

Die doel tydens die ontwikkeling van 'n doseervorm of die verbetering van 'n bestaande doseervorm is om te verseker dat die geneesmiddel die teikenarea bereik sodat 'n farmakologiese effek uitgeoefen kan word. 'n Doseervorm moet die stabiliteit van die geneesmiddel asook die veilige en effektiewe behandeling van 'n pasiënt bevorder. Ten einde 'n doseervorm te verkry wat aan hierdie eienskappe voldoen is dit noodsaaklik dat die geneesmiddel asook die hulpstowwe 'n eenheid vorm wat voldoen aan die vereistes van 'n aanvaarbare doseervorm.

Die doel van hierdie studie was om die invloed van partikeltipe en stempeltipe op die fisiese eienskappe van tablette te ondersoek. In hierdie studie is daar van 'n gedeeltelike faktoriaalontwerp gebruik gemaak om twintig verskillende poeiermengsels bestem vir tabletering in drie verskillende partikeltipes te berei. Die drie partikeltipes wat berei is, was droë poeiermengsels, granulaatmengsels en kraalmengsels. Die mengsels het verskil ten opsigte van die vulstof, bindmiddel, smeermiddel en disintegreermiddel. As vulstof is Avicel® (mikrokristallyne sellulose) en MicroceLac® (mikrokristallyne sellulose-laktosemengsel) gebruik. As disintegreermiddel is Ac-di-sol® (Superdisintegreermiddel) in twee verskillende konsentrasies (0.5 en 1% m/m) gebruik. As bindmiddel is Kollidon® VA 64 in twee konsentrasies van onderskeidelik 3 en 5% m/m vir die droë poeiermengsels en granulaatmengsels gebruik en in 'n konsentrasie van 1.5% m/m in die kraalmengsels. As smeermiddel is magnesium stearaat konstant gehou by 'n konsentrasie van 0.5% m/m. Die vloeie-eienskappe van die verskillende partikeltipe mengsels is bepaal. Die vloeie-eienskappe van die mengsels is bepaal in terme van rushoek, vloeitempo, kritiese openingsdeursnee, % saampersbaarheid en Hausner-verhouding. Vloeie-eienskappe is bepaal aangesien dit 'n belangrike rol speel tydens die algemene hantering van poeiers asook tydens tabletering.

Nadat die vloeie-eienskappe bepaal is, is die mengsels getabletteer met twee verskillende 9 mm deursnee stempeltipes, naamlik plat en konkawe stempels. Die tabletmassa is deurgaans tydens tabletering konstant gehou op 250 mg. Die tablette is vervolgens geëvalueer met betrekking tot massavariasie, breeksterkte, diameter en dikte, afsplyting, disintegrasie en dissolusiegedrag.

Die vloeiresultate het aangedui dat die kraalformulerings die beste vloei getoon het terwyl die granulaatformulerings die swakste vloei getoon het veral ten opsigte van vloeitempo vir beide die 10 en 15 mm openingsdeursnee. Verder het die granules 'n onreëlmatige vorm vertoon met growwe oppervlaktes teenoor die sferiese en oorwegend gladde voorkoms van die kraalformulerings. Hierdie voorkoms het bygedra tot die goeie vloei van die krale.

Al die bereide tabletlotte het voldoen aan die spesifikasies van die Britse Farmakopie (BP) ten opsigte van massavariasie, disintegrasie en afspleting. Alhoewel die tablette wat berei is vanaf die granulaatmengsels voldoen het aan die spesifikasies vir massavariasie het hulle 'n groter variasie getoon as tabbletlotte wat berei is vanaf die droë poeiermengsels en kraalmengsels. Verder was daar ook 'n beduidende verskil tussen die gemiddelde breeksterkte van die tablette wat berei is met Avicel® en MicroceLac®. Dit was duidelik dat tablette wat berei is met MicroceLac® oor 'n hoër gemiddelde breeksterkte beskik het.

Die dissolusieprofiele van die verskillende formulerings is gekarakteriseer ten opsigte van gemiddelde dissolusietyd (GDT) asook aanvanklike dissolusiesnelheid (I_{dr}). Die data het getoon dat al die Avicel® bevattende formules (vir al drie partikeltipes) 'n barsvrystelling getoon het en gevolglik die kortse gemiddelde GDT asook die vinnigste gemiddelde I_{ds} getoon het. Dit was dis duidelik dat hierdie formulerings die aktiewe bestanddeel vinniger vrygestel het as die ooreenstemmende MicroceLac® bevattende formulerings. Die Avicel® bevattende formulerings het 'n algehele GDT van 12.22 ± 9.406 min teenoor die 23.80 ± 11.441 min van die MicroceLac® bevattende formulerings getoon. In terme van die I_{ds} , het die Avicel® bevattende formulerings 'n algehele gemiddelde I_{ds} van $4.59 \pm 0.444 \text{ } \%. \text{min}^{-1}$ teenoor die $3.38 \pm 1.305 \text{ } \%. \text{min}^{-1}$ van die MicroceLac® bevattende formulerings getoon. Met betrekking tot die verskillende partikeltipes het die MicroceLac® bevattende granulaatformulerings 'n merkbaar langer GDT en stadiger gemiddelde I_{ds} getoon. Stempeltipe het egter geen betekenisvolle invloed op die dissolusieresultate getoon nie. Onafhanklik van die verskille tussen die verskillende formulerings, het al die tabletformulerings dissolusieprofiele getoon wat ooreengestem het met 'n geneesmiddelvrystelling van 90 – 100% van die geneesmiddelinhoud binne 4 ure.

Dit is duidelik uit die resultate van hierdie studie dat die vulstof wat gebruik is, 'n uitgesproke effek gehad het op die fisiese tableteienskappe asook die vrystelling van die geneesmiddel vanuit die tablette. Dit is ook duidelik dat die partikeltipe die vloeie-eienskappe van mengsels beïnvloed. Die formulering van soliede doseervorms soos tablette is dus afhanklik van partikeltipe asook die hulpstowwe wat gebruik word aangesien dit die fisiese eienskappe van tablette asook geneesmiddelvrystelling beïnvloed. Die keuse van die hulpstowwe en die partikeltipe moet dus met oorleg gedoen word aangesien dit die kwaliteit van die finale doseervorm beïnvloed.

1 CHAPTER 1: PROBLEM STATEMENT, AIM AND OBJECTIVES

1.1 BACKGROUND

A tablet may be defined as a solid dosage form that varies in size, weight and shape. This dosage form can be prepared by compression or moulding techniques and contains a medicinal substance (active pharmaceutical ingredient), as well as excipients (Medical dictionary online, 2015). Tablets are used worldwide as the most common dosage form to administer drugs (active pharmaceutical ingredients) to the human body for relief of a certain symptom or to treat a certain illness (Jivraj *et al.*, 2000:58).

According to Fridrun and Podczeck (2012:215), the first person ever to compress a tablet for medicinal use by using the method of powder compaction, was William Brockedon. He was also responsible for the first patent of a machine used for the compression of tablets in 1843. The compression of tablets as dosage forms date back far into history and has been an essential part of the pharmaceutical industry for centuries.

Tablets are generally accepted by patients with a high compliance rate and are instrumental in medicinal treatment of patients. It is therefore of the utmost importance that this dosage form be modernised and further evolved to produce the best drug delivery system possible for the patient. Modern techniques include tablets produced with beads and granules rather than powders in order to enhance the manufacturing process (Juban *et al.*, 2015:438).

The popularity of tablets as a dosage form may in part be attributed to the following advantages:

- This dosage form is relatively easy to develop and manufacture,
- the manufacturing costs are relatively low, whereas the throughput is high,
- the administration of the dosage form is straight forward and easy to understand by the patient,
- it is a convenient dosage form in terms of handling and storage that can easily be kept close by the patient,
- a tablet can be manufactured in different shapes and sizes, and
- tablets with modified drug release properties can be developed (Sam *et al.*, 2012:115; Zhang *et al.*, 2004:372).

Tablets also have some disadvantages as dosage forms, including:

- Older patients often struggle to swallow tablets because of dysphagia,
- the breaking and crushing of tablets are not always possible, and
- tablets have a limit to the percentage drug that can be present in one unit (Sam *et al.*, 2012:115; Zhang *et al.*, 2004:372).

In general, the advantages outweigh the disadvantages. Furthermore, some of these disadvantages can be resolved. Elderly patients struggling with dysphagia can use orally disintegrating, sublingual or effervescent tablets. It is important that research must continue to optimise the tablet as dosage form and to make it more patient friendly to promote patient compliance and to ensure efficient treatment of the patient (Sam *et al.*, 2012:115; Zhang *et al.*, 2004:372).

1.1.1 PARTICLE SIZE AND SHAPE

When developing a tablet, one of the most important aspects to consider is the shape and size of the ingredient particles. The shape and size of the particles have an important influence on the flowability of the material, which influences the movement of the material from the hopper into the tablet press die. When the flowability of these particles is poor, the uniformity and effectiveness of the resultant dosage form will be affected. Changing the flow properties of the particles, e.g. by means of granulation techniques, will make a difference in the quality of the final dosage form (Hamad *et al.*, 2010:5625-5626).

1.1.2 TABLET PRESS PUNCH TYPE

During the tablet development process, an often overlooked but very important aspect that needs to be considered is the shape and size of the punch in order to produce a tablet with a specific shape and size. Modernised technology allows manufacturers to choose between a wide variety of punches, for example flat faced or concave shaped punches. Differently shaped tablets present with different mechanical properties. This may have an effect on the packaging method to be used. Therefore, it is imminent that the choice of tablet shape be based on the requirements with respect to the physical properties of the final product. It is important that the tablet stay intact during packaging and handling to ensure a safe, effective and stable solid oral dosage form (Kadiri & Michrafy 2013:467-468; Diara *et al.*, 2015:121-122).

1.2 RESEARCH QUESTION

The quality and performance of dosage forms such as tablets are determined by the properties of the ingredients (i.e. the active ingredient and excipients). Materials with

different particle types and sizes may be used as excipients to formulate tablets. This includes dry powder mixtures with relatively small particles, granules prepared by aggregating dry powder particles into larger agglomerates by adding granulating fluids and spherically shaped uniform beads prepared from dry powders by controlled manufacturing processes such as the extrusion spheronisation technique. The particle type as well as punch shape influence tablet physical properties and dissolution behaviour.

1.3 AIM AND OBJECTIVES

The aim of this study is to investigate the effect of particle type (i.e. fine powder particles, granules and beads) as well as punch type (i.e. concave and flat faced) on the physical properties and dissolution behaviour of tablets prepared from different excipients (i.e. microcrystalline cellulose [Avicel®] and co-processed microcrystalline cellulose with lactose monohydrate [MicroceLac®]) that contain 20% w/w pyridoxine hydrochloride as model active ingredient. In order to reach this aim, the following objectives were set:

- Conduct a literature review on tablets as solid oral dosage forms including manufacturing methods, excipients, single-unit as well as multiple-unit solid oral dosage forms and release mechanisms.
- Prepare three different solid particle types namely fine powder particle mixtures, granules and beads based on a fractional factorial design to optimise each formulation for each of the two selected filler materials (Avicel® and MicroceLac®).
- Prepare tablets from the different particle types of each filler material by means of compression with two different types of punches namely concave and flat faced shaped punches.
- Evaluate the different tablet formulations with respect to physical properties including weight variation, disintegration, crushing strength, friability and dissolution profiles for comparison of tablet performance.

1.4 OUTLINE OF CHAPTERS

The dissertation will be divided in the following chapters:

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

2 CHAPTER 2: TABLETS AS SOLID ORAL DOSAGE FORMS

2.1 INTRODUCTION

The oral route is the preferred route of drug administration due to its versatility, ease of administration and patient compliance (Daugherty & Mrsny, 1999:2; Rekhi, 2010:14). A variety of dosage forms are commonly administered via the oral route such as tablets, capsules, syrups, solutions and suspensions. However, tablets represent one of the most popular dosage forms, which accounts for more than 80% of all dosage forms administered to humans (Jivraj *et al.*, 2000:58). Tablets are solid oral dosage forms that consist of compressed powder mixtures. They contain a certain quantity of a single or a combination of active pharmaceutical ingredients (API's) together with a number of excipients. The main purpose of the excipients in the tablet formulation is to fulfil certain functions to ensure acceptable manufacturability, stability, drug release and drug delivery (Hamman & Tarirai, 2006:5; Hamman & Steenekamp, 2012:220).

The identification of inert substances to be used as excipients and compatibility of these excipients with the API, are crucial aspects during the design and development of tablets (Craw *et al.*, 1998:359). Furthermore, the correct concentrations of each excipient must be included to ensure optimum manufacturability, tablet uniformity and the best possible performance (Hlinak *et al.*, 2006:12-13).

Tablets can be manufactured by means of different techniques including direct compression, wet granulation or dry granulation. During direct compression, the powders are compressed into a tablet directly after mixing without any further processing. Wet granulation involves the addition of a wetting agent to the powder mixture to form coarse aggregates or granules to improve flow during the tableting process. Dry granulation makes use of roller compaction of the powder mixture and crushing thereof into small granules before compression of these granules on the tablet press. Each technique has its own advantages and disadvantages (Al-Mohizea *et al.*, 2007:254).

In the case of conventional immediate release tablets, the active ingredient should be released from the tablet directly after administration. On the other hand, controlled release tablets can modify the drug release by means of different mechanisms. The physical properties of tablets as well as their dissolution behaviour are dependent upon various formulation factors (Furlanetto *et al.*, 2006:77). For example, by using erodible polymers in the tablet formulation, controlled release of the API can be established, providing a longer

and more sufficient release of the active ingredient for a more optimal pharmacological effect (Rosca *et al.*, 2008:668).

2.2 TABLET MANUFACTURING TECHNIQUES

2.2.1 WET GRANULATION

The process of wet granulation involves wetting of the powder mixture with a fluid to form granules before compaction in a tablet press. Granulation of the powder bed not only causes particle enlargement, but also improves particle uniformity. A powder with more uniform particles has better flow properties and this will ensure faster and improved tablet manufacture. Granulation is especially useful for tablets manufactured with powders that have very fine particles and are therefore difficult to handle due to poor flow properties. Granulation reduces the chances of segregation of the powder due to the more uniform particle size in the powder bed. In addition, granulating the powder mixture also reduces cake formation. It is important that the porosity of the granules as well as the granule size distribution is optimal for the manufacture of tablets (Kumar *et al.*, 2013:85).

The interaction forces between the particles during the granulation process as well as their influence on drug release kinetics are not yet fully understood yet (Rosenboom *et al.*, 2015:396). Tablets that are manufactured using the wet granulation technique may show longer disintegration times resulting in delayed or insufficient release of the drug from the tablet. A granulating liquid is needed for wet granulation and the wet granulation process also takes a long time because the particles need to be dried. The need for a granulating liquid as well as the drying step render wet granulation a more expensive process than dry granulation (Bacher *et al.*, 2008:69).

During the wetting of a powder for the manufacture of granules through wet granulation, the wetting liquid migrates through the powder mass and the API may dissolve partially or completely in the wetting liquid, depending on the solubility of the API. Hydrolysis of the API may occur, which may result in failed drug therapy. Furthermore, during drying of the granules in an oven at elevated temperatures, the stability of the formulation may be affected because certain excipients and active ingredients may be heat sensitive. It is therefore important that no heat sensitive materials are used in the wet granulation method and that the heat of the oven remains constant and within the prescribed parameters (Kapsidou *et al.*, 2001:98).

During the wet granulation process there is a possibility that the wetting liquid may not distribute evenly throughout the entire powder mass. The reason for the uneven distribution

may be due to an inadequate mixing process. If the wetting liquid is not mixed thoroughly, it will result in insufficient wetting of the powder mass causing only partial formation of acceptable granules. This will result in segregation and powder loss, which will most probably result in reduced cost effectiveness (Coste *et al.*, 2011:454). Another disadvantage that may occur during wet granulation, is lump formation after the powder has moved through the sieve. This may occur due to over wetting of the powder mass (Coste *et al.*, 2011:454).

2.2.2 DRY GRANULATION

During dry granulation (also known as slugging), the powder mixture is compacted and then milled to form granules. Roller compaction is a popular technique to produce dry granules, which entails passing the powder mixture between two cylindrical rollers that are rotating to form a compact layer that is broken into smaller granule sized bits by means of milling. The granules obtained from the dry granulation process are then compacted within a tablet press (Šantl *et al.*, 2011:414).

The presence of dust and fines can become a problem during the dry granulation process. Furthermore, the compressibility of some powders may decrease when using particles produced by dry granulation. Powder sticking to the rollers during the dry granulation process may also present problems (Kleinebudde, 2004:325).

Tablets manufactured with granules produced by the dry granulation technique tend to have lower tensile strengths compared to tablets produced by direct compression because of the increase in particle size. The decrease in tensile strength tends to increase with powders that exhibit plastic deformation properties (Herting *et al.*, 2008:372).

2.2.3 DIRECT COMPRESSION

Direct compression is a technique of tablet manufacture where the powder mixture is compacted into tablets directly after mixing the powders. No water or moisture is used in this manufacturing process and no drying process is thus needed. This makes it an efficient and relatively easy technique to manufacture tablets (Rojas *et al.*, 2014:103).

Tablets produced by direct compression are limited in terms of API concentration (approximately 30 – 50% of the total formulation may consist of active ingredient). This is a disadvantage of the direct compression technique and occurs because a relatively large quantity of excipients is needed to ensure acceptable properties of the tablet produced. The flow properties of the powder mixture may be another problem during direct compression,

because powders that show poor flow properties cannot produce tablets with a uniform mass (Jivraj *et al.*, 2000:59).

Pharmaceutical manufacturing companies prefer direct compression over the other tablet manufacturing techniques because it only consists of three quick and easy steps, namely weighing of the powders, mixing of the powders and the compression of the tablets. The cost of preparing tablets by means of direct compression is therefore relatively low (Villanova *et al.*, 2011:665).

2.3 FACTORS INFLUENCING TABLET FORMULATION AND MANUFACTURING

2.3.1 COMPRESSION FORCE

The disintegration of a tablet is directly correlated to the compression force applied during tablet manufacture. If the compression force is increased, the porosity of the tablet will be lower and the disintegration of the tablet will take place over a longer period of time. If the compression force is decreased, the disintegration of the tablet will occur faster due to a faster uptake and distribution of water throughout the tablet. It is very important that the compression force is suitable for each particular tablet formulation because it may have a pronounced influence on the bioavailability of the drug in the human body (Corá *et al.*, 2008:69).

The ideal characteristics of an immediate release oral tablet would be to have a sufficient mechanical strength, but a fast disintegration time. The compression force applied to the tablet during the tableting process has a significant influence on both the mechanical strength and the disintegration time of the tablet. It is therefore important that the perfect balance be maintained between these physical properties of a tablet by using the correct compression force during tablet manufacture (Pabari *et al.*, 2012:18).

2.3.2 COMPATIBILITY BETWEEN EXCIPIENTS AND ACTIVE INGREDIENTS

It is important that the active ingredient is compatible with the excipients included in the tablet. Compatibility between excipients and the active ingredient should be verified experimentally during pre-formulation with techniques such as infrared spectroscopy and differential scanning calorimetry. It is important that humidity, time and temperature are taken into consideration when testing for compatibility. Due to the possibility of reactions between the drug and the different excipients, the tablet ingredients should be selected based on compatibility (Wyttenbach *et al.*, 2005:10).

Excipients may exhibit physical or chemical interactions with the API(s) used in the formulations. These interactions may cause degradation of the API and thereby reduce the shelf life of the tablet. That is why excipients need to be chosen very carefully to ensure acceptable stability, efficacy and bioavailability; and to avoid formation of potential toxic compounds (Abdellah *et al.*, 2015:9).

2.3.3 POWDER PROPERTIES

The size and the shape of the powder particles used for tablet manufacturing play an important role in the quality of the final product. The powder particle size and shape will determine the powder flow properties, which in turn plays a role in tablet mass uniformity. It is also important that the physical properties of the excipients such as the elastic and plastic behaviour are suitable for the formation of acceptable tablets. When the powder particles have high compressibility, better and more effective tablets will be manufactured with efficient mechanical strength and therefore acceptable friability. It is very important that the physical properties of the excipient particles are examined during the pre-formulation phase to ensure good compressibility. If the powder particles show too much elasticity, it will result in capping of the tablet. On the other hand, too much plasticity will result in tablets that are extremely hard with prolonged disintegration times (Li *et al.*, 2013:47).

Furthermore, there is a need for control of the particle size and particle size distribution of powders and powder mixtures intended for solid oral dosage form manufacture. Powder particle size influences powder flow, tablet weight uniformity and the mechanical strength of the tablet. The particle size distribution influences homogeneity and segregation of powder mixtures during tablet manufacture (Fichtner *et al.*, 2005:292).

Wettability of powders is of vital importance when the wet granulation technique is used for tablet manufacture and for bead production by extrusion spheronisation. Wettability can be tested with the contact angle test, the flotation test, the isothermal micro-calorimetry test and the inverse gas chromatography test (Zhang *et al.*, 2002:548). Ingredients of tablets produced through wet granulation as well as beads produced by extrusion spheronisation must be compatible with the wetting agent to avoid degradation (Galland *et al.*, 2009:48).

2.4 EXCIPIENTS IN TABLET FORMULATION

2.4.1 DILUENTS/FILLERS

The main purpose of diluents or fillers was originally to make up the volume of the tablet in addition to the API. In the modern way of designing tablets, diluents are not only used to fill the volume, but are also used to enhance tablet properties such as cohesiveness,

compressibility and mechanical strength. Adding a diluent to the tablet formulation can ease the process of direct compression because adding a diluent with good flow properties will enhance the fluidity of the powder mixture, which consequently leads to faster manufacturing of tablets and tablets with a more uniform mass (Vaidya *et al.*, 2011:375).

Diluents with tailor made physico-chemical properties are nowadays added to tablet formulations to change the physical properties of the tablet, the drug release profile as well as the compression properties. Therefore, it is of utmost importance to choose the correct diluent considering the following characteristics: it should be compatible with the other ingredients, have suitable flow properties, have suitable compressibility properties and provide acceptable drug release from the tablets (Vaidya *et al.*, 2011:375).

2.4.2 DISINTEGRANTS

A disintegrant is an excipient that is used to break the bonds between the compacted powder particles that hold the tablet together. After these bonds are broken, the tablet can disintegrate into smaller particles and the dissolution process can follow. There are different mechanisms by which disintegration of a tablet can be mediated such as swelling, heat of wetting, particle repulsion, deformation recovery, wicking and the creation of a capillary microstructure (Adebayo *et al.*, 2008:98).

Different types of disintegrants are used to achieve different disintegrating mechanisms inside the tablet during the disintegration and dissolution process, however, disintegrants may act according to more than one mechanism. The swelling mechanism can be achieved using super-disintegrants such as croscarmellose sodium (Ac-di-sol[®]), sodium starch glycolate (Explotab[®]) and also carboxymethylcellulose calcium. The wicking mechanism will take place when using croscarmellose sodium (Ac-di-sol[®]), sodium starch glycolate (Explotab[®]), carboxymethylcellulose calcium or polacrillin potassium (Srinarong *et al.*, 2009:155).

New generation super-disintegrants are frequently used in the formulation of modern dosage forms to enhance dissolution and disintegration rates. The super-disintegrants include sodium starch glycolate (Primojel[®]), croscarmellose sodium (Ac-di-sol[®]) and crosslinked polyvinyl pyrrolidone (Polyplasdone[®] XL and XL-10) (Srinarong *et al.*, 2009:155).

2.4.3 LUBRICANTS

Lubricants form an essential part of the tablet formulation, especially when the direct compression technique is used to manufacture the tablets. Lubricants are used to lower the

friction between the powder particles and the die wall during the compaction process by providing a lubricating film on the surface of each powder particle (Late *et al.*, 2009:4).

A lubricant can also improve the fluidity and filling of the die, which will result in more uniform tablets. Adding a lubricant to the formulation also makes the powder anti-adherent with its main purpose to prevent the powder sticking to the sides of the punches during the tableting process. Many lubricants unfortunately affect the disintegration, mechanical strength and the dissolution properties of the tablet, due to their hydrophobic nature, which necessitates selection of the most suitable lubricant for each tablet formulation (Late *et al.*, 2009:4).

2.4.4 BINDERS

Binders are included in a tablet formulation to provide better compressibility of the tablets and to provide tablets with better mechanical strength. Binders are specifically used in the process of wet granulation because of the binding quality of the excipient to improve the strength of the granules. Different binders provide different drug release properties because of their different mechanisms of action. The most common binders used in tablet formulations are plant gums and polymers (Gowthamarajan *et al.*, 2011:506). Polymers can be used as binders and they can either be hydrophobic or hydrophilic. The hydrophobic polymeric binders facilitate water inlet into the tablet by means of erosion and pore diffusion. Hydrophilic polymeric binders produce a viscous layer that looks like a gel when water comes in contact with the tablet through which a drug can diffuse out of the tablet (Tan *et al.*, 2014:89).

2.4.5 GLIDANTS

Acceptable powder flow during the tableting process is of utmost importance. Without good powder flow, the tablet press die cannot be filled with repeatable quantities of powder resulting in tablets with excessive mass variation (Meyer *et al.*, 2004:40). Glidants can be added to the powder mixture of the tablet formulation to overcome poor powder flow. The main objective of adding a glidant to the powder mixture is to lower the Van der Waals forces between the individual powder particles. These forces cause adhesion between particles and thereby affect the powder flow properties. Glidants are powders with relatively small sized particles, which accumulate on the surfaces of powder mixture particles and thereby enhance powder flow (Meyer *et al.*, 2004:40).

2.5 BEADS AS SOLID ORAL DOSAGE FORMS

Beads (or pellets) are spherical agglomerates of powder particles formed by appropriate techniques and processing equipment. Pharmaceutical pellets are usually produced in sizes

ranging from 0.25 – 2 mm depending on the method and equipment used. Pellets or beads that are produced, each have their own properties contributing to the modified release kinetics of the final dosage form. Beads are used to produce multiple-unit pellet systems (MUPS) such as hard gelatine capsules filled with the beads (MUPS capsules) or beads compressed into tablets (MUPS tablets). Beads can be manufactured by different techniques including extrusion spheronisation, powder layering, suspension layering, spherical agglomeration, spray drying, spray congealing, melt spheronisation and cryopelletisation (Dash *et al.*, 2012:19-25).

The spherical shape and size of the beads are a very important advantage when producing tablets and other dosage forms due to better flow properties. A higher drug load can be achieved with beads and the volume or size ratio of the beads can be controlled. Film coating and powder layering of beads are relatively easy to do and drug release can be delayed or modified for a prolonged effect in the human body. There is a lower chance of dose dumping, but irritation of the mucosa in certain areas of the body can occur (Santos *et al.*, 2002:246).

Compared to wet granulation, the preparation of beads through extrusion-spheronisation is more cost effective and it is easier to set up the equipment needed for the preparation of beads. The process of preparing beads is relatively fast, but do include drying of the beads and is thus longer than direct compression. A prolonged pharmacological effect can be established by coating the beads with a thin layer of polymer coating material or by embedding the drug in a matrix type bead (Howard *et al.*, 2006:66).

2.5.1 EXTRUSION-SPHERONISATION

2.5.1.1 The extrusion-spheronisation technique

The most popular and the most modern method of producing pharmaceutical pellets or beads are through extrusion-spheronisation. The extrusion-spheronisation process consists of four steps namely mixing of the powder mass, extrusion of the wetted powder mass, spheronisation of the extrudate produced by the extruder; and then drying of the spheronised pellets. The fourth step can occur by means of oven drying or using the freeze-drying method (Ghandi *et al.*, 1999:162-163).

The active ingredient together with the rest of the excipients, form the powder mass. This powder will then be mixed with a binder solution or a liquid ensuring that the powder is dense and moist enough to produce a strong extrudate for spheronisation. Beads or pellets are produced by forcing the wet powder mass through a screen/die causing a spaghetti-like

extrudate to form with a certain diameter depending on the type of screen/die that was used to produce the extrudate. Spaghetti-like extrudate is spheronised in a multi-bowl spheroniser that uses a spinning disc to form spherical beads or pellets (Dukić *et al.*, 2009:39). Spheronisation is also known as marumerisation. The extrudate that was formed during the process of extrusion will be rounded into spherical shapes through collision forces. Energy needed to provide the collision forces will be provided by the spheroniser and the spinning disc (Bryan *et al.*, 2015:2).

2.5.1.2 Factors influencing the process of extrusion-spheronisation

There are numerous factors influencing the process of extrusion-spheronisation. It is important that care is taken to ensure that these factors are managed correctly to produce an acceptable extrudate.

One of the main factors influencing the process of extrusion-spheronisation is the amount of bonding liquid/wetting agent added to the powder mass during the mixing process before extrusion. It is important that the right amount of wetting agent is added to the mixture to ensure that the extrudate has the correct texture and properties to produce acceptable beads or pellets after spheronisation. It is therefore important that the powder is not over-liquidised or under-liquidised; the texture must be perfect to ensure that the extrudate will hold its form and spheronise correctly after extrusion (Bryan *et al.*, 2015:3).

Another important factor that influences the process of extrusion-spheronisation is the rate at which the liquid is added to the powder mass during the mixing process. Furthermore, it is very important that thorough mixing takes place during the wetting process to ensure that the wetting agent is spread throughout the whole powder bed. Adding the liquid too slowly may result in evaporation of the liquid and the mixture will consequently be too dry. Adding the liquid too fast will cause the ingredients to dissolve and hydrolysis may occur, which can affect the stability of the end product. It is important that the liquid adding rate correlates with the mixing speed in order to find the correct texture before extrusion (Bryan *et al.*, 2015:3).

Not only is the mixing speed of importance, but also the type of mixer or mixing method used during the mixing of the dry powder before further processing. The mixing of the powder during the wetting process is also very important. The above properties are very important and can have a pronounced effect on the beads or pellets formed at the end of the process. Different types of mixers are used in the industry depending on the properties of the excipients and active ingredient(s) used in the specific formula. Mixing can occur with a rotary blade mixer that uses strain forces to push the mixture onto the walls of the mixing

bowl and then cut through it again mixing the powder mass thoroughly. Another method of mixing is by using a kneeder. Using this method, the mixture will be pressed onto the bottom of the mixing bowl and broken up; and then pressed again. It is important that the mixing speed and the mixing method correlate with the type of excipient and active ingredient used in the formula to ensure that the chemical and physical properties of the mixture stay in place and that the end product is effective and stable (Bryan *et al.*, 2015:3).

The type of extruder used during the extrusion-spheronisation technique also influences the properties of the pellets formed at the end of the process. Different types of extruders are available including roller screen extruders and screw driven extruders that will either pump the powder through the screen using an external force or wipe the powder through the screen with rollers. The type of extruder is chosen based on the powder mixture properties in order to produce the best extrudate (Zhang *et al.*, 2013:490).

Extrusion speed has a potential influence on the bead properties produced by extrusion-spheronisation. In general practice, it makes sense to set the extrusion speed as high as possible to ensure a cost effective manufacturing process that is fast enough to produce high volumes of extrudate. Unfortunately, stepping up the extrusion speed usually results in a lower extrudate quality. When the speed is too high, the extrudate will not have the correct texture and surface properties to produce acceptable pellets or beads. The extrudate will not have the correct thickness and length and too much fines will also occur later in the extrusion-spheronisation process (Ghandi *et al.*, 1999:165).

The type of spheroniser used is of considerable importance. Spheronisers may have different friction plates namely the cross hatch geometry plate and the radial geometry plate. This may have an influence on the shape of the pellets and also the sizes that are produced (Ghandi *et al.*, 1999:163).

The spheronising speed is another important factor to consider during the extrusion-spheronisation process. Spheronising speed will not only effect the size of the pellets that are formed but also the mechanical and physical properties of the pellets; namely porosity, friability, surface properties, hardness and sphericity of the pellets. It is important that the correct speed is established ensuring pellets with acceptable qualities and properties (Ghandi *et al.*, 1999:165).

A key factor that is often forgotten during the extrusion-spheronisation process is heat that is generated during the process of mixing, extrusion and spheronisation. It is important to note that friction is generated during these processes which may cause some of the liquid to

evaporate. If the amount of wetting is not sufficient to compensate for loss due to evaporation, the end product will not be acceptable (Ghandi *et al.*, 1999:165-166).

2.6 SINGLE-UNIT SOLID ORAL DOSAGE FORMS

A single-unit dosage form consists of one unit intended for a singular administration and that contains the complete dose of the drug in that single unit. A single-unit solid oral dosage form can be manufactured in the form of tablets or capsules (Ghandi *et al.*, 1999:160).

The reason why single-unit solid oral dosage forms are popular is because they are relatively simple to produce, are well-known and generally well accepted by patients. It is not difficult to administer and the cooperation of patients (i.e. patient compliance) using these types of dosage forms are generally high. The costs needed to produce single-unit dosage forms are relatively low and a fast manufacturing speed contributes to the advantages of producing single-unit dosage forms (Zhang *et al.*, 2004:372).

Disadvantages with regard to single-unit solid oral dosage forms include: difficulty of formulating certain API(s) into dosage forms where specific properties are required. The physico-chemical properties of the excipients and the active ingredients to be included in the specific dosage form should be taken into consideration as this has an important influence on the formulation process. For example, good flow of the powder mixture is needed to ensure fast tableting and to increase the cost effectiveness of the production process. It is also important to select excipients that will ensure acceptable compressibility properties for the manufacture of tablets (Zhang *et al.*, 2004:372). Furthermore, a failure in the formulation of sustained release single-unit solid oral dosage forms may result in dose dumping of the API. Immediate release single-unit solid oral dosage forms have to be administered more frequently than their modified release counterparts. Furthermore, patient compliance tends to be lower during extended treatment periods when a large number of doses need to be taken. Producing modified release dosage forms that can reduce the number of dosages to be taken, will contribute to solve this problem (Di Pretoro *et al.*, 2012:159).

Other disadvantages of immediate release single-unit solid oral dosage forms include insufficient distribution of the dose through the gastro-intestinal tract with consequent relatively high intra- and inter-subject variation in drug pharmacokinetics (Di Pretoro *et al.*, 2012:159).

2.6.1 IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS

Immediate release dosage forms are manufactured and formulated for the main purpose of delivering the active ingredient to the blood circulation directly after administration of the

dosage form. It is therefore important that the excipients used to produce this type of dosage form ensure rapid disintegration so that an increased particle surface area contributing to efficient dissolution can follow as soon as possible (Azarmi *et al.*, 2007:13).

Immediate release dosage forms will commonly be used in treatments where a relatively quick and rapid steady state plasma drug concentration is needed. Therefore, the drug needs to be released and absorbed relatively fast to reach the systemic circulation directly after administration. Immediate release dosage forms will have to be administered repeatedly to maintain the steady state drug plasma level (Löbenberg *et al.*, 2005:18).

The main disadvantage of using immediate release dosage forms is therefore poor patient compliance. When frequent doses are required to maintain therapeutic drug plasma levels, it can lead to treatment failure when doses are skipped as a result of practical challenges at the work place. Patients therefore prefer treatments with lower dose frequencies (preferably once or twice a day). Another disadvantage is that treatment with immediate release dosage forms can become expensive because of the multiple dosages that need to be taken, making it less cost effective (Löbenberg *et al.*, 2005:18).

Another disadvantage of using immediate release solid oral dosage forms is the potential to cause damage to the esophagus. The objective of the immediate release solid oral dosage form is to release the active ingredient relatively fast after administration and it is possible that the tablet or capsule can start to disintegrate while the patient is swallowing the dosage form. When the dosage form or parts of it stick to the side of the esophagus, it can result in damaging the surrounding tissue (Smart *et al.*, 2013:200).

2.6.2 MODIFIED RELEASE SOLID ORAL DOSAGE FORMS

A modified release dosage form is a dosage form that delays the release of a drug for stability or side-effect considerations; or improves the availability of drug inside the human body by means of prolonged delivery and sustained or extended release of drug from the dosage form. Administering this dosage form ultimately results in a prolonged therapeutic effect after a single administration (Lopes *et al.*, 2006:93-95; Ishida *et al.*, 2008:47).

The main objective with modified release dosage forms is to achieve more stable drug plasma concentrations over the treatment period with administration of a lower number of doses. Administering modified release dosage forms will most probably improve patient compliance because a lower number of daily doses is required for effective drug therapy (Lopes *et al.*, 2006:93-95).

Because different modified release mechanisms can be employed, a drug can be released at a specified rate or at different time points (pulsatile release). Modified drug release from the dosage form can be implemented by means of modifying the dosage form such as forming a matrix in which the drug is dispersed or by coating the dosage form with a polymeric film (Lopes *et al.*, 2006:93-95; Ishida *et al.*, 2008:47).

Modified release dosage forms can also be referred to as controlled release dosage forms. This means that the dosage regimen is controlled and the drug release at the site of absorption can also be controlled, making constant drug levels in the systemic circulation a possibility. The most common regimen used to provide the controlled/modified release mechanism in the body is the regimen where an initial rapid release of drug is initiated to get the level of drug in the body to the steady state concentration. After the rapid release, the dosage form is modified with a barrier system keeping the drug trapped in the dosage form until the time, or the physiological properties are acceptable to release the next maintenance dose, keeping the concentration in the body at that very important steady state for chronic treatment of certain illnesses (Staniforth & Aulton, 2007:485-486).

Two basic mechanisms that mediate controlled release from a modified release from dosage form are by means of diffusion and dissolution. Wetting of the dosage form will take place when administered; the active ingredient will undergo dissolution and will then leave the dosage form through diffusion from a region of high concentration to a region of lower concentration (Staniforth & Aulton, 2007:485).

The diagram below (Figure 2.1) illustrates the mechanisms by which formulators implement controlled release in dosage forms. Controlled release is mediated by diffusion control, dissolution control, erosion control or an osmosis control/osmotic pump system.

Diffusion of the active ingredient from the dosage form can be controlled by a matrix system and by a reservoir system. In a matrix system the active ingredient is dispersed in a soluble or insoluble matrix, depending on the area where the drug needs to be released and how fast it should be released. The active ingredient will then be released from the dosage form as the matrix dissolves slowly providing a controlled release of drug into the body. The reservoir system is a membrane controlled system where the active ingredient can only leave the dosage form by permeating the membrane and diffusing through it. For this membrane to become permeable it needs to come in contact with fluid. This will be the gastrointestinal fluids. Once the membrane is wetted by the intestinal fluids, the active ingredient will start permeating through the membrane into the human circulation, causing a controlled release of drug throughout the system (Staniforth & Aulton, 2007:490).

Erosion controlled release of the active ingredient from a dosage form is another mechanism of modified release. The active ingredient is dispersed in an erodible matrix. If the intestinal fluid comes into contact with the dosage form, pores in the dosage form will allow the fluid to pass through. The active ingredient will start dissolving in the fluid and controlled release of active ingredient is established (Staniforth & Aulton, 2007:495-497).

Modified release can also be mediated with an osmotic unit displaying osmotic controlled release of the active ingredient from the dosage form. This dosage form is comprised of a water soluble core coated with a semi-permeable membrane. The dosage form also has a whole drilled in it. When the osmotic unit comes into contact with the intestinal fluid, the fluid will pass through the semi-permeable membrane and the water soluble core will start dissolving forming a suspension inside the coating. The osmotic pressure will start building inside the dosage form and the suspension will be released through the drilled hole little by little implementing an extended release of active ingredient into the human body for absorption (Staniforth and Aulton, 2007:490-493).

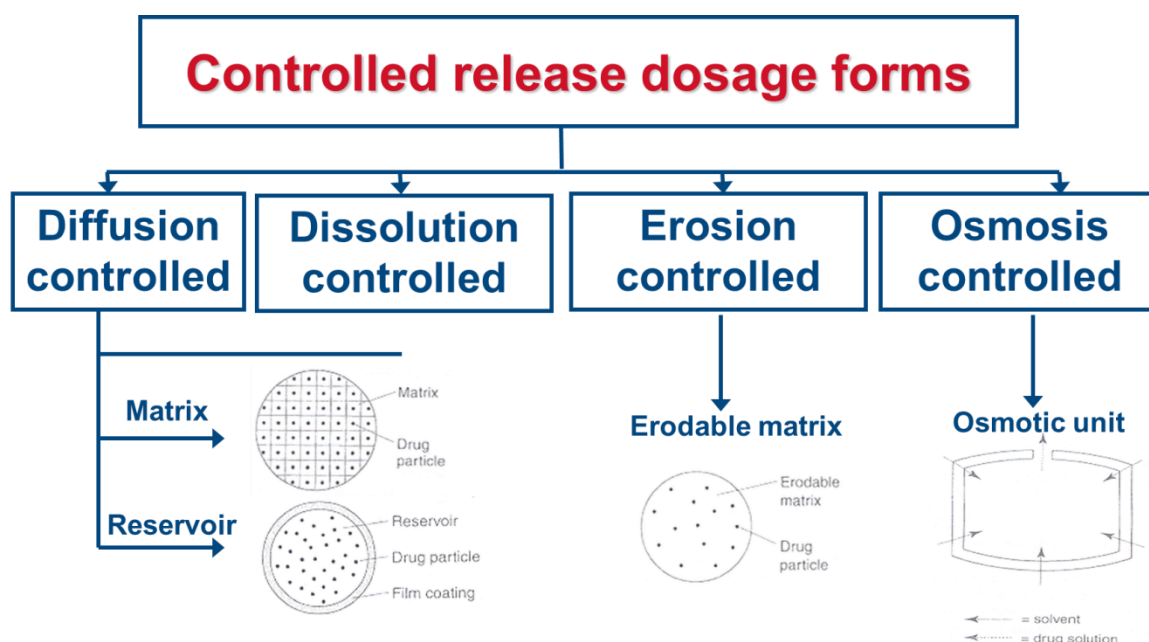


Figure 2.1: Figure illustrating the controlled release mechanisms

2.7 MULTIPLE-UNIT DOSAGE FORMS

Multiple-unit dosage forms refer to drug delivery systems consisting of more than one unit combined together into a dosage form. Each of these units within the dosage form contains a portion of the total drug dose. Examples of multiple-unit dosage forms are granules, beads, mini-tablets or micro-particles that are combined into solid dosage forms such as

tablets or hard gelatin capsules. After administration, the dosage form will disintegrate into the individual pellets or beads. These multiple-unit particle systems namely pellets/beads, granules or mini-tablets can be modified to produce a dosage form producing an immediate release or a modified release mechanism; or a combination of both, making it a very effective system to produce dosage forms (Goole *et al.*, 2007:35-36). The pellets or beads can serve as matrices or can be coated to provide extended drug release (Shajahan *et al.*, 2010:3-4; Lopes *et al.*, 2006:93).

A major advantage of formulating a multiple-unit dosage form is the increasing dispersion percentage of drug through the gastro-intestinal tract because the pellets and granules that are used in the development of new generation multiple-unit dosage forms provide greater resistance against the metabolising entities in the gastro-intestinal tract. Pellets and granules are used to manufacture dosage forms ensuring that the drug is not metabolised in the stomach acids. Pellets and granules are formulated into capsules or tablets to protect the active ingredient from the highly acidic environment of the stomach (Goole *et al.*, 2007:35-36).

Pellets and granules can be formulated in various ways and their properties can be manipulated in more than one way resulting in dosage forms that have a wide variety of disintegration, dissolution and absorption properties. The dosage forms can be manipulated and the formulator can decide when drug needs to be released from the pellets or granules and also when the multiple-unit particles (pellets and granules) should be released from the dosage form (Shajahan *et al.*, 2010:4).

Producing beads, pellets and granules can be a time consuming process because of the different steps involved (e.g. extrusion, spheronisation and drying), whereafter the particles need to be incorporated into a combined dosage form. Compaction of beads, pellets and granules into a tablet can be challenging, whereas specific equipment may be needed to fill hard gelatin capsules with mini-tablets (Shajahan *et al.*, 2010:4).

2.7.1 MULTIPLE-UNIT PELLET SYSTEM (MUPS) TABLETS

Multiple unit pellet systems (MUPS) formed by compressing particles such as granules and pellets (coated, uncoated or matrix type), into a tablet dosage form are referred to as MUPS tablets (Shajahan *et al.*, 2010:3).

Tablets are manufactured by direct compression of the multiple units mostly consisting of coated or uncoated spherical pellets by means of a series of four steps. The first step is volume reduction by means of pellet rearrangement in the tablet press die where the pellets

will be rearranged to fill the voids between the pellets. The second step includes further volume reduction of the pellet mass by means of flattening of the pellets on the surface of the lower punch when the upper punch starts to press down on the pellet mass. The third step is where the rest of the pellets will undergo reformation. The fourth and final step is the stopping of volume reduction, allowing sufficient inter- and intra-granular porosity to occur. Under ideal circumstances, the pellets should not fuse into one large non-disintegrating tablet core. After administration, the tablet should disintegrate into the separate pellets and these pellets must then disintegrate further into powder particles to improve dissolution (Shajahan *et al.*, 2010:3-4).

Multiple-unit pellet systems (e.g. MUPS tablet) can provide modified release of drugs depending on the formulation approach. This can be accomplished by using matrix type pellets or coated pellets that release the drug slowly by means of diffusion through the film coating layer. A prolonged release and a prolonged pharmacologic effect will thus be achieved. Formulating MUPS tablets will lower the probability of adverse effects of the drug because it is less probable that dose dumping may occur using a multiple-unit dosage form. If the release modifying mechanism is compromised in one sub-unit (e.g. pellet), it will still be applied by the other sub-units and thereby decreasing the possibility for dose dumping (Shajahan *et al.*, 2010:3-4).

Some of the factors critical to the successful formulation and manufacture of MUPS tablets are the same as those experienced for the normal tableting process. If the compression force is too high, the integrity of the pellets may be destroyed causing the dosage form to compress into one congregated powder mass that will not disintegrate into the individual pellets. Furthermore, when compressing coated or matrix type pellets into a tablet, it is important that the pellets are not crushed because the prolonged drug release effect of the pellets will then be compromised (Shajahan *et al.*, 2010:3-4).

Another factor that may influence the manufacture of MUPS tablets is the inter-pellet bonding force. If the bonding force is not sufficient enough to form a solid tablet, it will break up into smaller pieces directly after compression. It is important to use the correct pellet size and employ a suitable compression force to ensure sufficient inter-pellet bonding. It is also important to ensure that the inter- and intra-granular spaces in, and between the pellets, are suitable to ensure acceptable disintegration and dissolution (Shajahan *et al.*, 2010:3-6).

2.7.2 MULTIPLE-UNIT PELLET SYSTEM (MUPS) CAPSULES

Multiple-unit pellet system capsules (MUPS capsules) consist of granules, pellets, crystals or mini-tablets that are placed in a capsule to provide a multiple-unit solid oral dosage form.

The pellets loaded into the hard gelatin capsules can be uncoated, coated or matrix type pellets. This process is achieved with a capsule filling machine. Because of the relatively low output of the production of capsules, it is normally less cost effective compared to MUPS tablets (Chopra *et al.*, 2002:327).

Filling hard gelatin capsules with pellets or beads provides a number of advantages in the treatment of patients. A capsule is capable of masking bad tastes, making it more acceptable in terms of the organoleptic properties. MUPS capsules can be formulated with a combination of pellets and dry powders, thereby providing a pulsatile drug release effect that may be advantageous in the treatment of certain diseases. Placing pellets, with different types of release kinetics, inside the hard gelatin capsule will have the potential to overcome the problem of dose dumping because the complete dose will not be released at once, but will rather be released using a pulsatile release mechanism, assuring that the drug levels in the blood stay stable and effective (Chopra *et al.*, 2002:327; Löbenberg *et al.*, 2005:18).

A disadvantage of producing MUPS capsules is that filling the capsules is time consuming and it is also more expensive than producing tablets. During the process of capsule filling the pellets/granules may produce an electric charge between one another resulting in weaker flow that may cause under-filling of the capsules. It is important that uniform spherical shapes are formed during the manufacture of the pellets, as this will ensure better flow of the pellets during capsule filling and will also speed up the process. The surface texture of the pellets or granules may contribute to problems in terms of fluidity of the pellet system (Chopra *et al.*, 2002:327).

Both single-unit and multiple-unit dosage forms have advantages and disadvantages and a certain type of dosage form will be more appropriate in the treatment of a specific disease or circumstance (Zhang *et al.*, 2004:372-373)

2.8 SUMMARY

Solid oral dosage forms such as tablets are usually well accepted by patients and associated with a high level of patient compliance. Selection of excipients, manufacturing technique and knowledge of the factors that influence formulation, are key aspects in ensuring safe and effective therapy. Solid oral dosage forms may be manufactured as single-unit systems or multiple-unit systems. Multiple-unit solid oral dosage forms include tablets and hard gelatin capsules comprising particles such as granules, pellets or beads. Multiple-unit dosage forms possess certain advantages such as improved dispersion of the active ingredient(s) through the gastrointestinal tract, possibility to render modified release, and a limited possibility of side effects such as dose dumping. These advantages render multiple-

unit solid dosage forms an attractive possibility in terms of drug therapy although formulation might be associated with some challenges.

3 CHAPTER 3: EXPERIMENTAL METHODS

3.1 INTRODUCTION

Whenever a solid oral dosage form such as a tablet is formulated for medicinal use, it is important that the product is safe, effective and render a reproducible pharmacological response. The tablet must therefore contribute to the stability of the active ingredient during storage; it must be suitable for human consumption and safe during long term use. When combining excipients to form an acceptable tablet, it is important that the appropriate quantity or ratio of each excipient is used. It is also important that the tablet excipients possess the correct physico-chemical properties to ensure sufficient flow into the tablet press die; to undergo appropriate deformation during compression, and to provide sufficient adhesion to form a tablet that can withstand mechanical stresses during handling. Manipulation of excipients is sometimes necessary to improve physical characteristics such as the use of granulation to improve powder flow properties (Jivraj *et al.*, 2000:58-60).

In this chapter, the materials used in the study are listed and the experimental methods that were used to formulate, manufacture and evaluate the solid oral dosage forms are described.

3.2 MATERIALS

Information on the tablet excipients and active ingredient that were used in the study is given in Table 3.1.

Table 3.1: List of materials used in the study

Material type	Material name	Batch/Lot number	Supplier
Active ingredient	Pyridoxine hydrochloride	Batch: Y03201407066	Warren Chemical Specialities
Fillers	MicroceLac®100	Lot no: 416 300	MEGGLE, Germany
	Avicel® PH 200	Lot no: M939C	FMC, Ireland
	Avicel® PH 101	Lot no: 60839C	FMC, Ireland
Disintegrant	Ac-di-sol®	Lot no: T017C	FMC, Ireland
Binder	Kollidon® VA64	Lot no: 19960109TO	BASF, Germany
Lubricant	Magnesium stearate	Lot no: 21203	PharmaVarsity

3.3 METHODS

3.3.1 SELECTION OF ACTIVE INGREDIENT

Pyridoxine hydrochloride was used as model drug in all the tablet formulations in a concentration of 20% w/w. Pyridoxine was specifically selected based on the fact that it is freely water soluble (Taguchi *et al.*, 2014:270-271). The aim of this study was to investigate the influence of particle type and punch type on tablet properties and therefore a drug with good water solubility was selected rather than a drug that presented with poor water solubility to exclude solubility as a factor that may interfere with tablet performance.

Pyridoxine or otherwise known as vitamin B6 is an essential vitamin to the human body. Pyridoxine serves as a precursor to important enzymes in the human body and it is crucial that the vitamin B6 levels in the body remains at an adequate level (García *et al.*, 2001:193-194; Aboul-Enein *et al.*, 1984:447-486).

Three similar forms of vitamin B6 exists namely pyridoxal, pyridoxamine and pyridoxine hydrochloride. Pyridoxine hydrochloride is the most stable of the three forms of vitamin B6, and makes it the most popular form to use in commercial products (García *et al.*, 2001:193-194; Aboul-Enein *et al.*, 1984:447-486).

3.3.2 SELECTION OF FILLERS

The selection of the fillers to be used was based on the objective that the fillers will be compared in terms of tablets prepared from different particle types, namely:

- a conventional powder particle-type,
- a granule-type particle, and
- a bead-type particle.

Based on this objective, microcrystalline cellulose (Avicel® PH 200 and Avicel® PH 101) as well as a co-processed filler comprised of Microcrystalline cellulose (MCC) and lactose monohydrate (MicroceLac® 100) were selected to prepare the different particle types.

MCC was used in two different grades namely Avicel® PH 200 and Avicel® PH 101. Avicel® PH 200 was used to formulate and prepare tablets by means of direct compression by using dry powder formulations (MCC in this particle size range are difficult to granulate, but is an excellent direct compression filler). On the other hand, Avicel® PH 101 was used to formulate and prepare granule- and bead formulations for compression into tablets (MCC in this particle range does not provide tablets by direct compression). MicroceLac® 100 was used to formulate and prepare tablets by means of direct compression of dry powder

formulations as well as the production of granule- and bead formulations for compression into tablets.

3.3.3 SELECTION OF DISINTEGRANT

It is of utmost importance when formulating a tablet that the formulation includes a disintegrant in order for the tablet to break down into smaller particles in the gastro-intestinal tract to render granules and/or primary particles to increase the surface area available for drug release and dissolution. Ac-di-sol® was selected as disintegrant in this study. The disintegrant was used in two different concentrations, namely 0.5 and 1% w/w. Ac-di-sol® is classified as a super-disintegrant, which is popular to use because rapid disintegration is initiated as soon as the tablet comes into contact with an aqueous environment, breaking the tablet into the primary particles used to compress the tablet (Srinarong *et al.*, 2009:155).

3.3.4 SELECTION OF BINDER

Kollidon® VA 64 was used as a binder at a concentration of 1.5, 3 and 5% w/w depending on the formulation. The inclusion of a binder is a necessity for the successful formulation of granules and beads. Kollidon® VA 64 was selected based on its versatility as a binder in solid oral dosage form formulations (Mellert *et al.*, 2004:1573).

3.3.5 SELECTION OF LUBRICANT

The concentration of magnesium stearate as the lubricant was kept constant at 0.5% w/w for all formulations. Magnesium stearate is the most popular lubricant used to produce solid dosage forms such as tablets because of the low concentrations needed in formulations. The concentration of magnesium stearate rarely exceeds 2% w/w in formulations used to manufacture solid oral dosage forms. It ensures that sufficient lubrication of the punches and dies takes place during the tablet compression process, thus allowing a faster and more effective manufacturing process as well as protecting the tablet press against damage (Rashid *et al.*, 2010:609-610). Furthermore, magnesium stearate plays an important role in ensuring that inter-particulate friction remains low and thus improving the flowability of the powder mass (Rashid *et al.*, 2010:609).

3.4 COMPOSITION OF FORMULATIONS

A factorial design was used to provide different formulations to compare the two filler materials in terms of tablet performance, which were prepared from powders, granules and beads. The factorial design for general formulations applied to powders, granules and bead compositions is shown in Table 3.2.

Table 3.2: Factorial design indicating the different factors and levels employed in the formulations

		Diluent A (Avicel® PH200) or Avicel® PH101		Diluent B (MicroceLac®)	
		Disintegrant			
		Ac-di-Sol® (0.5% w/w)	Ac-di-Sol® (1.0% w/w)	Ac-di-Sol® (0.5% w/w)	Ac-di-Sol® (1.0% w/w)
Binder	Kollidon® VA 64 (1.5% w/w)	Beads Formulation 1	Beads Formulation 2	Beads Formulation 1	Beads Formulation 2
	Kollidon® VA 64 (3% w/w)		Dry powder + Granule Formulation 2		Dry powder + Granule Formulation 2
		Dry powder + Granule Formulation 1		Dry powder + Granule Formulation 1	
	Kollidon® VA 64 (5% w/w)	Dry powder + Granule Formulation 3		Dry powder+ Granule Formulation 3	
			Dry powder + Granule Formulation 4		Dry powder + Granule Formulation 4

The formulations (4 formulations for each filler) as indicated in Table 3.2 were used to prepare dry powder and granule formulations. Each formulation was also punched with two types of punches (9 mm diameter) namely flat faced and concave. Formulation for the bead formulations also started off with 8 formulations (4 formulations for each filler), but the formulations were adjusted because of tableting difficulties. During the process of compressing the tablets it was clear that the beads used for compression of tablets were too hard. After the tablets were compressed and ejected from the die, the tablets disintegrated immediately into the original bead particles and tablets were therefore not able to withstand normal handling. Based on these initial results, only formulation 1 and 2 were used to manufacture tablets with Avicel® and MicroceLac® beads, respectively. Formulation 1 and 2 with a 1.5% w/w Kollidon VA 64 concentration were used to formulate beads for compression. These bead formulations produced tablets of acceptable quality and were able to withstand normal handling. The success of these tablets is most likely related to the lower binder concentration that rendered softer beads that could be successfully compressed into tablets.

In Table 3.4, the abbreviations that were used to identify the different formulations are given. These abbreviations were used to refer to and distinguish between the different formulations for discussion purposes.

Table 3.3: Table of abbreviations used in figures 4.4 to 4.10 to identify the different formulations

Abbreviation	Description
A	Avicel®
M	MicroceLac®
DP F1	Dry powder formula 1
DP F2	Dry powder formula 2
DP F3	Dry powder formula 3
DP F4	Dry powder formula 4
G F1	Granules prepared from formula 1
G F2	Granules prepared from formula 2
G F3	Granules prepared from formula 3
G F4	Granules prepared from formula 4
B F1	Beads prepared from formula 1
B F2	Beads prepared from formula 2
A FF	Avicel® flat faced tablets
A C	Avicel® concave tablets
M FF	MicroceLac® flat faced tablets
M C	MicroceLac® concave tablets

Table 3.4: Table of abbreviations identifying different formulations used in the figures and tables in chapter 4 to explain the results of powder flow and tablet evaluation tests

Abbreviation	Description
ADP	Avicel® dry powder
AG	Avicel® granules
AB	Avicel® beads
MDP	MicroceLac® dry powder
MG	MicroceLac® granules
MB	MicroceLac® beads
ADPF1 - 4	Avicel® dry powder formulation 1 to 4
AGF1 - 4	Avicel® granule formulation 1 to 4
ABF1 - 4	Avicel® bead formulation 1 to 4
MDPF1 - 4	MicroceLac® dry powder formulation 1 to 4
MGF1 - 4	MicroceLac® granules formulation 1 to 4
MBF1 - 4	MicroceLac® bead formulation 1 to 4
ADPFF1 - 4	Flat faced tablet formulations 1 to 4 containing Avicel® dry powder particles
AGFF1 - 4	Flat faced tablet formulations 1 to 4 containing Avicel® granule particles
ABFF1 - 4	Flat faced tablet formulations 1 to 4 containing Avicel® bead particles
MDPFF1 - 4	Flat faced tablet formulations 1 to 4 containing MicroceLac® dry powder particles
MGFF1 - 4	Flat faced tablet formulations 1 to 4 containing MicroceLac® granule particles
MBFF1 - 4	Flat faced tablet formulations 1 to 4 containing MicroceLac® bead particles
ADPCF1 - 4	Concave tablet formulations 1 to 4 containing Avicel® dry powder particles
AG CF1 - 4	Concave tablet formulations 1 to 4 containing Avicel® granule particles
AB CF1 - 4	Concave tablet formulations 1 to 4 containing Avicel® bead particles
MDP CF1 - 4	Concave tablet formulations 1 to 4 containing MicroceLac® dry powder particles
MG CF1 - 4	Concave tablet formulations 1 to 4 containing MicroceLac® granule particles
MB CF1 - 4	Concave tablet formulations 1 to 4 containing MicroceLac® bead particles

3.5 THE MIXING PROCESS

A critical step in the formulation process of solid oral pharmaceutical products such as tablets is the mixing process of the dry powders and in some cases the mixing of granules and beads. It is important that uniform dispersion of the particles of every pharmaceutical ingredient or excipient takes place during the mixing process. This will provide a batch of dosage form units with a uniform dosage concentration in each unit (Ervasti *et al.*, 2015:291).

The mixer used to perform all mixing processes during this study was the Turbula® mixer (Type T2C, Willy A Bachofen, Germany) (See Figure 3.1). The mixing speed varied between 69 and 47 rpm (revolutions per minute) depending on the type of material mixed (powder/granules/beads).



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

3.6 POWDER, GRANULE AND BEAD FORMULATIONS

3.6.1 POWDER FORMULATION

The direct compression formulations formulated with dry powders consisted of 16 formulations (8 formulations per filler for concave and flatfaced tablets respectively) (refer to Table 3.2). The excipients of each formulation were weighed off correctly and carefully with a Mettler Toledo® electronic balance (Mettler, Germany, Model MS205DU). The different powders for each formulation was then combined and mixed in a Turbula® mixer at 69 rpm

for a duration of 5 min and stored in a cool, dry and dark place until direct compression could commence.

3.6.2 THE GRANULATION PROCESS

Granulation of powder mixtures is known to improve powder flow as well as improve dosage form uniformity. A total of eight different formulations were granulated (refer to Table 3.2), depending on the filler (Avicel® PH 101 and MicroceLac® 100) and concentration of the disintegrant (Ac-di-sol®) and the binder (Kollidon® VA 64).

The filler together with the API (pyridoxine hydrochloride 20% w/w) and the disintegrant was weighed and placed in a glass bottle for mixing. The powder mass was mixed using a Turbula® mixer (Type T2C, Willy A Bachofen, Germany). The mixing speed was set at 69 rpm and mixing time was 5 min.

The mixed powder was transferred into a clean mortar. The wetting liquid that was prepared comprised of the binder (either 3 or 5% w/w Kolidon® VA 64 depending on the formulation) dissolved in ethanol 99% v/v. The binder was mixed thoroughly with the ethanol until no undissolved particles could be observed macroscopically in the wetting liquid. The wetting liquid was then added slowly to the powder mass while stirring with a pestle.

This wetted powder mass was subsequently passed through a size 20 mesh screen using a steel spatula. Long spaghetti like strains were then placed in an oven to dry at $60 \pm 1^\circ\text{C}$ for 30 – 45 minutes. These dried strains were then passed through the 20 mesh screen again to render granules. Granules were transferred to a glass bottle. A lubricant (magnesium stearate) was finally added to the granules and mixed for 5 min at 47 rpm in a Turbula® mixer. A slower mixing speed was employed to keep the granules intact during the mixing process. Granules were stored in isolated glass bottles and stored in a cool, dry and dark place until compression.

3.6.3 THE PRODUCTION OF BEADS

Production of beads is one of the most effective ways to improve the flowability of powder mixtures intended for tableting by improving particle size and shape uniformity. Beads were produced using the process of extrusion-spheronisation.

The different excipients (depending on the formulation as shown in Table 3.2) were accurately weighed. Powders were placed in a glass bottle and mixed with a Turbula® mixer (Type T2C, Willy A Bachofen, Germany) for 5 min at 69 rpm. After mixing, the powder mixture was transferred to a clean mortar. The wetting liquid consisted of a mixture of ethanol 99% v/v and distilled water (50:50). For the MicroceLac® formulations, the volume of

wetting liquid varied between 40 and 50 ml for 100 g of powder mixture. For the Avicel® formulations the volume of wetting liquid ranged between 77 and 90 ml for 100 g of powder mixture. The ethanol:water ratio was 80:20 for all the Avicel® formulations. The wetting liquid was added very slowly to the powder mixture using a burette while stirring continuously with a pestle.

After addition of the wetting liquid to the powder mixtures and the correct texture was obtained, the powder mass was added to the pan of the Caleva® Extruder (Type 20 Caleva®, Caleva Process Solutions, England). Extrusion was done at 25 rpm using a 1 mm screen. The extrusion process rendered spaghetti-like strands in the bottom pan (See Figure 3.2a) which were subsequently added to the Caleva® spheroniser (Caleva Process Solutions, England) (See Figure 3.2b). The strands were now spheronised into uniform pellets/beads using the spheronising action. The spheroniser was set at 1550 rpm for 5 min. Upon collection of the beads, they were freeze-dried for an hour at -80°C and freeze-dried using a VirTis bench top freeze drier (SP Industries Company). The beads were freeze-dried for 24 h and stored in a cool, dry and dark environment until compression (See Figure 3.2c).



a



b



a

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

3.7 SCANNING ELECTRON MICROSCOPY

The morphology of the raw materials used in this study as well as the powder, granule and bead formulations was investigated using a Quanta 250 FEG electron microscope (FEI Company, Netherlands).

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

3.8 PARTICLE SIZE ANALYSIS

The size and shape of particles as well as the size distribution of particles influence the flow behaviour and compaction properties of the particles of powders, granules or beads. As a consequence the quality and/or performance of a dosage form will be affected. Therefore, particle size analysis is a useful tool in pharmaceutical formulation and manufacturing (Horiba Instruments, 2014).

Particle size analysis was conducted on all powder, granule and bead formulations with a Malvern Mastersizer 2000 fitted with a Hydro 2000SM dispersion unit (Malvern Instruments, Malvern, England). The small volume dispersion unit was filled with 100 ml ethanol (dry powder and bead formulations) or 100 ml cyclohexane (granule formulations) and a background measurement was taken to compensate for electrical interference as well as possible interference from the dispersion medium. Upon completion of the background measurement, a sample of the appropriate formulation (powder, granule or bead) was added to the dispersion unit. A sufficient quantity of the sample was added to obtain an obscuration of between 10 and 20%. After a suitable obscuration was obtained, the particle size of the sample was measured. Each measurement consisted of 12000 sweeps. The particle size distribution of each formulation was measured in triplicate. The particle size distribution of the sample was calculated with the Malvern software.

3.9 FLOWABILITY CHARACTERISATION

3.9.1 ANGLE OF REPOSE (AOR)

A 100 g mass of the powder/granule/bead formulations was emptied into a funnel that was closed with a shutter at the bottom. The funnel was fixed at a height of 10 cm. The shutter was opened and the particles were allowed to flow through under the influence of gravity onto the collection plate under the funnel and the powder then formed a heap on the collection plate. Thereafter the diameter and the height of the powder, granule or bead heap were measured with a graduated ruler (See Figure 3.3). The AOR test was done in triplicate.



Figure 3.3: Image depicting the angle of repose apparatus

The Angle of repose was calculated with the following formula:

$$\tan \theta = \frac{H}{R} \quad \text{Equation 1}$$

Where θ is the angle of repose,

H, the height of the powder heap, and

R, the radius of the powder heap.

The AOR was calculated to characterise the flow properties of each formulation used in the study. Powders having an AOR of 30° or less usually exhibit good flow with little or no cohesiveness. An AOR of $30 - 45^\circ$ indicates that cohesiveness is present. An AOR of $45 - 55^\circ$ indicates true cohesiveness and an AOR of $\geq 55^\circ$ indicates that the powder shows excessive cohesive behaviour (Geldart *et al.*, 2006:4). All tests were done according to the specifications of the British Pharmacopeia (BP) (2015).

3.9.2 CRITICAL ORIFICE DIAMETER (COD)

The COD test consisted of tapered copper discs stacked on top of each other. Each disc had a different diameter size. The discs were stacked on top of each other starting with the smallest diameter disc at the bottom and the largest at the top of the stack, providing a funnel like shape (due to the tapering) when looking from the top of the stack. A shutter was fitted to the top of the disc stack to control the flow of the particles when starting the test (See Figure 3.4).



Figure 3.4: Image depicting the copper discs and the shutter used

A funnel was also fitted on top of the shutter to hold the powder before starting the test (See Figure 3.5). Tapered copper discs were stacked on top of a stand at a fixed height. The shutter was opened and the 100 g powder/granule/bead mass was permitted to flow through the funnel. The discs were removed one by one until flow of the powder/granule/bead mass started to flow through an orifice. When powder flow occurred without any blockage, the diameter of the disc was recorded. This diameter represented the COD. The test was done in triplicate and according to the specifications of the BP (2015).



Figure 3.5: Image depicting the COD apparatus with funnel fitted to the top

3.9.3 POWDER DENSITY

A sample (100 g) from each of the powder/granule/bead formulations was placed in a 250 ml graduated measuring cylinder. The bulk volume (V_0) was recorded. The cylinder with the powder in it was placed on an Erweka® powder density apparatus (Type SVM 223, Erweka® GmbH, Heusenstamm, Germany) which was set to vibrate for 180 s (See Figure 3.6). The tapped volume (V_{tap}) was recorded whereafter the bulk density (ρ_{bulk}) and the tapped density (ρ_{tap}) were calculated with equation 2 and 3, respectively:

$$\rho_{bulk} = \frac{M}{V_0} \quad \text{Equation 2}$$

With ρ_{bulk} , the bulk density of the powder,

M, the mass of the powder, and

V_0 , the bulk volume of the powder.

$$\rho_{tap} = \frac{M}{V_{tap}} \quad \text{Equation 3}$$

Where ρ_{tap} , is the tapped density of the powder,

M, the mass of the powder, and

V_{tap} , is the tapped volume of the powder (Staniforth and Aulton, 2007:171).

3.9.3.1 Hausner ratio

This indirect method describes the inter-particulate friction between powder particles. Powders with less friction between the particles will have better flow, but powders with more friction between the particles will show poor flow. This test was conducted according to the specifications of the BP (2015). The Hausner ratio was calculated with equation 4 (Staniforth and Aulton, 2007:176).

$$\text{Hausner ratio} = \frac{\rho_{tap}}{\rho_{bulk}} \quad \text{Equation 4}$$

3.9.3.2 Carr's index

Carr's index (or % compressibility) is also an indirect method for determining the flowability of a powder. This test was conducted according to the specifications of the BP (2015). Equation 5 was used to calculate Carr's index (Staniforth and Aulton, 2007:177).

$$\% \text{ compressibility} = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \quad \text{Equation 5}$$



Figure 3.6: Image depicting the Erweka[®] density apparatus

3.9.4 FLOW RATE

Flow rate was calculated using an Erweka[®] granulate flow tester (Type GTL, Erweka[®]GmbH, Heusenstamm, Germany). A funnel was filled with 100 g of powder/granule/bead formulation. A shutter was consequently opened and the time taken by the powder/granule/bead mass to flow through the fixed diameter, at the bottom of the funnel was recorded. The diameters used were 10 and 15 mm. The test was done in triplicate for each diameter (See Figure 3.7). This study was conducted according to the specifications of the BP (2015).



Figure 3.7: Image depicting the Erweka[®] granulate flow tester

3.10 COMPRESSION OF TABLETS

Tablets were compressed using a Korsch® XP1 single station tablet press (Korsch AG, Berlin, Germany) connected to a PharmaResearch® unit (Korsch AG, Berlin, Germany) (See Figure 3.8a and 3.8b). Two hundred tablets of each formulation were compressed. Tablets were compressed using flat faced as well as concave punches with a 9 mm diameter. Two different punch types were used to determine whether punch-type has an influence on the tableting process of the different types of particles. The weight of the tablets was kept constant at 250 mg throughout the study.



a



b

Figure 3.8: Images depicting the a) Korsch XP1® tablet press, b) PharmaResearch® unit

Powder/granules/beads were poured into the filling shoe, prior to compression. The first few test tablets were compressed manually using the turning wheel to ensure the correct tablet weight and acceptable tablet hardness were used, whereafter the automatic functionality of the press was used to compress 200 tablets of each formulation. The first 10 tablets of each formulation were discarded. This method was used for all formulations. After compression, the tablets were placed in a glass bottle, sealed with a lid and placed in a dark environment.

3.11 TABLET EVALUATION

3.11.1 WEIGHT VARIATION

Twenty tablets were randomly selected, each tablet was dusted and individually weighed individually with a Mettler Toledo® balance (Mettler, Germany, Model MS205DU). The average weight of the twenty tablets was calculated and the specifications of the BP (2015)

were used. Furthermore, the standard deviation (SD) and the percentage relative standard deviation (%RSD) were also calculated. The percentage relative standard deviation (%RSD) was calculated using equation 6.

$$\% RSD = \frac{SD}{Average} \times 100$$

Equation 6

3.11.2 DISINTEGRATION

Six tablets of each formulation were randomly chosen to be used in the disintegration test. This test was conducted with an Erweka® disintegration apparatus (Type ZT 323, Erweka® GmbH, Heusenstamm, Germany). This disintegration test was conducted according to the specifications of the BP (2015). The disintegration medium used for this test was distilled water kept at a constant temperature of $37 \pm 1^{\circ}\text{C}$. A thermostat was fitted to the test unit to regulate the temperature throughout the testing period. As the disintegration apparatus was equipped with three separate compartments, each comprised of six individual glass tubes, it was possible to perform disintegration testing on three different formulations at a time. Tablets from one formulation were individually placed into the glass tubes of one of the three compartments whereafter the disintegration test commenced (See Figure 3.9a). The different disintegration times for each of the six tablets of each formulation were recorded separately. The test was halted when no tablet fragments were left to be seen on the screen (See Figure 3.9b).



a



b

Figure 3.9: Images depicting the a) six tube compartment of the disintegration apparatus, b) screen at the bottom of the glass tubes

3.11.3 CRUSHING STRENGTH, THICKNESS AND DIAMETER

Ten tablets were randomly selected. The thickness, diameter and the crushing strength of each of these ten tablets were measured using the Erweka® crushing strength apparatus (Type: TBH 425 TD, Erweka® GmbH, Heusenstramm, Germany). The apparatus is depicted in Figure 3.10.



Figure 3.10: Image depicting the Erweka® crushing strength apparatus

3.11.4 FRIABILITY

Friability testing was conducted according to the specifications of the BP (2015). Ten tablets from each formulation were randomly selected. The tablets were individually dusted to remove any dust or particles from the tablets, whereafter the total weight of the ten tablets was determined with a Mettler Toledo® balance (Mettler, Germany, Model MS205DU). After weighing the tablets, they were placed in the drum of the Erweka® friabilitor (Type: TAR 220, Erweka® GmbH, Heusenstramm, Germany). The friabilitor was switched on for four minutes, rotating at 25 rpm. After four minutes the tablets were weighed again after careful dusting (see Figure 3.11).



Figure 3.11: Image depicting the Erweka® friabilitor

The percentage friability was calculated using equation 7. The percentage friability gives an indication of the weight lost during the friability test.

$$\% \text{ Friability} = \frac{m_1 - m_2}{m_1} \times 100 \quad \text{Equation 7}$$

Where m_1 , is the initial total mass of the ten tablets and m_2 , is the total mass of the ten tablets after the test was conducted.

3.11.5 DISSOLUTION

3.11.5.1 Apparatus

Dissolution studies were conducted, using a six station Distek® dissolution apparatus (Model: Distek® 2500, Distek, North Brunswick, NJ, USA) (See Figure 3.12). The apparatus was fitted with the USP specified paddles. Samples were taken manually. The UV (Ultra violet) absorbancies of each of the samples were measured spectrophotometrically (Specord® Type: 200 Plus, Analytik Jena AG, Germany).



Figure 3.12: Image depicting the Distek® dissolution apparatus

3.11.5.2 Standard curve

Standard curves were constructed daily. A stock solution containing 50 mg of pyridoxine hydrochloride in 100 ml of the 0.1 M HCl solution was prepared daily to be used for constructing a standard curve. From the stock solution, 6 standard solutions were prepared consisting of concentrations of 2, 5, 10, 15, 25; and 50 $\mu\text{g} \cdot \text{ml}^{-1}$. The volumetric flasks were wrapped with tin foil and the room was kept dark to avoid photosensitive breakdown of the pyridoxine HCl. The UV-absorbance of the standard solutions was determined at a

wavelength of 291 nm using a Specord spectrophotometer. Linear regression was used to confirm that Beer's law was obeyed at the specified concentration range.

3.11.5.3 Dissolution method

The dissolution media used were 600 cm³ 0.1 M HCl (pH = 1.5) for the first 2 hours of the dissolution study whereafter the volume was adjusted to 900 ml with phosphate buffer (pH6.8). The temperature was kept at 37 ± 1°C and a stirring rate of 50 rpm was used. Samples of 5 ml were taken at t = 2, 5, 10, 15, 30, 60, 90, 120, 180 and 240 minutes. The stirring rate was then adjusted to 200 rpm and a final sample was taken. The samples were placed in glass tubes ready for analysis of the drug concentration in the withdrawn samples. Each sample was diluted using 1.5 ml of the sample and diluting it with 1.5 ml of the dissolution media. After withdrawal of the samples, the amount withdrawn was replaced with fresh dissolution media to ensure a constant volume. Corrections for the quantity of pyridoxine lost through withdrawal were done by means of equation 5.5.

$$CP_{(t)} = P_{(t)} + \frac{V_m}{V_d} \sum_{t=1} CP \quad \text{Equation 8}$$

Where $CP_{(t)}$, is the corrected peak area of sample at time t , $P_{(t)}$ is the peak area of sample at time t , V_d , is the sampling volume, V_m , is the dissolution medium volume, and $\sum_{t=1} CP$, is the sum of all the corrected peak areas prior to the sample at time t .

3.12 STATISTICAL ANALYSIS

Data was evaluated for statistically significant differences by means of ANOVA.

4 CHAPTER 4: SOLID PARTICLE FORMULATION

FLOWABILITY AND TABLET EVALUATION RESULTS

4.1 INTRODUCTION

In this chapter, the flowability results of the different particle type formulations (powder/granule/bead) as well as the physical properties and dissolution behaviour results of the tablets prepared from the different particle formulations are presented and discussed.

Optimal flow properties of powders are one of the key aspects in developing a safe, stable and effective tablet dosage form. Adequate flow of the particles of the powder formulation is of the utmost importance for compression to be successful. Particle formulations presenting with good flow will allow the compression process to proceed fast and efficient, producing tablets with suitable quality for effective drug delivery (Sinka *et al.*, 2004:27-28).

During the formulation of dosage forms, every step in the formulation and production process has an effect on the properties of the final dosage form. It is therefore important to ensure that every step of the formulation process is carefully considered and evaluated to ensure that a dosage form with the optimal performance is produced (Tejedor *et al.*, 2015:315-316).

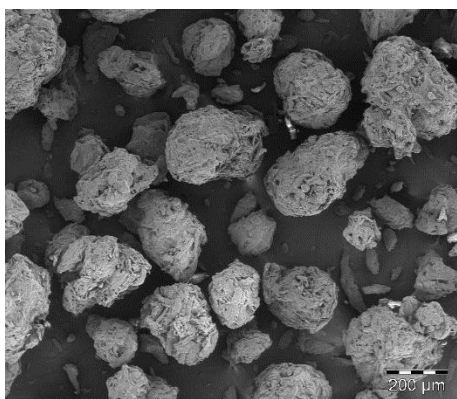
In this study, formulations of MicroceLac[®] and Avicel[®] containing powder, granulation and bead formulations were used to produce tablets with flat faced and concave punches. Due to difficulties during tableting, only selected formulations with decreased binder concentration were suitable for preparing beads that rendered tablets of acceptable mechanical strength as discussed in section 3.4.

4.2 SCANNING ELECTRON MICROSCOPY

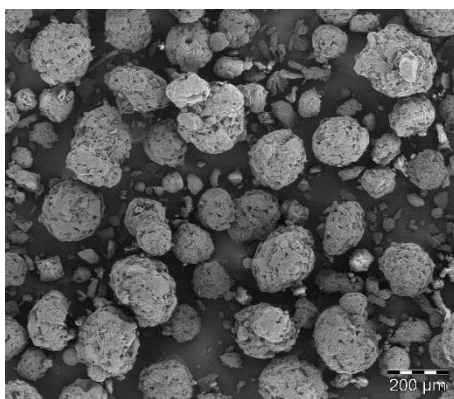
Micrographs of the particles of the individual ingredients (i.e. active ingredients and excipients) used in the formulations investigated in this study are depicted in Figure 4.1a – f. An exception for notification is that an image of Avicel® PH101 was not included because it is similar to Avicel® PH200 in shape, while the particles only differ in size.

It is clear from the micrographs (Figure 4.1) that the different fillers exhibit a different particle size, shape and texture. The Avicel® raw material is comprised of larger particles that are less spherical compared to that of the MicroceLac® particles. Even the granule and bead particles produced with different fillers exhibited observable differences with respect to shape, size and texture. It appears that the Avicel®-containing dry powder formulations also show less particle size variation than the MicroceLac®-containing dry powder formulations.

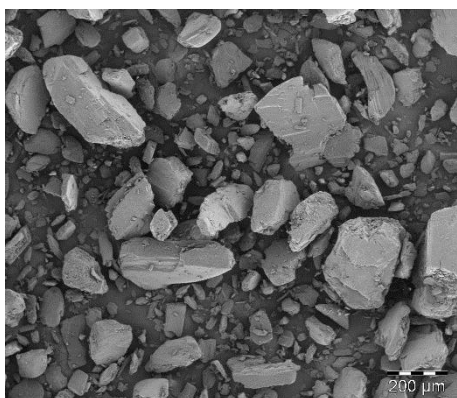
In Figure 4.2a to c, the different particle types (i.e. powder particles, granules and beads) used in this study are depicted. Only one micrograph of each particle type formulation was included because the other formulations exhibited similar images with no observable differences.



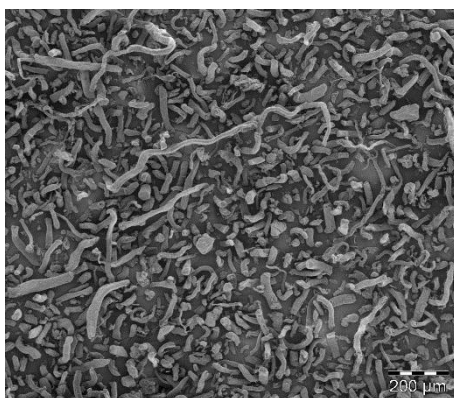
a



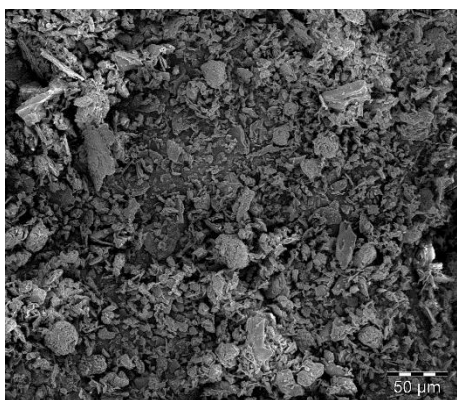
b



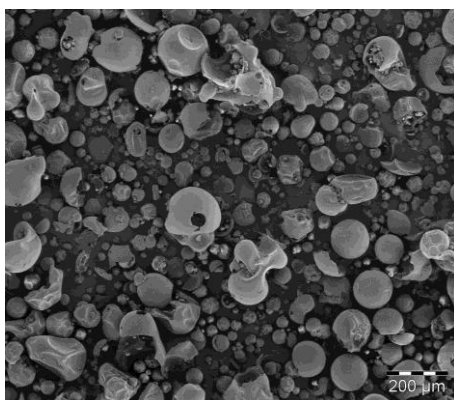
c



d

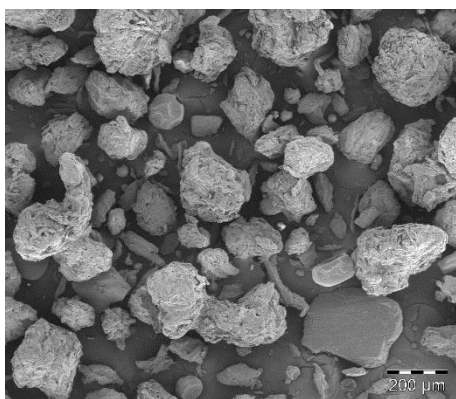


e

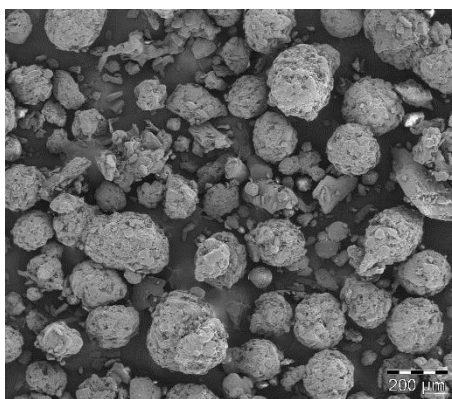


f

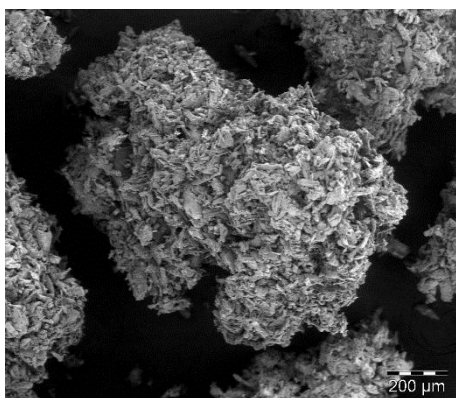
Figure 4.1: Micrographs depicting the particles of a) Avicel® PH200, b) MicroceLac® 200 c) pyridoxine hydrochloride d) Ac-di-sol® e) magnesium stearate and f) Kollidon® VA 64



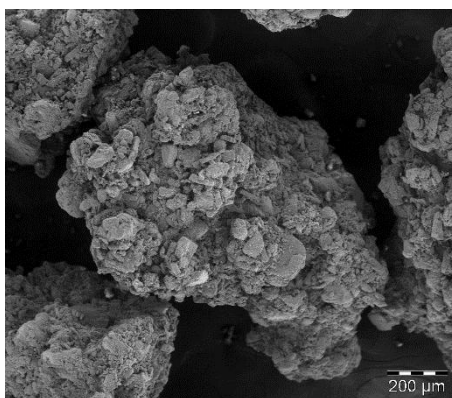
a (I)



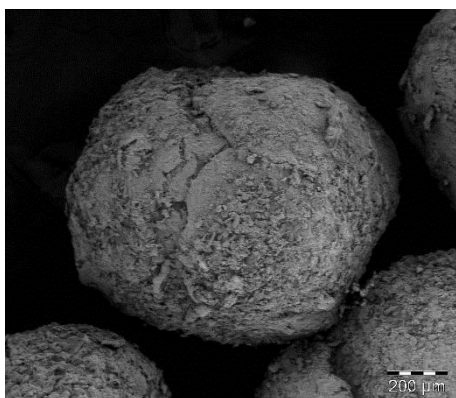
a (II)



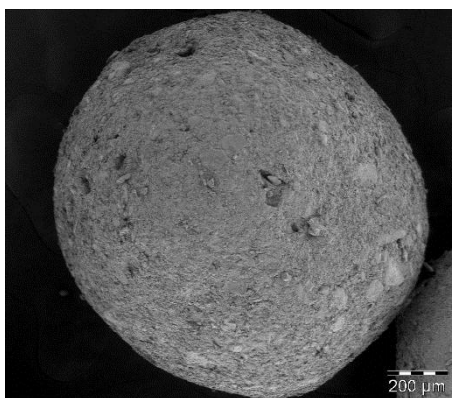
b (I)



b (II)



c (I)



c (II)

Figure 4.2: Micrographs depicting a) (I) Avicel® dry powder formulation particles, a) (II) MicroceLac® dry powder formulation particles, b) (I) Avicel®-containing granules, b) (II) MicroceLac®-containing granules, c) (I) Avicel®-containing beads, c) (II) MicroceLac®-containing beads

It is clear from Figure 4.2b (I) and (II) that the textures of the two granule types presented differ. The MicroceLac®-containing granules appear to have a more ragged surface with

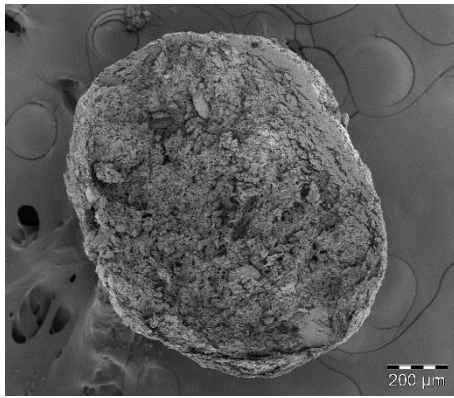
protruding points. This rough shape and protruding points might have a negative influence on powder flow. Although the Avicel®-containing granules do not have a smooth surface, there are no protruding points that are visible. The size and overall shape of the particles depicted in the two micrographs, however, are similar.

In Figure 4.2c (I) and (II) Avicel®- and MicroceLac®-containing beads can be seen. In contrast to the granules, the Avicel®-containing bead particles show a more rough textured surface, with more micropores visible when compared to that of the MicroceLac®-containing bead particle. Figure 4.3 provides a view of the internal structure of the respective beads. In these images it is clear that both bead particles show an evenly dense matrix structure inside the beads, with some micropores and voids visible.

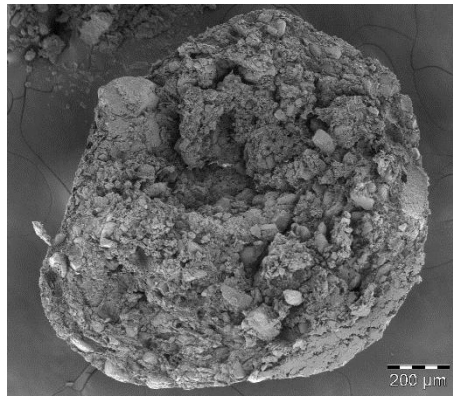
Considering all the particle types depicted in Figure 4.2, the bead particles show the most spherical particles with the smoothest surface geometry. The MicroceLac®-containing bead particles exhibited the smoothest surfaces. The bead particles also possessed the largest size, relative to the other two particle types. The granule particles showed the most rugged surface textures, specifically the MicroceLac®-containing granule particles. The dry powder formulations were comprised of the smallest particles, specifically MicroceLac®-containing dry powder formulations.

The rationale for formulating granule and bead particles is to increase average particle size and decrease particle size distribution in order to improve the flow properties of formulations and consequently improving the tablet manufacturing process. It is clear from the micrographs that an increase in particle size was achieved with both granule and bead type formulations. Furthermore, smoother surface textures as well as a decrease in particle size distribution were achieved with the bead particles.

In Figure 4.3a and b, micrographs of an Avicel®-containing bead cut in half and a MicroceLac®-containing bead cut in half are shown. These micrographs depict a detailed picture of the internal structure of each bead type.



a



b

Figure 4.3: Micrographs depicting the internal structure of a) an Avicel®-containing bead and, b) a MicroceLac®-containing bead

4.3 PARTICLE SIZE ANALYSIS

In Table 4.1 a summary of the data obtained from the particle size analyses of the different particle type mixtures are presented.

Table 4.1: Summary of the particle size analyses results of the different MicroceLac®- and Avicel®-containing formulations

Formulation	Average span	± SD	Average volume mean diameter D[4.3] µm	± SD	Average median particle size distribution d(0.5) µm	± SD
ADP F1	1.74	0.015	211.81	1.646	192.80	1.758
ADP F2	1.62	0.027	229.52	2.569	213.05	2.988
ADP F3	1.65	0.012	212.83	1.943	193.44	2.207
ADP F4	1.57	0.011	231.19	1.937	213.84	1.467
AVG	1.65	0.016	221.34	2.024	203.28	2.105
MDP F1	1.58	0.018	181.36	1.904	166.14	1.397
MDP F2	1.63	0.018	188.97	1.124	174.10	1.303
MDP F3	1.64	0.018	180.02	1.115	166.01	1.423
MDP F4	1.60	0.013	186.20	0.412	176.95	7.666
AVG	1.61	0.017	184.14	1.139	170.80	2.947
AG F1	1.82	0.058	597.76	19.933	572.74	18.580
AG F2	1.72	0.108	644.69	14.275	621.57	13.918
AG F3	1.62	0.098	665.17	31.215	660.78	30.998
AG F4	1.45	0.309	674.54	39.168	668.71	32.746
AVG	1.65	0.143	645.54	26.148	630.95	24.060
MG F1	1.82	0.012	702.69	6.917	663.31	4.493
MG F2	1.32	0.033	797.48	13.227	748.27	9.166
MG F3	1.68	0.031	751.93	11.820	716.52	12.262
MG F4	1.86	0.016	639.47	18.486	609.32	18.026
AVG	1.67	0.023	722.89	12.612	684.35	10.987
AB F1	0.90	0.037	1055.27	7.691	1008.96	10.062
AB F2	1.11	0.010	910.65	6.705	850.83	7.293
AVG	1.00	0.023	982.96	7.198	929.90	8.677
MB F1	1.37	0.124	816.08	27.415	781.67	24.022
MB F2	1.14	0.061	804.82	34.450	768.91	29.563
AVG	1.23	0.093	810.45	30.932	775.29	26.793

*ADP = Avicel® dry powder formulation; *MDP = MicroceLac® dry powder formulation; *AG = Avicel® granule formulation; *MG = MicroceLac® granule formulation; *AB = Avicel® bead formulation; *MB = MicroceLac® bead formulation; *AVG = Average. *SD = Standard deviation

It is evident from the data in Table 4.1 that the Avicel® dry powder formulations rendered mean particle size values between 211.81 ± 1.646 – 231.19 ± 1.937 µm. The MicroceLac® dry powder formulations had mean particle size values similar to that of the Avicel® dry powder formulations ranging between 181.36 ± 1.904 and 186.20 ± 0.412 µm. Although there is a ± 40 µm difference in mean particle size between the Avicel® and MicroceLac® formulations, the influence of this difference on powder flow should be negligible as powders

exhibiting a particle size between 100 and 250 μm usually exhibits free flow (Staniforth and Aulton, 2007:170).

The granule formulations exhibited mean particle size values of $597.76 \pm 19.933 - 674.54 \pm 39.168 \mu\text{m}$ and $639.47 \pm 18.486 - 797.48 \pm 13.227 \mu\text{m}$ for the Avicel® and MicroceLac® granule formulations, respectively. As is expected, the granule formulations exhibited larger mean as well as median particle size values in comparison to the dry powder formulations due to the granulation process – confirming the SEM results. The bead formulations possessed the largest mean particle size values. The mean particle size values ranged between $910.65 \pm 6.705 \mu\text{m} - 1055.27 \pm 7.691$ and $804.82 \pm 34.450 - 816.08 \pm 27.415 \mu\text{m}$ for the Avicel® and MicroceLac® bead formulations, respectively. The phenomenon that the bead formulations exhibited the largest mean and median particle size values are attributable to the fact that the bead formulations were prepared using a screen with 1 mm diameter perforations.

In terms of particle size distribution width, it can be noted that the dry powder and granule formulations exhibited similar distribution widths, irrespective of the filler being used. The mean span values ranged between 1.614 and 1.672. Similar distribution widths are likely due to the fact that the different excipients used in preparing the dry powder formulations had different particle size distributions. In the case of the granule formulations, the process of granulation rendered a distribution of particles due to the presence of smaller powder particles in between the granules. It should be noted that the bead formulations exhibited narrower distribution widths compared to the dry powder and granule formulations as indicated by span values ranging between 0.900 ± 0.037 and 1.374 ± 0.124 .

4.4 FLOWABILITY CHARACTERISATION

Flowability was characterised in terms of angle of repose (AOR), critical orifice diameter (COD), Hausner ratio, Carr's index and the flow rate (10 mm and 15 mm orifice). In Table 4.2, a summary of the flowability data of the different particle type formulations are presented. Each of the flow test results are discussed in the sections below.

Table 4.2: Summary of the flowability results of the different particle formulations (i.e. dry powders, granules and beads) prepared from Avicel® and MicroceLac®

Formulation	Avicel® and MicroceLac® flowability results										
	Angle of repose (°)	± SD	Critical orifice diameter (mm)	Flow rate 10 mm orifice (gram/sec)	± SD	Flow rate 15 mm orifice (gram/sec)	± SD	Hausner ratio	± SD	Carr's index (%)	± SD
Avicel® dry powder											
F1	23.23	0.785	1.5	4.73	0.153	12.40	0.265	1.09	0.010	8.45	1.760
F2	23.98	0.394	1.5	4.07	0.115	11.40	0.265	1.13	0.008	11.11	0.434
F3	25.41	1.316	1.5	3.77	0.058	10.00	0.300	1.16	0.006	13.93	0.607
F4	25.95	0.803	1.5	3.20	0	9.30	0.400	1.16	0.004	13.57	0.206
MicroceLac® dry powder											
F1	20.52	1.113	3	3.83	0.058	10.60	0.361	1.22	0.010	18.11	0.678
F2	21.07	0.815	3	3.53	0.058	10.77	0.577	1.21	0.008	17.54	0.542
F3	22.33	0.454	3	3.17	0.115	9.23	0.208	1.20	0.006	16.54	0.386
F4	22.52	0.523	3	2.97	0.058	8.97	0.723	1.23	0.004	18.60	0.236
Avicel® granules											
F1	28.82	1.960	8	11.67	0.115	35.70	0	1.23	0.013	18.78	0.838
F2	29.87	0.551	8	11.63	0.153	2.87	0.058	1.23	0.012	18.41	0.832
F3	29.78	0.470	12	11.00	0.100	34.40	0.458	1.24	0.013	19.54	0.851
F4	31.17	1.060	12	11.37	0.321	34.80	0.900	1.24	0.005	19.62	0.348
MicroceLac® granules											
F1	28.15	3.498	12	3.87	0.058	11.90	0.608	1.22	0.011	18.30	0.749
F2	30.09	0.816	12	3.10	0	10.30	0	1.23	0.015	18.57	0.963
F3	30.50	1.166	12	0	0	9.70	0.346	1.20	0.005	16.75	0.378
F4	29.03	0.703	12	3.40	0	11.10	0	1.21	0.006	17.13	0.439
Avicel® beads											
F1	18.77	0.839	8	10.77	0.252	32.40	0.755	1.21	0.027	17.10	1.848
F2	18.83	0.808	8	10.23	0.058	31.50	0.800	1.14	0.006	12.04	0.438
MicroceLac® beads											
F1	14.88	0.196	8	11.00	0	33.30	0	1.09	0.012	8.27	1.032
F2	14.43	0.749	8	10.60	0	32.30	0	1.10	0.007	9.23	0.575

*Values reported as average ± SD (n = 3)

*SD values for COD were constant at 0 and therefore not reported in the table.

4.4.1 ANGLE OF REPOSE (AOR)

In Figure 4.4, the angle of repose results for the different particle types are presented.

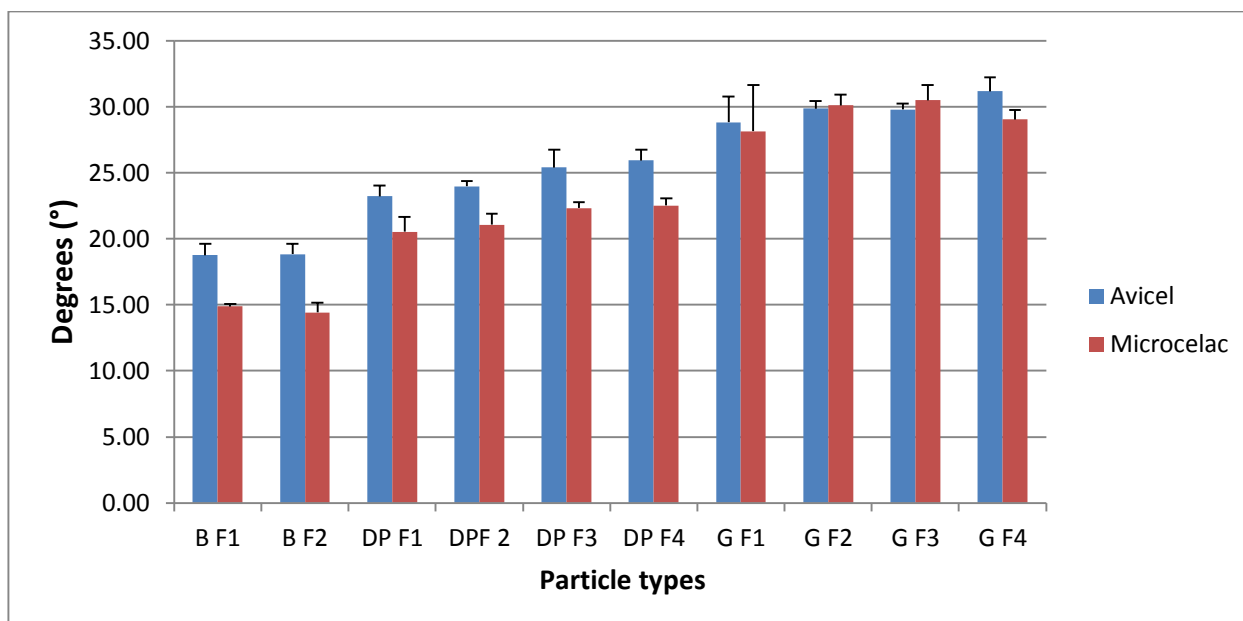


Figure 4.4: Angle of repose results for all formulations. B = bead, DP = dry powder, G = granule

The criteria of the British Pharmacopoeia (2015) for interpretation of the powder flow as related to the angle of repose values are given in Table 4.3. These criteria will be referred to in the discussion that follows.

Table 4.3: Criteria for interpretation of the angle of repose values in terms of powder flow classification

Classification of flow	Angle of repose (°)
Excellent	25 – 30
Good	31 – 35
Fair	36 – 40

It is clear from Table 4.2 and Figure 4.4 that the dry powder formulations presented with AOR values between those of the bead and granule formulations (between 20 and 26°). Irrespective of the particle type, all formulations exhibited average AOR values associated with good to excellent flow (BP, 2015 online).

The highest AOR values were exhibited by the granule formulations (between 28 and 32°). The AOR values for the different granule formulations were relatively similar. According to the AOR results, the granule formulations exhibited the weakest flow properties when compared to that of the dry powder and bead formulations. The granules prepared in this study did not have the smooth surface textures and the spherical shape of the beads (See figure 4.2 b (I) and II)), which have contributed to their poor flowability. Furthermore, the granules' rough surfaces as well as irregular shapes may have caused increased inter-

particular friction and interlocking between the particles resulting in a decreased flowability and an increase in the AOR (Charinpanitkul *et al.*, 2008:665).

According to the data in Table 4.2 and Figure 4.4, the bead formulations exhibited the best flow properties in terms of the AOR results with average values ranging between 14 and 19°. The reasons why the bead formulations exhibited the best flowability include their relatively large particle size, spherical shape and uniformity in terms of size, shape and texture. The beads were notably larger than the dry powder particles. Furthermore, the beads have a spherical shape and they also have more smooth surface textures (see Figure 4.2c (I) and (II)). One of the main reasons for the manufacture of beads is for the improvement of powder flow properties. With the combination of all the above mentioned properties, beads have excellent flow properties that may contribute to the faster and more efficient manufacturing of solid oral dosage forms (Charinpanitkul *et al.*, 2008:665).

The AOR results demonstrated that all the particle formulations prepared in this study have good to excellent flow properties according to the BP classification. The MicroceLac®-containing beads showed very good flow properties. To be more specific, formulation 2 of the MicroceLac® beads exhibited the best flow of all the formulations although only marginally better than the Avicel® bead formulations. However, powder flow characterisation should not be based on a single test such as AOR and therefore other tests were also conducted.

4.4.2 CRITICAL ORIFICE DIAMETER (COD)

The results of the COD test of the different formulations are graphically depicted in Figure 4.5.

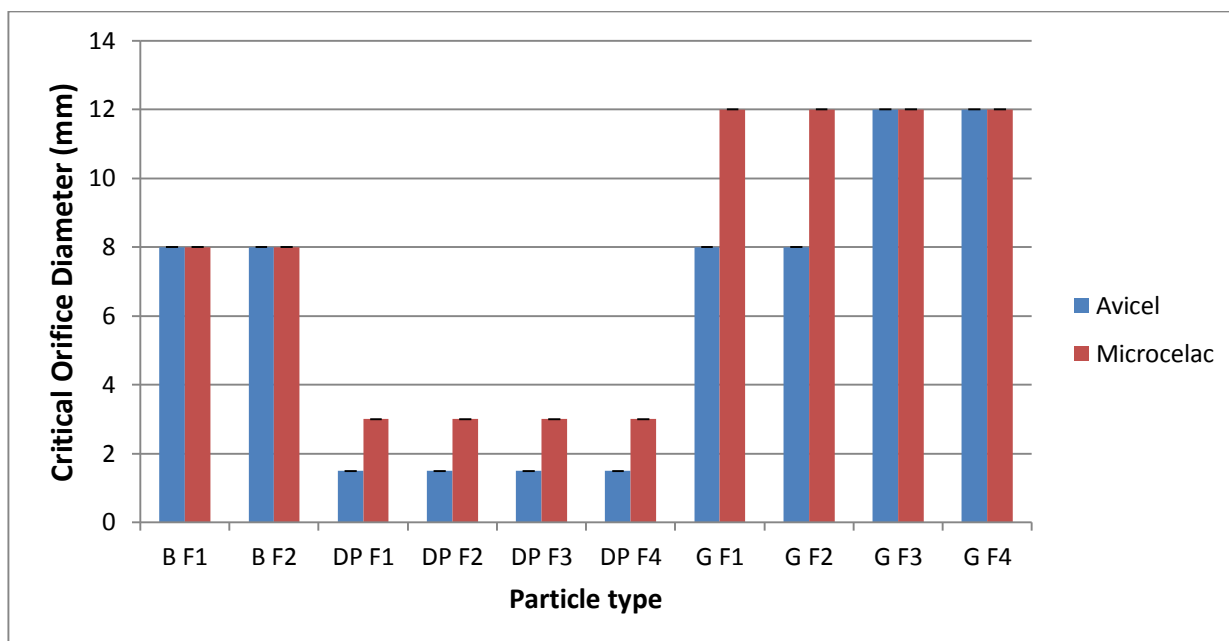


Figure 4.5: Critical orifice diameter results for all formulations. B = bead, DP = dry powder, G = granules

In Table 4.4 an in-house, arbitrary classification with regards to critical orifice diameter is given.

Table 4.4: Criteria for interpretation of the critical orifice diameter results

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

The dry powder formulations showed excellent flow properties according to the criteria outlined in Table 4.4. All Avicel® dry powder formulations flowed through the 1.5 mm diameter orifice, whereas the MicroceLac® dry powder formulations flowed through the 3 mm diameter orifice. This variation in flow properties can be explained in terms of the difference in particle size between the Avicel® PH 200 and the MicroceLac®. From the particle size data in Table 4.1 it can be seen that the average particle sizes of the different Avicel® dry powder formulations were slightly larger compared to the MicroceLac® dry powder formulations. Avicel® dry powder formulations had an average particle size of 221.34 µm compared to an average particle size of 184.14 µm for the MicroceLac® dry powder formulations. Larger particle sizes produce better overall flowability of the formulation because smaller particles tend to develop more cohesive forces between themselves and other particles causing the particles to stick together and this will influence the flowability of the formulation (Zhou *et al.*, 2011:414).

All the MicroceLac® granule formulations as well as two of the Avicel® granule formulations exhibited a COD value of 12 mm. Two of the Avicel®-containing granule formulations exhibited a COD value of 8 mm. All of the granule formulations presented fair flow properties according to the classification in Table 4.4, except for Avicel® granule formulations 1 and 2 that showed good flow properties. Granule formulations exhibited larger COD values compared to the dry powder formulations due the larger size of the granule formulations ($645.54 \pm 16.148 \mu\text{m}$ and $722.89 \pm 12.612 \mu\text{m}$ for the Avicel® and MicroceLac® granule formulations, respectively). Although a higher particle size is associated with improved flow, granule formulations are expected to flow through a larger diameter COD than dry powder formulations purely due to the larger size of the individual granules and the physical space of a small orifice diameter such as 1.5 mm.

All the bead formulations presented COD values of 8 mm. The uniformity in particle size and shape could contribute to the good flow properties. The beads flowed through an orifice of a larger size than the dry powders because the average particle sizes were larger than that of the dry powders. The overall average bead particle size for Avicel® and MicroceLac® bead formulations were $982.97 \pm 7.198 \mu\text{m}$ and $810.45 \pm 30.932 \mu\text{m}$, respectively. A much smaller particle size span was noted for the beads compared to that of the dry powders, which may contribute to improved and constant flow properties (Zhou *et al.*, 2011:414). Although the beads and the granules presented with comparable average particle sizes, their surface texture differed markedly. The beads clearly possessed smoother surface textures than the granules and this allowed the beads to flow through a smaller orifice because interlocking of the particles would be avoided.

From the COD results, it is evident that the particle type had an influence on the flowability. The particle geometry of the solid particles had an influence on the COD results. Although the dry powders consisted of smaller particles, they could still be classified as free flowing according to the arbitrary flow property classification of the COD test above.

It is also evident from Figure 4.5 and the data in Table 4.2 that the type of filler material affected the COD value. This may be attributed to the different properties of the two fillers. Avicel® consisting of MCC (microcrystalline cellulose) and MicroceLac® being a combination of MCC and lactose. Lactose may contribute to cohesive interactions between the particles which may influence the flowability of the filler powder. It is possible that the cohesive forces between the particles may have influenced the flowability of the MicroceLac® dry powder and kept it from flowing freely through the smaller orifice of 1.5 mm (Charinpanitkul *et al.*, 2008:665 – 666).

4.4.3 HAUSNER RATIO

The Hausner ratio data of the different formulations are presented in Figure 4.6.

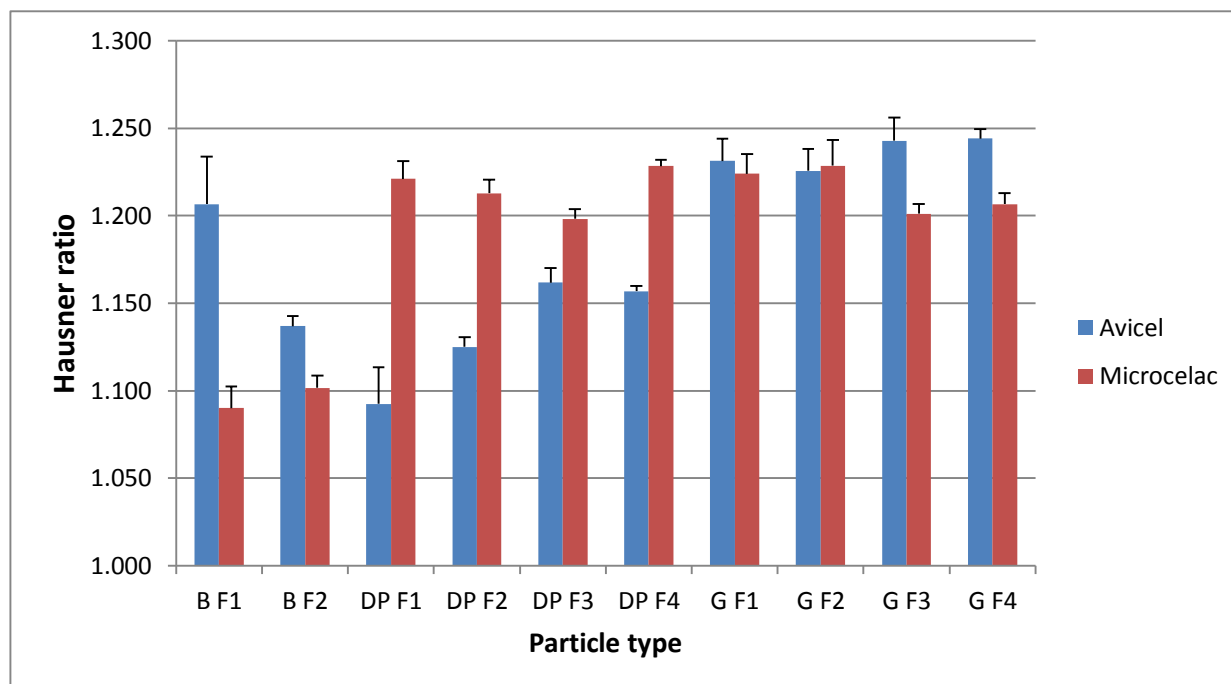


Figure 4.6: Hausner ratio results for all formulations. B = bead, DP = dry powder, G = granule

In Table 4.5, the criteria to interpret Hausner ratio values in terms of powder flow are given (BP, 2015).

Table 4.5: Criteria for interpretation of Hausner ratio values in terms of powder flow classification

Classification of flow	Hausner ratio
Excellent	1.00 - 1.11
Good	1.12 - 1.18
Fair	1.19 - 1.25

The dry powder formulations exhibited a wide variety of Hausner ratio values of 1.09 – 1.23 (Table 4.2). By examining the Hausner ratio's of the different dry powder formulations, it is clear that the MicroceLac® dry powder formulations produced higher values (1.20 – 1.23) than the Avicel® dry powder formulations (1.09 – 1.16). According to Table 4.5, the flow of the MicroceLac®-containing dry powder formulations therefore exhibited fair flow versus the Avicel®-containing formulations that exhibited excellent flow. This may also be attributed to the inclusion of lactose in the co-processed filler, MicroceLac® (MCC-lactose). The lactose in the MicroceLac® may have caused cohesive forces between the particles and thereby

decreasing the flow of the powder and consequently negatively affected the Hausner ratio value (Zhou *et al.*, 2011:414).

The granule formulations exhibited Hausner ratio values of 1.21 – 1.24, which can be classified as fair flow. All the bead formulations exhibited Hausner ratio values of 1.09 – 1.14 with the exception of Formulation 1 of the Avicel®-containing bead formulations. This formulation exhibited a Hausner ratio value of 1.21, which can be classified as fair flow.

It is clear from the data in Tables 4.1 and 4.5; and Figure 4.6 that the bead formulations and the dry powder formulations exhibited the best flow in terms of Hausner ratio values as measurement of powder flow. As mentioned before, the beads were more uniform in terms of size, shape and structure compared to the particles of the granule formulations. The granules also exhibited rough surface textures and irregular shaped particles (See figure 4.2 b (I) and (II)). As a consequence, the granules may be exposed to friction and interlocking that will negatively affect flow. Furthermore, the particles will not always be able to rearrange optimally during the Hausner ratio test because of large voids or spaces left between the particles caused by the irregular shapes. To possess a Hausner ratio value representing excellent to good flow, it is important that particles are able to rearrange close together with little space left between the particles. This provides higher densities and smaller Hausner ratios and therefore might explain why the bead and dry powder formulations tended to produce better flow in terms of the Hausner ratio (Charinpanitkul *et al.*, 2008:665-666).

It is evident from Figure 4.1a and b as well as Figure 4.2a (I) and (II), that the MicroceLac® filler on its own and the MicroceLac®-containing dry powder formulations contained a notable presence of smaller particles. This observation is supported by the smaller average particle size values in Table 4.1 for the MicroceLac®-containing dry powder formulations in comparison to the Avicel®-containing dry powder formulations. The presence of a notable proportion of smaller particles in powder mixtures may lead to flowability issues because better flow is usually observed with larger and more uniform particles. This may in part explain why the MicroceLac®-containing dry powder formulations displayed higher Hausner ratio's.

4.4.4 CARR'S INDEX (% COMPRESSIBILITY)

The Carr's index values (or % compressibility) of the different formulations are depicted in Figure 4.7

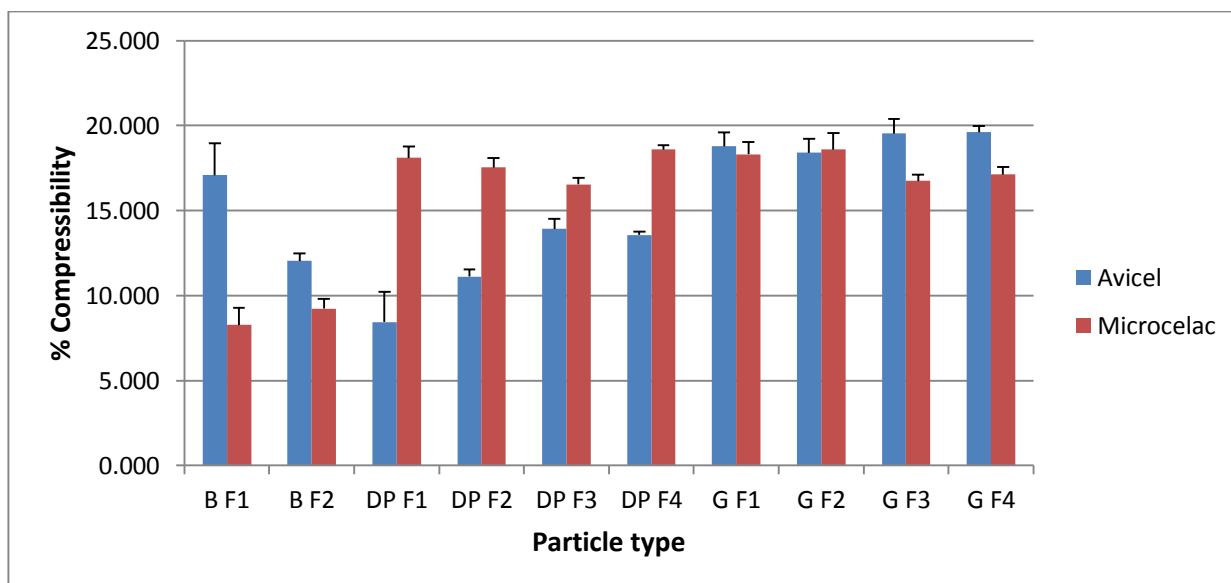


Figure 4.7: Image depicting the % compressibility results for all formulations. B = bead, DP = dry powder, G = granule

In Table 4.6, the classification of powder flow is given in terms of Carr's index (BP, 2015). This Table will be used in the discussion that follows.

Table 4.6: Criteria for interpretation of %compressibility for powder flow classification

Classification of flow properties	% compressibility
Excellent	1 – 10
Good	11 – 15
Fair	16 – 20

All the Avicel®-containing dry powder formulations exhibited Carr's indices ranging from 11 to 14, with the exception of formulation 1 which had a Carr's index of 8. According to Table 4.6, the flow of the Avicel®-containing dry powder formulations can be classified as good to excellent and this is in agreement with the results obtained from the AOR and Hausner ratio powder flow assessment methods. MicroceLac® dry powder formulations exhibited fair flow with Carr's indices ranging from 17 to 19. These results were also in agreement with the data obtained from the AOR and Hausner ratio methods.

MicroceLac® and Avicel® granule formulations exhibited fair flow with Carr's indices ranging from 17 to 20, corroborating in general the flow classification as reflected by AOR and Hausner ratio.

MicroceLac®-containing bead formulations had Carr's indices of 8 and 9 for formulation 1 and 2 respectively, indicative of excellent flow properties. Avicel®-containing beads had

Carr's indices of 12 and 17 for formulation 1 and 2 respectively, indicative of good and fair flow respectively.

4.4.5 FLOW RATE (10 MM AND 15 MM ORIFICE)

The flow rate data (using a 10 and 15 mm orifice) for the different formulations are depicted in Figure 4.8.

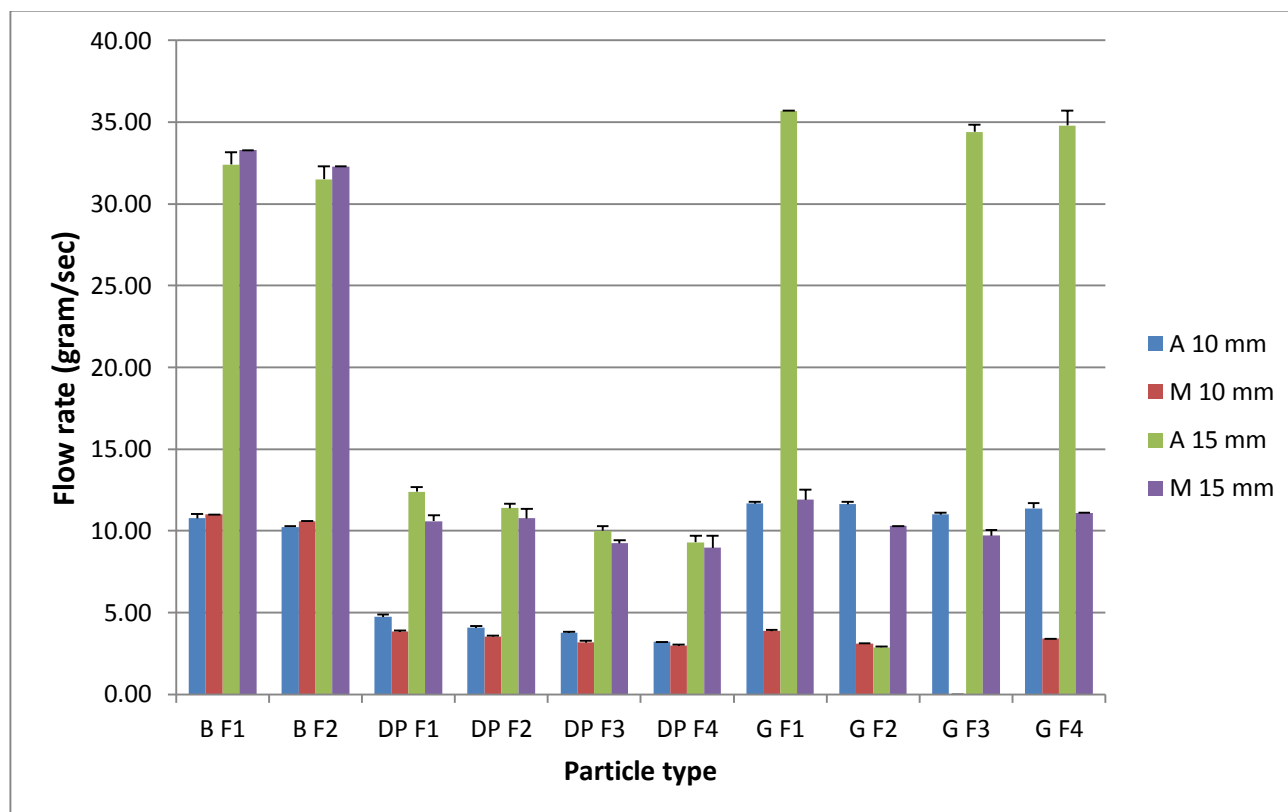


Figure 4.8: Flow rate of the different formulations. B = bead, DP = dry powder, G = granule, A = Avicel®, M = MicroceLac®

In Tables 4.7 and 4.8 an arbitrary classification of powder flow in this study is shown.

Table 4.7: Criteria for interpretation of the flow rate through a 10 mm diameter orifice

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

Table 4.8: Criteria for interpretation of the flow rate through a 15 mm diameter orifice

Classification of flow	Flow rate (g/s)
Excellent	20 and upwards
Good	12 – 19.99
Fair	8.5 – 11.99

Avicel® dry powder formulations exhibited a flow rate of 3.2 to 4.7 g/s and 9.3 to 12.4 g/s for the 10 mm and 15 mm orifice diameters, respectively. The MicroceLac® dry powder formulations exhibited similar flow rates with a flow rate of 3.0 to 3.8 grams/sec and 9 to 10.8 grams/sec for the 10 mm and 15 mm orifice diameters, respectively. According to Tables 4.7 and 4.8 all dry powder formulations presented with excellent flow properties in terms of flow rate specifications.

Avicel®-containing granule formulations exhibited a similar tendency to the dry powder formulations with flow rates of 11.0 – 11.7 g/s and 34.4 – 35.7 g/s for the 10 mm and 15 mm orifices respectively. However, formulation 2 gave an unexpected low flow rate of 2.9 g/s with the 15 mm orifice that cannot be explained. All the MicroceLac® granule formulations exhibited flow rates of 3.1 – 3.9 g/s for the 10 mm orifice with the exception of formulation 4 that failed to flow through the 10 mm orifice. With respect to the 15 mm orifice, all four formulations were able to flow with flow rates ranging from 9.7 – 11.9 g/s.

The bead formulations exhibited flow rates comparable to the Avicel®-containing granule formulations with values ranging from 10.2 – 11.0 and 31.5 – 33.3 g/s for the 10 and 15 mm orifices respectively. These flow rates can be classified as excellent according to Tables 4.7 and 4.8.

Considering the flow rate results of the granule formulations, it is clear that irregular flow behaviour occurred. Inconsistent flow results can be seen in Figure 4.8 regarding the flow rate results of the MicroceLac®-containing granule formulation 3 through the 10 mm orifice and also the Avicel®-containing granule formulation 2 through the 15 mm orifice. Upon evaluation of the data in Table 4.9, it was identified that there were patterns of irregular flow where the granule formulations did not flow at all through the orifice of 10 and 15 mm diameter. This may possibly be explained in terms of the shape and size of the granule particles at hand (See Figure 4.2 b (I) and (II)). The particles do not have spherical shapes but rather irregular shapes. The textures of the particles are rough and not smooth like that of beads (Zhou *et al.*, 2011:414; Charinpanitkul *et al.*, 2008:665-666).

4.4.6 FLOW CHARACTERISATION SUMMARY

A summary of the flow classification of all the particle formulations investigated in this study is given in Table 4.9.

Table 4.9: Summary of the flow classification of the different powder, granule and bead formulations

Formulation	Classification of flow properties					
	Angle of repose (°)	Critical orifice diameter (mm)	Flow rate 10mm orifice (g/sec)	Flow rate 15mm orifice (g/sec)	Hausner ratio	Carr's index (%)
Avicel® dry powder						
F1	E	E	F	G	E	E
F2	E	E	F	F	G	G
F3	E	E	F	F	G	G
F4	E	E	F	F	G	G
MicroceLac® dry powder						
F1	E	E	F	F	F	F
F2	E	E	F	F	F	F
F3	E	E	F	F	F	F
F4	E	E	F	F	F	F
Avicel® granules						
F1	E	G	E	E	F	F
F2	E	G	E	P	F	F
F3	E	F	E	E	F	F
F4	G	F	E	E	F	F
MicroceLac® granules						
F1	E	F	F	F	F	F
F2	G	F	F	F	F	F
F3	G	F	P	F	F	F
F4	E	F	F	F	F	F
Avicel® beads						
F1	E	G	E	E	F	F
F2	E	G	E	E	G	G
MicroceLac® beads						
F1	E	G	E	E	E	E
F2	E	G	E	E	E	E

*E - Excellent flow, *G – Good flow, *F – Fair flow, *P – Poor flow.

It is evident that particle size, shape and texture influenced the flow properties of the formulations consisting of different types of particles. It is critical that the correct particle type is selected during formulation to render a dosage form with high quality that can be produced effectively. It was clear that larger particles, with a spherical geometry and a smooth surface texture exhibited improved flow. When considering the flow characterisation

data from all the flow tests, it is evident that the bead formulations exhibited superior flow compared to that of the dry powders and granules.

4.5 TABLET EVALUATION

In Table 4.10 the tablet evaluation results for all Avicel®-containing tablets (flat faced and concave) are presented.

Table 4.10: Physical evaluation results for all Avicel® tablet formulations

Formulation	Physical properties of Avicel® tablet formulations												
	Average crushing strength (N)	± SD	Average thickness (mm)	± SD	Average diameter (mm)	± SD	Average disintegration time (s)	± SD	% Friability	± SD	Average tablet mass (gram)	± SD	%RSD
	Concave dry powder tablets												
F1	87.00	1.886	4.16	0.012	9.00	0.012	22.00	0.000	0	0.000	0.250	0.001	0.54
F2	107.60	3.806	4.04	0.015	8.98	0.004	37.33	2.582	0.04	0.001	0.251	0.001	0.51
F3	96.70	2.312	4.13	0.013	8.99	0.011	34.00	0.000	0	0.000	0.250	0.001	0.30
F4	95.90	2.961	4.13	0.017	8.98	0.003	32.00	2.191	0	0.000	0.251	0.001	0.39
	Flat faced dry powder tablets												
F1	94.20	1.989	3.30	0.007	8.98	0.004	21.00	2.449	0	0.000	0.248	0.001	0.45
F2	95.50	1.434	3.34	0.009	8.98	0.003	20.50	4.416	0.08	0.001	0.250	0.001	0.40
F3	89.70	2.406	3.43	0.012	9.08	0.315	25.00	0.000	0.08	0.001	0.252	0.001	0.41
F4	95.50	1.958	3.36	0.010	8.98	0.003	32.00	0.000	0.04	0.001	0.250	0.002	0.69
	Concave granule tablets												
F1	70.80	11.23	4.65	0.013	9.01	0.014	13.00	0.000	0.08	0.001	0.255	0.003	1.30
F2	64.40	5.19	4.65	0.011	9.00	0.018	13.00	1.549	0.24	0.004	0.253	0.005	1.99
F3	70.50	5.191	4.63	0.029	9.01	0.014	17.00	1.789	0.04	0.001	0.252	0.004	1.45
F4	58.20	6.779	4.65	0.016	9.01	0.017	16.17	4.021	0.40	0.007	0.252	0.005	1.82
	Flat faced granule tablets												
F1	78.50	4.994	3.77	0.007	8.99	0.006	20.00	0.000	0.04	0.001	0.255	0.002	0.95
F2	74.00	8.042	3.78	0.015	8.99	0.005	19.00	3.225	0.04	0.001	0.255	0.002	0.96
F3	104.10	13.75	3.61	0.013	8.99	0.009	112.67	20.116	0.08	0.001	0.254	0.007	2.62
F4	99.60	14.27	3.63	0.010	8.97	0.013	83.33	34.500	0	0.000	0.254	0.004	1.55
	Concave bead tablets												
F1	107.40	8.909	4.02	0.041	9.01	0.017	47.83	14.091	0	0.000	0.255	0.002	0.86
F2	88.80	5.75	4.11	0.011	9.01	0.023	22.50	8.216	0	0.000	0.257	0.003	1.19
	Flat faced bead tablets												
F1	100.80	7.843	3.17	0.011	8.98	0.013	23.00	7.746	0.08	0.001	0.255	0.004	1.48
F2	95.00	10.04	3.34	0.011	8.99	0.005	14.00	4.382	0.04	0.001	0.257	0.003	1.22

In Table 4.11 the tablet evaluation results for all MicroceLac[®]-containing tablets (flat faced and concave) are presented.

Table 4.11: Physical evaluation results for all MicroceLac[®] tablet formulations

Formulation	Physical properties of MicroceLac [®] tablet formulations												
	Average crushing strength (N)	± SD	Average thickness (mm)	± SD	Average diameter (mm)	± SD	Average disintegration time (s)	± SD	% Friability	SD	Average tablet mass	± SD	%RSD
	Concave dry powder tablets												
F1	130.50	2.991	3.85	0.013	8.99	0.007	411.33	16.753	0.12	0.001	0.251	0.002	0.65
F2	98.70	7.573	3.98	0.008	9.00	0.013	135.83	13.333	0.16	0.001	0.251	0.001	0.48
F3	104.50	2.014	3.98	0.010	8.99	0.013	289.33	13.171	0.08	0.001	0.250	0.001	0.53
F4	108.00	3.333	3.99	0.012	8.99	0.009	184.33	16.476	0.16	0.003	0.251	0.001	0.51
	Flat faced dry powder tablets												
F1	102.30	6.111	3.09	0.022	8.99	0.005	200.83	58.949	0.04	0.000	0.247	0.002	0.82
F2	106.70	2.452	3.17	0.007	8.99	0.004	158.33	10.838	0.08	0.001	0.251	0.001	0.44
F3	112.40	6.786	3.25	0.023	8.99	0.008	317.83	28.944	0	0	0.253	0.002	0.88
F4	106.20	4.077	3.26	0.012	8.99	0.008	215.00	11.713	0	0	0.254	0.001	0.37
	Concave granule tablets												
F1	117.30	9.945	4.14	0.017	8.99	0.010	471.17	81.212	0.08	0.001	0.254	0.005	1.88
F2	86.30	16.39	4.12	0.055	9.00	0.016	391.33	70.261	0.20	0.004	0.250	0.006	2.34
F3	121.70	13.43	4.17	0.029	8.99	0.010	672.17	107.667	0.12	0.002	0.256	0.004	1.58
F4	121.80	13.01	4.18	0.025	8.99	0.011	567.00	87.226	0	0	0.256	0.004	1.58
	Flat faced granule tablets												
F1	139.20	21.76	3.11	0.036	8.98	0.010	365.33	135.594	0.08	0.001	0.248	0.007	2.87
F2	142.10	20.59	3.06	0.037	8.99	0.005	464.67	77.650	0.16	0.003	0.250	0.007	2.94
F3	132.20	36.82	3.36	0.088	8.98	0.012	690.67	83.854	0	0	0.255	0.004	1.56
F4	109.50	7.649	3.33	0.018	8.87	0.317	534.33	122.707	0	0	0.248	0.005	2.21
	Concave bead tablets												
F1	104.40	10.66	3.99	0.031	9.00	0.011	805.33	90.155	0	0	0.255	0.005	1.78
F2	99.10	9.374	4.00	0.024	9.02	0.014	532.33	43.812	0.04	0.001	0.254	0.002	0.94
	Flat faced bead tablets												
F1	93.70	14.1	3.29	0.028	9.00	0.010	612.00	106.036	0.08	0.001	0.255	0.005	1.78
F2	97.30	8.97	3.22	0.026	9.00	0.019	545.00	109.360	0	0	0.255	0.003	1.14

4.5.1 MASS VARIATION

All tablet formulations for both Avicel® and MicroceLac® complied with the specifications for mass variation as set by the BP (2015). None of the tablets deviated by more than 5% from the average tablet mass for any of the formulations.

In Table 4.12, the average mass values are given for all tablet formulations (flat faced and concave) compressed from different particle types.

Table 4.12: Average tablet mass values as a function of filler, particle type and punch type

	Average tablet mass (g)	± SD	Average per particle type	± SD
ADP FF	0.250	0.002	0.250	0.001
ADP CF	0.250	0.001		
MDP FF	0.251	0.003	0.251	0.002
MDP CF	0.251	0.001		
AG FF	0.255	0.001	0.254	0.001
AG CF	0.253	0.001		
MG FF	0.250	0.003	0.252	0.003
MG CF	0.254	0.003		
AB FF	0.256	0.001	0.256	0.001
AB CF	0.256	0.001		
MB FF	0.255	0.000	0.255	0.001
MB CF	0.255	0.001		

A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule, B = bead, FF = flat faced, CF= concave faced

Although all the formulations complied with the test for mass variation, small differences in mass variation were noted. According to Table 4.10 and 4.11, the tablet formulations compressed from dry powder mixtures exhibited the most uniform tablet mass distribution with a %RSD < 1, followed by the bead formulations with %RSD values < 2%. The tablets compressed from granules exhibited the highest %RSD values reaching almost 3 %. It should be noted, however, that a %RSD < 3% is still acceptable as all the tablet formulations still complied with the specifications set by the BP for mass variation (BP, 2015).

The higher mass variation of the granule formulations can be related to the weaker flow as reflected by the results obtained for AOR, Hausner ratio and Carr's index. The weaker flow properties of the granules as reflected by the different parameters can most probably be attributed to the uneven particle size and shape. Poor particle flow causes uneven filling of the tablet press die during the process of tableting. This causes the tablets to vary in mass (Sinka *et al.*, 2004:27-28).

Furthermore, due to the geometry and size of the granules and to a lesser extent the beads, more voids and spaces will be present between particles and this causes the mass of the tablets to exhibit a higher variation compared to the tablets compressed from the dry powder formulations (see Figure 4.2).

4.5.2 DISINTEGRATION TIME

In Figure 4.9, the disintegration data are presented of the tablets prepared from the different formulations

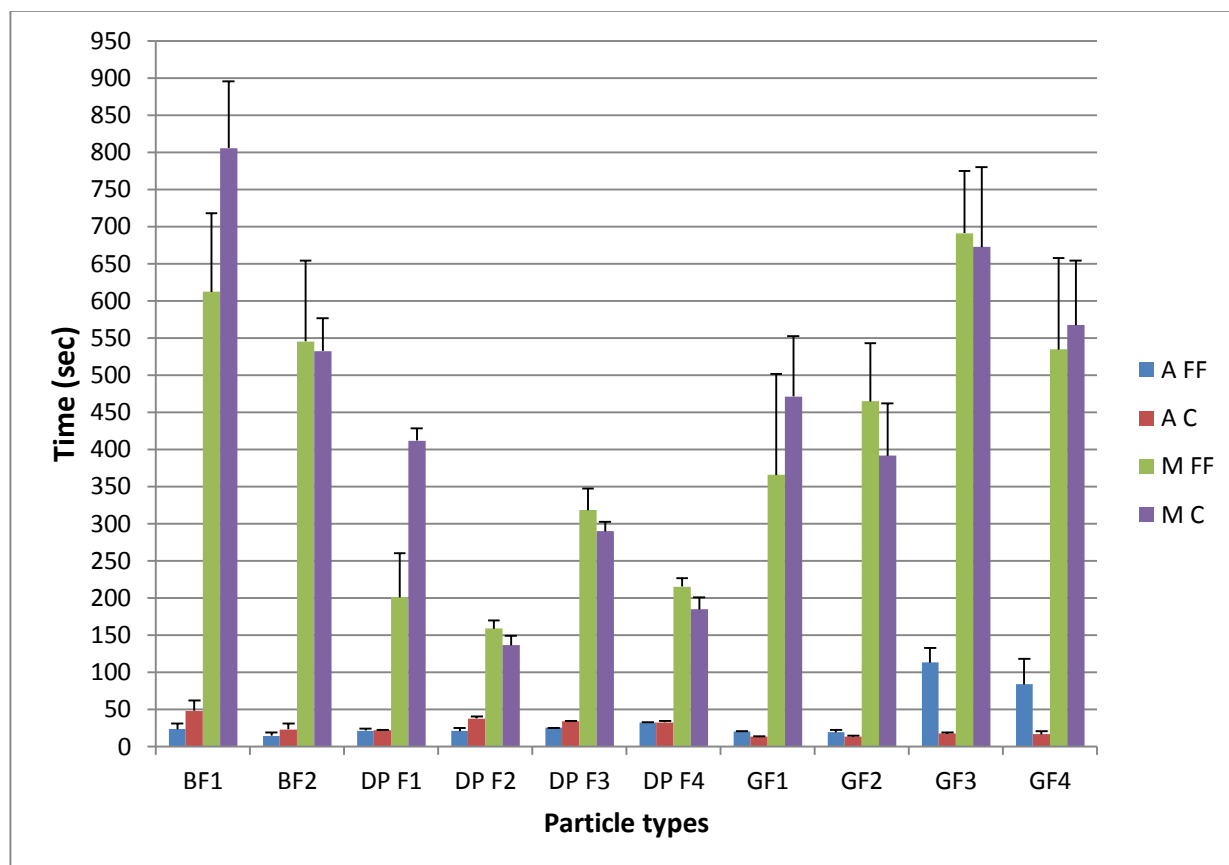


Figure 4.9: Average disintegration time of tablets prepared from the different formulations. B = bead, DP = dry powder, G = granule, A = Avicel®, M = MicroceLac®, FF = flat faced, C= concave faced

From Tables 4.10 and 4.11 as well as Figure 4.9 it is clear that all the tablet formulations for MicroceLac® and Avicel® complied with the specifications of the British Pharmacopoeia regarding disintegration as all tablets disintegrated within 15 min (BP 2015 online).

In Table 4.13 the overall average disintegration times for all tablet formulations (flat faced and concave) compressed with different particle types are given.

Table 4.13: Average disintegration times as a function of filler, particle type and punch type

	Average disintegration time (s)	± SD	Average disintegration time (s) per particle type	± SD
ADP FF	24.63	5.313	27.98	6.605
ADP CF	31.33	6.600		
MDP FF	223.00	67.652	239.10	93.058
MDP CF	255.21	122.220		
AG FF	58.75	46.879	36.77	38.676
AG CF	14.79	2.097		
MG FF	513.75	136.821	519.58	119.892
MG CF	525.42	121.362		
AB FF	18.50	6.364	26.83	14.596
AB CF	35.17	17.913		
MB FF	578.50	47.376	623.67	126.054
MB CF	668.83	193.040		

A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule, B = bead, FF = flat faced, CF= concave faced

It is evident from the data in Table 4.13 that the MicroceLac®-containing formulations exhibited notably longer disintegration times in comparison to the Avicel®-containing formulations. Avicel®-containing formulations had relatively short disintegration times between 14.79 and 58.75 s, whereas the MicroceLac®-containing formulations disintegrated on average between 223.00 and 668.83 s. This phenomenon was apparent for all the MicroceLac®-containing formulations irrespective of particle type or punch type.

This can be probably be explained in terms of the lactose component that is present in the co-processed filler MicroceLac®. MicroceLac® consists of microcrystalline cellulose (MCC) and lactose. The MCC-lactose combination shows a significant sensitivity towards the binder component in the particular formulation. When MicroceLac® is formulated with a binder like Kolidon® VA 64, the binding effect is stronger than with MCC alone (as evident from the hardness/crushing strength as shown in Table 4.14). When the tablet binds stronger, pores in the tablet matrix/core will be smaller and there will also be fewer pores on the tablet surface. This caused less water/fluid to pass into the tablet and the disintegration time of the tablet prolonged, explaining the longer disintegration times of the MicroceLac®-containing formulations in comparison to the Avicel®-containing formulations. (Chitu *et al.*, 2011:441-442).

It is also evident that the tablets compressed from dry powder formulations (both MicroceLac®- and Avicel®-containing) disintegrated on average faster than granule and bead

formulations with a similar composition. These differences can be explained in terms of the particle type used during compression. Granules and beads as particles are larger compared to that of the dry powder mixtures. When disintegration of the tablet takes place, the tablet will disintegrate into the original powder particles, then each of these particles also have to disintegrate to render the primary powder particles. Therefore, a longer disintegration time can be expected for tablets comprising of multiple-unit particles such as granules and beads. No clear differences for punch type were observed with regard to disintegration time of the tablets.

4.5.3 CRUSHING STRENGTH

In Figure 4.10, the crushing strength data are presented of the tablets prepared from the different formulations.

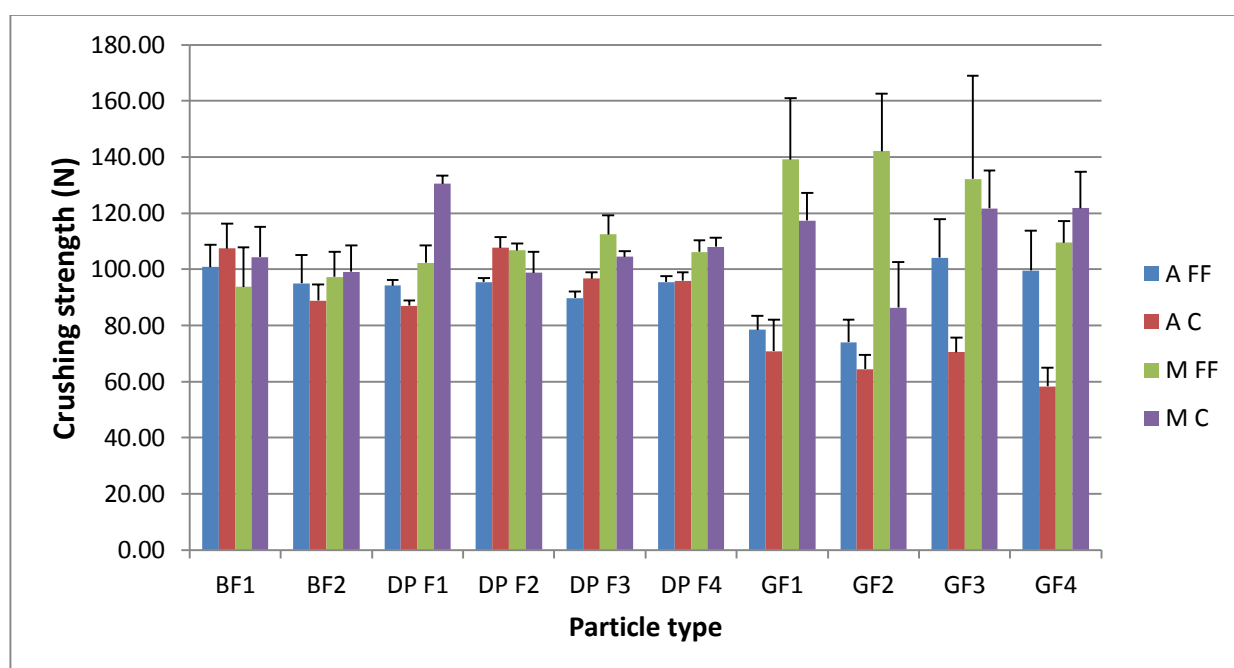


Figure 4.10: Crushing strength results for all formulations. B = bead, DP = dry powder, G = granule, A = Avicel®, M = MicroceLac®, FF = flat faced, C= concave faced

In Table 4.14, the average crushing strength values are given for all tablets (flat faced and concave faced) compressed from the different particle types.

Table 4.14: Average crushing strength values as a function of filler, particle type and punch type

	Average crushing strength (N)	± SD	Average per particle type	± SD
ADP FF	93.73	2.752	95.26	6.037
ADP CF	96.80	8.436		
MDP FF	106.90	4.161	108.66	9.697
MDP CF	110.43	13.922		
AG FF	89.05	15.007	77.51	16.245
AG CF	65.98	5.963		
MG FF	130.75	14.764	121.26	17.938
MG CF	111.78	17.112		
AB FF	97.90	4.101	98.00	7.955
AB CF	98.10	13.152		
MB FF	95.50	2.546	98.63	4.457
MB CF	101.75	3.748		

A = Avicel[®], M = MicroceLac[®], DP = dry powder, G = granule, B = bead, FF = flat faced, CF= concave faced

It is evident from the data in Tables 4.10, 4.11 and 4.14 that in general, the tablets compressed from the Avicel[®]-containing dry powder formulations exhibited lower crushing strength values in comparison to the MicroceLac[®]-containing formulations with a similar composition. This indicated that the diluent had a significant effect on the crushing strength of the tablets (ANOVA, $p < 0.05$). Avicel[®]-containing dry powder formulations exhibited crushing strength values ranging between 93.73 N and 96.80 N and MicroceLac[®]-containing dry powder formulations exhibited crushing strength values between 106.90 N and 110.43 N. The same tendency was observed for the granule formulations; 65.98 N – 89.05 N compared to 111.78 N – 130.75 N for the Avicel[®]- and MicroceLac[®]-containing granule formulations, respectively. The higher average crushing strength values for the MicroceLac[®] formulations were, however, not evident for the tablets compressed from the bead formulations.

As the stroke length and filling volume was kept constant throughout the process of compressing the tablets, these differences in tablet hardness may be attributed to the compaction properties of the filler. This can be explained in terms of MicroceLac[®] being a co-processed filler comprised of a MCC-lactose combination.

In this study, Kolidon[®] VA 64 was used as binder. During the granulation process prior to tableting, the Kolidon[®] VA 64 was dissolved in the wetting liquid (99 % ethanol) and then

added to the rest of the formulation prior to granulation. This allowed the Kollidon® VA 64 to distribute thoroughly through the mixture and the binding effect of the lactose will then be improved. Lactose is known to increase the tensile strength and hardness of the tablet when compressed. During the mixing process and during the compression of the tablets, the MCC-lactose component facilitated a stronger binding action than that of MCC-single excipient fillers like Avicel® (as evident from the crushing strength values). This caused the particles inside the tablet to bind stronger and to produce a harder tablet (Sebhato & Alderborn, 1999:241).

On average, the tablets compressed from Avicel®-containing granule formulations had a lower crushing strength compared to the tablets compressed from the dry powder formulations (77.51 ± 16.24 N vs 96.26 ± 6.04 N). It therefore appears that in the process of manufacturing granules, the binding ability of the microcrystalline cellulose during compression was negatively affected. The tablets prepared from the MicroceLac®-containing granule formulations exhibited an increase in tablet hardness as a result of the granulation process (121.26 ± 4.46 N vs 108.66 ± 9.70 N).

Tablets compressed from the bead formulations exhibited crushing strength values similar to that of the dry powder formulations.

Punch type did not have a significant effect on the hardness of the tablets prepared from dry powder and bead formulations as similar crushing strength values were obtained for flat faced and concave punch types (see Table 4.14). However, tablets prepared from granule formulations exhibited a significant difference in average hardness (ANOVA, $p < 0.05$). This difference was due to an interplay between particle type and punch type as shown by the statistical analysis that needs to be investigated further in future studies.

4.5.4 TABLET DIAMETER AND THICKNESS

Tablets prepared from the different formulations all exhibited similar diameter and thickness values.

The tablet diameter of all the tablets ranged between 8.85 mm and 9.1 mm. This is expected as all tablet compressions were done with 9 mm diameter punches.

According to Tables 4.10 and 4.11, all of the tablets that were tested showed a tablet thickness between 3.06 mm and 4.65 mm. The thickness of tablets compressed from Avicel®-containing formulations ranged between 3.30 and 4.65 mm, whereas the thickness of tablets compressed from the MicroceLac®-containing formulations ranged between 3.06 and 4.18 mm. It is therefore apparent that the difference between the minimum and maximum tablet thickness of the tablets compressed from the Avicel®-containing

formulations was higher. These differences can be attributed to the lower bulk and tapped density values (see Table 4.15) of the different Avicel®-containing formulations. The Avicel®-containing dry powder and granule formulations presented with significantly lower density values than that of the MicroceLac®-containing formulations. The Avicel® -containing dry powder and granule formulations reached bulk densities from 0.256 – 0.456 g/cm³ and tapped densities from 0.317 – 0.513 g/cm³ with the granule formulations having the lowest densities. MicroceLac®-containing dry powder formulations reached bulk densities from 0.315 – 0.565 g/cm³ and tapped densities from 0.382 – 0.687 g/cm³. The bead formulations showed more or less the same densities and therefore produced tablets with a similar diameter and thickness.

Table 4.15: Bulk and tapped densities of all Avicel®- and MicroceLac®-containing particle types

	Bulk density	Tapped density
ADP	0.456	0.513
AG	0.256	0.317
AB	0.775	0.908
MDP	0.565	0.687
MG	0.315	0.382
MB	0.737	0.806

A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule, B = bead

4.5.5 FRIABILITY

In Table 4.16, the average % friability is reported for all tablets (flat faced and concave) compressed from the different particle formulations.

Table 4.16: Average % friability as a function of filler, particle type and punch type

	Average % friability	± SD	Average per particle type	± SD
ADP FF	0.05	0.038	0.03	0.035
ADP CF	0.01	0.020		
MDP FF	0.03	0.038	0.08	0.064
MDP CF	0.13	0.038		
AG FF	0.04	0.032	0.11	0.135
AG CF	0.19	0.163		
MG FF	0.06	0.079	0.08	0.078
MG CF	0.10	0.083		
AB FF	0.06	0.028	0.03	0.038
AB CF	0.00	0.000		
MB FF	0.04	0.055	0.03	0.037
MB CF	0.02	0.028		

A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule, B = bead

It is evident from Tables 4.10, 4.11 and 4.16 that all the tablet formulations for both Avicel® and MicroceLac® complied with the requirements for friability (BP, 2015). The % friability of tablets compressed from Avicel®-containing formulations ranged between 0.04 % and 0.4 %, whereas the friability of tablets compressed from the MicroceLac®-containing formulations ranged between 0.04 % and 0.2 %. The lower percentage friability of the MicroceLac®-containing formulations may be the consequence of the higher mechanical strength of these tablets as evidenced by the higher crushing strength values in general for these tablets.

The concave Avicel®-containing tablets compressed from granule formulations exhibited the highest % friability with values reaching 0.4 % however, as stated earlier this still complied with BP specifications. Tablets from the granule formulations also had the lowest average crushing strength values and the fastest disintegration times in general. Keeping these results in mind, it is clear that these formulations produced softer tablets during the compaction process.

4.5.6 TABLET EVALUATION SUMMARY

It is important to note that during the selection process of a formulation intended for direct compression of tablets, all the evaluation results must be reviewed and taken into consideration.

Tablets were successfully compressed from different particle types (dry powders, granules and beads). All powder, granule and bead formulations rendered tablets that complied with specifications as set by the BP (2015 online) regarding mass variation, disintegration time

and friability. Furthermore, all tablets exhibited sufficient mechanical strength as indicated by crushing strength.

Although all tablet batches complied to specifications, it was observed that in general, tablets compressed from MicroceLac[®]-containing formulations exhibited higher crushing strength values and longer disintegration times for all particle types in comparison to Avicel[®]-containing formulations.

Tablets compressed from dry powder and bead formulations rendered tablets with a slightly lower variation in tablet mass and tablets with a similar mechanical strength in comparison to tablets compressed from granule formulations. The lower variation in tablet mass of the tablets compressed from the dry powder and bead formulations can probably be attributed to the better flow properties of these formulations.

4.6 DISSOLUTION BEHAVIOUR OF DIFFERENT TABLET FORMULATIONS

The dissolution profiles of the tablets prepared from formulation 1 (for both dry powder and granule formulations) compressed with flat faced and concave punches are depicted in Figure 4.11. The dissolution results are discussed in detail in sections 4.6.1 and 4.6.2 below.

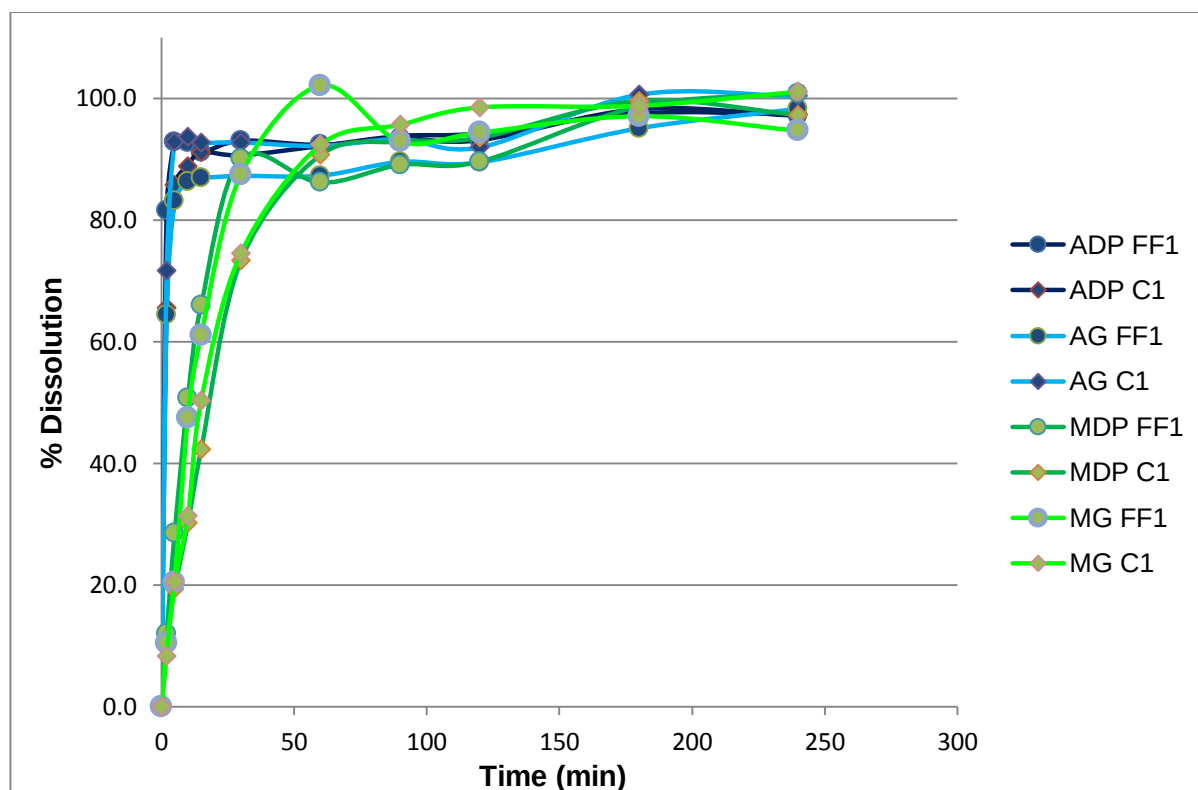


Figure 4.11: Dissolution profiles of tablets prepared from formulation 1 of the dry powder and granule formulations. A = Avicel[®], M = MicroceLac[®], DP = dry powder, G = granule

The dissolution profiles of the tablets prepared from formulation 2 (for both dry powder and granule formulations) compressed with flat faced and concave punches are depicted in Figure 4.12.

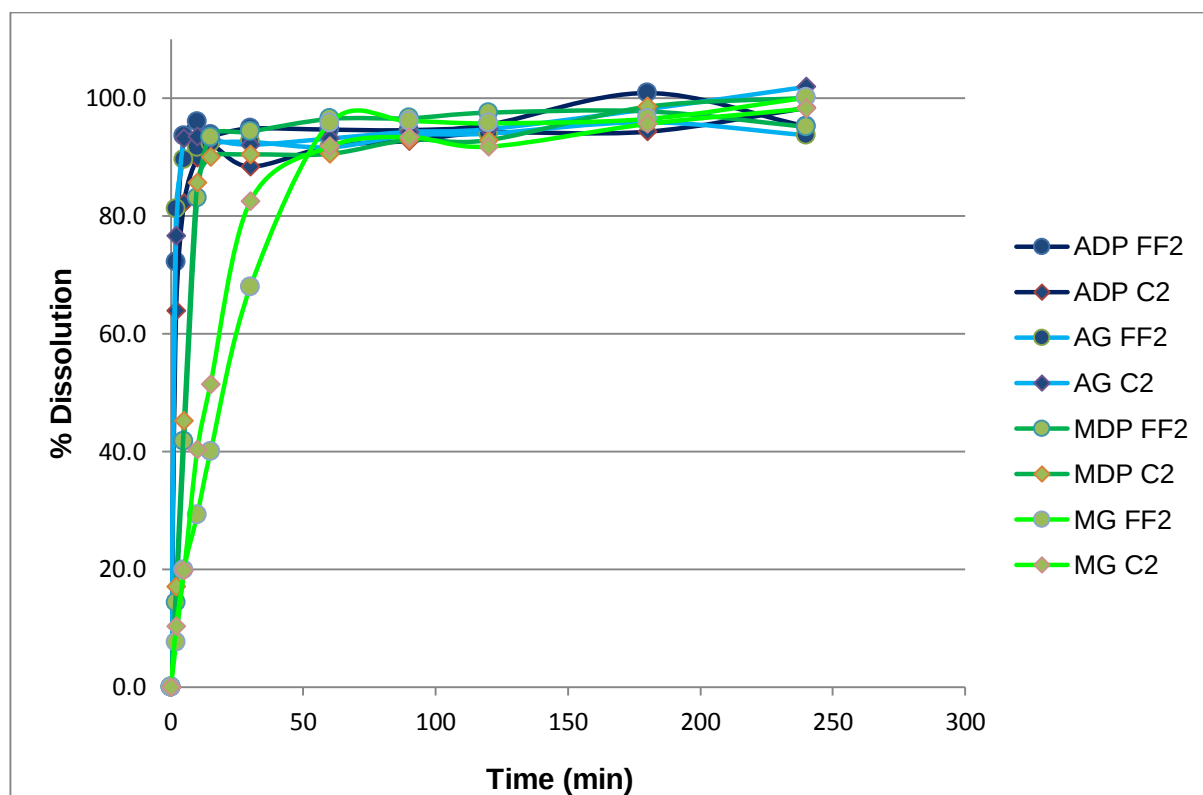


Figure 4.12: Dissolution profiles of tablets prepared from formulation 2 of the dry powder and granule formulations. A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule

The dissolution profiles of the tablets prepared from formulation 3 (for both dry powder and granule formulations), compressed with flat faced and concave punches are depicted in Figure 4.13.

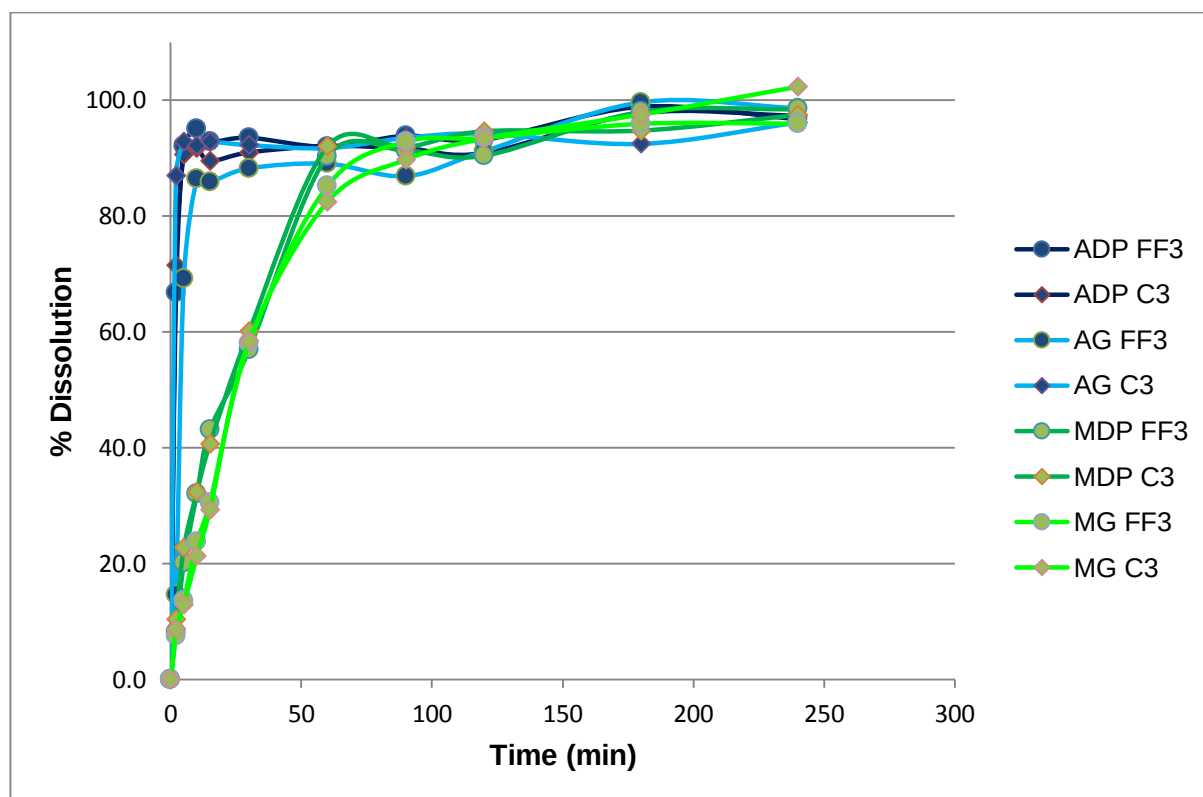


Figure 4.13: Dissolution profiles of tablets prepared from formulation 3 of the dry powder and granule formulations. A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule

The dissolution profiles of the tablets prepared from formulation 4 (for both dry powder and granule formulations), compressed with flat faced and concave punches are depicted in Figure 4.14.

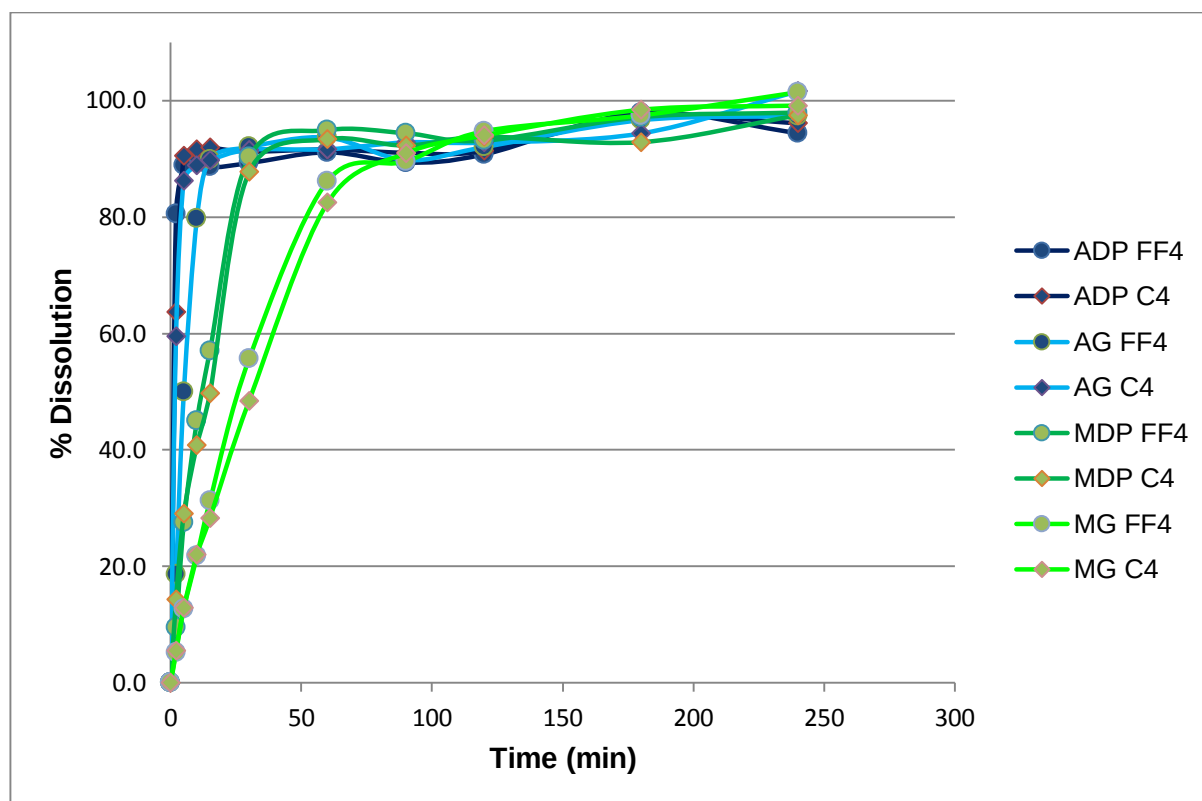


Figure 4.14: Dissolution profiles of tablets prepared from formulation 4 of the dry powder and granule formulations. A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule

The dissolution profiles of the tablets prepared from formulation 1 and 2 (bead formulations), compressed with flat faced and concave punches are depicted in Figure 4.15.

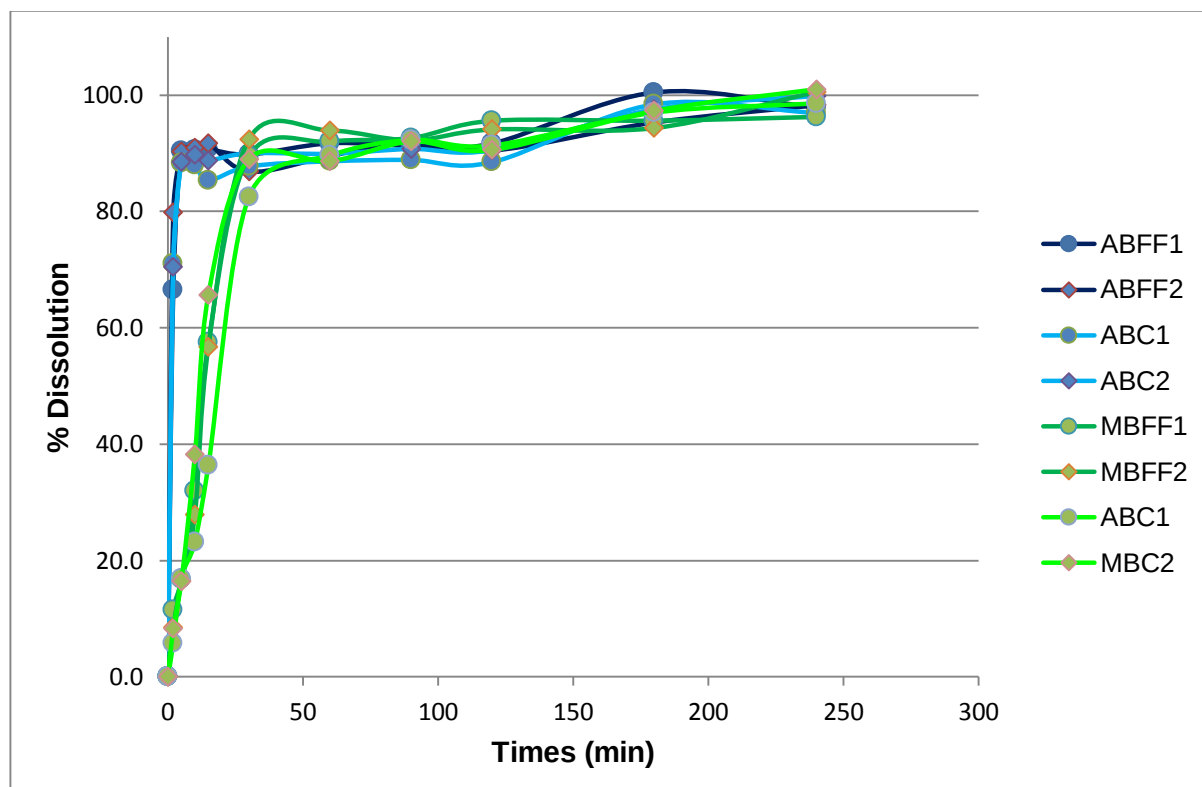


Figure 4.15: Dissolution profiles of tablets prepared from formulation 1 and 2 of the bead formulations. A = Avicel®, M = MicroceLac®, DP = dry powder, G = granule

The average mean dissolution time (MDT) and average initial dissolution rates (I_{dr}) of the dissolution profiles of the different tablet formulations (as outlined in Table 3.2 and Table 3.4) are given in Table 4.17.

In Table 4.17 the average MDT and I_{dr} values are grouped by particle and punch type.

Table 4.17: The average* MDT and I_{dr} values of the different formulations grouped by particle and punch type

	MDT (min)	± SD	I_{dr} (%.min ⁻¹)	± SD	Disinte- gration time (s)	± SD	Crushing strength (N)	± SD
ADP FF1-4	5.49	5.502	4.46	0.422	20.85	9.835	93.73	3.072
ADP CF1-4	10.94	10.216	4.67	0.371	31.33	6.048	96.80	7.884
AG FF1-4	13.47	9.185	5.19	0.915	58.75	45.485	89.05	16.867
AG CF1-4	14.36	11.597	4.50	0.413	14.79	2.859	65.98	8.917
AB FF1+2	13.70	10.563	4.44	0.308	18.50	7.622	97.90	9.262
AB CF1+2	15.53	9.372	4.25	0.235	35.17	17.204	98.10	12.013
MDP FF1-4	19.00	11.258	4.41	1.530	223.00	67.637	106.90	6.147
MDP CF1-4	20.11	7.118	3.68	1.633	255.21	109.027	110.43	12.957
MG FF1-4	23.21	13.478	2.70	1.218	513.75	157.353	130.75	26.479
MG CF1-4	28.55	10.631	2.59	0.939	525.42	134.936	111.78	19.767
MB FF1+2	22.86	17.199	3.56	0.816	578.50	108.495	95.50	11.866
MB CF1+2	29.04	8.962	3.32	1.695	668.83	157.775	101.75	10.140

*n = 4 (dry powder and granule formulations) and n = 2 (bead formulations)

4.6.1 TABLETS COMPRESSED FROM DRY POWDER FORMULATIONS

There is a marked difference between the Avicel®-containing dry powder tablet formulations and the MicroceLac®-containing dry powder tablets. The dissolution profiles of the tablets prepared from the MicroceLac®-containing formulations exhibited higher MDT values and lower average I_{dr} values in comparison to the Avicel®-containing formulations with a similar composition. This means that the dissolution rates of the Avicel®-containing tablets, especially during the first 15 min, were faster than that of the MicroceLac®-containing tablets. This phenomenon is known as a burst release, as more than 80 % of the active ingredient in the tablet formulations were released and dissolved within a few minutes. Tablets prepared from the MicroceLac®-containing dry powder formulations exhibited overall average MDT values of 19.00 ± 11.258 and 20.11 ± 7.118 min for the flat faced and concave tablets respectively, whereas the corresponding I_{dr} values were 4.41 ± 1.530 and 3.68 ± 1.633 %.min⁻¹ respectively. It should be noted, that formulation 2, for both filler types exhibited the smallest MDT value and highest I_{dr} value, especially for the flat faced tablets.

The average MDT values were 2.37 ± 4.113 and 3.65 ± 3.769 min for the Avicel® and MicroceLac®-containing tablets, respectively. The corresponding I_{dr} values were 4.72 ± 0.139 and 6.57 ± 0.226 %.min⁻¹ for the Avicel® and MicroceLac®-containing tablets, respectively. The fast dissolution rate of this formulation may be attributed to the

combination of the lowest binder concentration (3% w/w) and highest disintegrant concentration (1% w/w). The MicroceLac[®]-containing tablets of formulation 2, however, were affected to a larger extent than the MicroceLac[®]-containing tablets.

The faster dissolution rate of the Avicel[®]-containing tablets is probably influenced by the faster disintegration times of these tablets in comparison to the MicroceLac[®]-containing tablets (27.98 ± 6.605 s and 239.10 ± 93.058 s, respectively). The faster dissolution rate may in part be explained in terms of Avicel[®] that is comprised of MCC (microcrystalline cellulose), which has inherent disintegration properties. Therefore, the combination of MCC with Ac-di-sol[®] facilitated an even faster disintegration process. It should also be noted that the MicroceLac[®]-containing tablets also produced harder tablets based on the average crushing strength values for tablets compressed with the same composition, that could have contributed to the slower disintegration of these formulations (Whang *et al.*, 2015:275-278).

4.6.2 TABLETS COMPRESSED FROM GRANULE FORMULATIONS

In comparison to the tablets prepared from the dry powder formulations, it can be noted that although the dissolution profiles of the tablets prepared from the granule formulations were similar to the profiles of the dry powder formulations, the overall MDT values of the tablets prepared from the granule formulations were higher although still below 15 min. The slightly higher MDT values may be attributed to the larger overall average size of the granules compared to the dry powders (645.54 ± 26.148 and 221.34 ± 2.034 μm). A larger particle size results in a smaller surface area exposed to the dissolution medium and consequently a slower dissolution rate (Patadai *et al.*, 2013:496).

Similar to the tablets prepared from the dry powder formulations, the MicroceLac[®]-containing granule tablets exhibited dissolution profiles appearing different than those of the Avicel[®]-containing granule tablets. The MicroceLac[®]-containing granule tablets exhibited a pattern of lengthened dissolution with overall MDT values of 23.21 ± 13.478 min and 28.55 ± 10.631 min for the flat faced and concave tablets, respectively. The corresponding I_{dr} values were 2.70 ± 1.218 $\%.\text{min}^{-1}$ and 2.59 ± 0.939 $\%.\text{min}^{-1}$. It is clear from the dissolution profiles depicted in Figure 4.11 – 4.14 that all the MicroceLac[®]-containing granule formulations exhibited a slower dissolution rate compared to that of the Avicel[®]-containing tablets. This is confirmed by the higher MDT values and lower I_{dr} values of the MicroceLac[®]-containing granule dissolution profiles.

It should also be noted that the tablets prepared from the MicroceLac[®]-containing granule formulations exhibited slightly higher MDT values and slightly lower I_{dr} values compared to those of the tablets prepared from the MicroceLac[®]-containing dry powder formulations. The

longer disintegration times of the MicroceLac[®]-containing tablets (for formulations with a similar composition compared to the dry powder formulations for both Avicel[®] and MicroceLac[®]) listed in Table 4.17 probably contributed to the fact that the tablets prepared from the MicroceLac[®]-containing granule formulations exhibiting higher MDT values as well as lower I_{dr} values than the MicroceLac[®]-containing dry powder tablets.

With regard to the MicroceLac[®]-containing tablets, formulation 3 and 4 exhibited markedly longer disintegration times for both the flat faced and concave tablets. These two tablet formulations exhibited higher disintegration times than formulation 1 and 2. This can be attributed to the fact that both these formulations contained Kollidon[®] VA 64 in a concentration of 5 % w/w in comparison to 3% w/w in formulations 1 and 2. The binding forces between the granule particles inside the tablet of these two formulations could have therefore been stronger, causing the tablets to disintegrate slower. The same phenomenon was observed for formulation 3 and 4 of the Avicel[®]-containing granule tablets, but only for the flat faced tablets. The tablets produced by flat faced punches presented with smaller thicknesses compared to the concave tablets (ranging from 3.61 – 3.63 mm and 4.63 – 4.65 mm, respectively). This implies that the granule contents of the flat faced tablet need to be compressed into a smaller space than that of a concave tablet. This entails that the particles would have been arranged closer together in the tablet and with the higher percentage of Kollidon[®] VA 64 present in formula 3 and 4, this would probably have produced a tablet with particles bound stronger together than the concave tablets. The stronger binding as evidenced by higher average crushing strength values resulted in a longer disintegration time and this might decrease the dissolution rate because disintegration increases the surface area available for dissolution.

4.6.3 TABLET COMPRESSED FROM BEAD FORMULATIONS

Tablets prepared from the bead-containing formulations exhibited the same trend that was observed for the tablets compressed from the dry powder and granule formulations. MicroceLac[®]-containing tablets exhibited higher MDT values and lower I_{dr} values than that of the Avicel[®]-containing tablets. The respective MDT values for the MicroceLac[®]-containing flat faced and concave tablets were 22.86 ± 17.199 min and 29.04 ± 8.962 min in comparison to 13.70 ± 10.563 min and 15.53 ± 9.372 min for the Avicel[®]-containing flat faced and concave tablets, respectively. This tendency corresponded with lower I_{dr} values for the MicroceLac[®]-containing tablets in comparison to the Avicel[®]-containing tablets. The respective overall average I_{dr} values for the MicroceLac[®]-containing flat faced and concave tablets were 3.56 ± 0.816 %.min⁻¹ and 3.32 ± 1.1695 %.min⁻¹ in comparison to 4.44 ± 0.308 %.min⁻¹ and 4.25 ± 0.235 %.min⁻¹ for the Avicel[®]-containing flat faced and concave tablets

respectively. In comparison to the dry powder and granule-containing tablets, the MicroceLac[®]-containing bead formulated tablet formulations exhibited MDT values and I_{dr} values similar to the MicroceLac[®]-containing granule tablets. However, the tablets prepared from the dry powder formulations exhibited on average shorter MDT values and faster I_{dr} values. Avicel[®]-containing bead tablets exhibited results similar to that of the Avicel[®]-containing granule tablets with regard to MDT and I_{dr} values.

4.6.4 INFLUENCE OF SPECIFIC FACTORS ON DISSOLUTION

4.6.4.1 Effect of diluent (filler)

It is evident from the dissolution profiles that in general, irrespective of the particle type and punch type, that the filler has a significant influence on the dissolution behaviour of the formulation (ANOVA, $p < 0.05$). This is confirmed by the faster average MDT values and faster I_{dr} values of the Avicel[®]-containing tablets in comparison to the MicroceLac[®]-containing tablets compressed from powder and granule formulations with a similar composition. The effect of the diluent on the dissolution process may in part be attributed to the higher mechanical strength as indicated by the crushing strength values of the MicroceLac[®]-containing tablets. The lower mechanical strength of the Avicel[®]-containing tablets in conjunction with the inherent disintegrant properties of microcrystalline cellulose (not evident as co-processed excipient) possibly contributed to the faster dissolution of the Avicel[®]-containing tablets. Furthermore, as mentioned earlier MicroceLac[®] consists of a MCC-lactose combination. The lactose component in this filler apparently mediated binding properties during the compression of tablets. Furthermore, the lactose component of the filler is very sensitive towards the binder used in tablet formulations and then mediates a stronger bound tablet with higher binding properties than that of Avicel[®]-containing formulations (Chitu *et al.*, 2011:441-442).

4.6.4.2 Particle type

Analysis of the dissolution data, especially MDT data indicated that besides the type of diluent, particle type in conjunction with disintegrant concentration (Ac-di-sol[®]) also had a significant effect on mean dissolution time (ANOVA, $p < 0.05$). An increase in disintegrant concentration resulted in a decrease in MDT for the dry powder tablets with average MDT values of 17.25 and 10.79 min for the 0.5% w/w and 1.0% w/w disintegrant concentration respectively. However, this same tendency was not observed for the granule tablets. The statistical analysis, however, indicated that the granule and bead tablets exhibited a tendency towards similar MDT values at a disintegrant concentration of 0.5% w/w, with average MDT values of 18.15 and 17.93 min for the granule and bead tablets, respectively. At a disintegrant concentration of 1.0% w/w, the MDT values of the granule and bead tablets

remained similar at 21.81 and 22.64 min, respectively. An increase in disintegrant concentration in granule and bead formulations therefore appeared to render no significant difference in MDT.

Statistical analysis (ANOVA) of I_{dr} data indicated that the particle type in conjunction (interaction) with the diluent had a significant effect on I_{dr} . For the dry powder tablets, MicroceLac®-containing tablets exhibited slightly slower average I_{dr} values (4.05 and 4.56 % $\cdot$ min⁻¹, respectively) than the Avicel®-containing dry powder tablets. However, this difference was more pronounced for the MicroceLac®-containing granule tablets in comparison to the Avicel®-containing granule tablets, with average I_{dr} values of 2.65 and 4.84 % $\cdot$ min⁻¹ respectively. The bead tablets exhibited a similar tendency.

The slower dissolution of the granule formulations is probably due to the larger size and a consequently slower dissolution rate of the granule and bead tablets, affecting both MDT and I_{dr} .

4.6.4.3 Punch type

The variation in punch type did not have a significant influence on the dissolution properties as characterised by MDT and I_{dr} of the different tablet formulations, irrespective of particle type or diluent used in this study (ANOVA).

4.7 SUMMARY

It is evident from the dissolution results that the excipients such as the diluent, binder and disintegrant; and their concentrations influence the dissolution rate even if it is formulated as immediate release tablets. Furthermore, the particle type (dry powder, granule or bead) also influences dissolution behaviour as characterised by MDT and I_{dr} . In general, the larger the particle size, the slower the dissolution rate. However, the influence of particle type on dissolution rate is also dependent on interactions between excipients included in a formulation, for instance the binder and the disintegrant. It is clear from the results, that the dissolution rate is affected by the type of diluent used and the interplay or interaction between the excipients. The interaction between the diluent and other excipients are highly dependent on the specific diluent, even for direct compressible diluents.

It is possible that the effect on dissolution is also related to the mechanical strength as indicated by crushing strength and consequently the disintegration time of the tablets. This is also dependent on the excipients used in the tablets. For instance, in general MicroceLac®-containing tablets exhibited higher crushing strength values than Avicel®-containing tablets with a similar composition. The MicroceLac®-containing tablets

consequently also exhibited higher average disintegration times in general. For the MicroceLac[®]-containing tablets, the increase in disintegration time was also dependent on the particle type with granule tablets and bead tablets exhibiting the longest disintegration times. The faster disintegration times of the Avicel[®]-containing tablets may be attributed to the fact that Avicel[®] is comprised of MCC as single ingredient. MCC has inherent disintegration properties and it is known that tablet disintegration commence fast as can be seen in the results in Table 4.19 and 4.20 (Whang *et al.*, 2015:275-278).

It is evident from the results that a burst release was observed for all the Avicel[®]-containing tablets. The multiple unit particle (beads and granules) MicroceLac[®]-containing tablets, exhibited a slower dissolution rate, with disintegration time and the hardness of the tablet playing a pronounced role. Furthermore, it is clear by examining Figure 4.11 – 4.15, that the formulations containing MicroceLac[®] showed a prolonged dissolution process throughout the study for all formulations. Most of the MicroceLac[®] formulations also exhibited harder tablets with significantly higher disintegrations times. All of these properties mediated the prolonged dissolution process of tablets containing MicroceLac[®].

5 CHAPTER 5: SUMMARY AND FUTURE PROSPECTS

5.1 SUMMARY

Delivering an active ingredient to the area of pharmacological action requires the formulation and manufacture of a suitable dosage form to administer the active ingredient. The dosage form should ideally be self-administered by the patient and ensure optimal stability and efficacy of the active ingredient. Tablets have been used as solid oral dosage forms since the early eighteen hundreds. Tablets are generally well accepted by patients and patient compliance is consequently high (Jivraj *et al.*, 2000:58; Fridrun & Podczek., 2012:215). It is important to keep modernising this well known dosage form to improve therapy and patient compliance.

In this study the effect of the particle type as well as punch type on the physical and compaction properties of the different particle type formulations was investigated. Twenty formulations were formulated varying with regard to the amount of disintegrant (Ac-di-sol®), binder (Kollidon® VA 64) and the type of filler (Avicel® or MicroceLac®). Formulations were prepared in three different particle types (dry powders, granules and beads). The different particle type formulations were characterised in terms of powder flow. Flow properties are one of the most important aspects influencing the compression process of tablets and the general handling of the formulations prior to compression. Acceptable flowability of formulations intended for tableting is of utmost importance to ensure a fluent compression process and tablets possessing good uniformity and stability. The flowability of the different formulations was characterised with regard to angle of repose (AOR), flow rate, critical orifice diameter (COD), % compressibility and Hausner ratio.

Flow results indicated that it was clear that the dry powder and bead-containing formulations exhibited the best flow properties. The granule formulations gave inconsistent results, especially with respect to flow rate, and this may be explained in terms of particle geometry and particle surface texture as the granules exhibited irregular shaped particles. The flow results indicated that the larger, more spherically shaped particles (beads) generally exhibited the best flowability.

Upon characterising the flow properties, concave and flat faced tablets were compressed using flat faced and concave 9 mm diameter punch sets. Thus, flat faced and concave tablets were compressed for each formulation evaluated in terms of powder flow in this study and a total of 40 formulations was compressed. The tablet mass were kept constant at 250 mg. Tablets were evaluated with respect to crushing strength, tablet diameter, tablet

thickness, disintegration time, friability and mass variation. All of the tablet batches compressed (from the different formulations) exhibited acceptable mechanical properties according to the specifications of the British Pharmacopoeia (BP). Differences were noted between the Avicel® and the MicroceLac®-containing tablet formulations with the MicroceLac®-containing tablet formulations producing harder tablets than the Avicel®-containing tablet formulations. Thus, higher average crushing strength and average disintegration time values were recorded for MicroceLac®-containing tablets. Granule-containing tablets showed more variation in tablet mass than the dry powder and bead-containing tablets, but still complied with BP specifications. It was evident from the results that the filler and particle type influenced the physical properties of the tablets. Different punch types did not have a pronounced effect on the physical properties of the tablets.

Dissolution studies were conducted to investigate the dissolution behaviour of the different tablet formulations. The dissolution studies were conducted over 4 hours. Dissolution profiles were characterised in terms of % dissolution, mean dissolution time (MDT) and initial dissolution rate (I_{dr}). All of the formulations exhibited a % dissolution of 90 – 100% within the 4 hour period indicating drug release from the different tablet formulations. Once again there was a pronounced difference between the Avicel® and the MicroceLac®-containing tablet formulations, with Avicel®-containing tablet formulations showing a burst release of the active ingredient and MicroceLac®-containing tablet formulations showing a release over a longer period of time. Dry powder formulations showed the fastest release profiles, specifically the Avicel®-containing dry powder tablets, with the shortest average MDT and the fastest average I_{dr} values. Bead-containing tablet formulations showed an almost similar pattern than the dry powder tablet formulations. Granule-containing tablet formulations showed a more delayed dissolution profile, especially the MicroceLac®-containing granule tablet formulations. It was clear from the dissolution results that the choice of filler had a significant effect (ANOVA) on the dissolution behaviour of the tablets. However, interplay between particle type and disintegrant also had a significant effect (ANOVA, $p < 0.05$) on the dissolution behaviour. Punch type however, did not have a significant effect on dissolution behaviour.

5.2 FUTURE PROSPECTS

This study highlighted a need for investigation regarding the following:

- The nature of the sensitivity of the MCC-lactose (MicroceLac®) combination towards different types of binders used for tablet formulations, including Kollidon® VA 64.
- If the insignificant effect of punch type is also applicable to different punch sizes when compressing tablets from different particle types using different fillers.

- The possibilities of improving the flow properties of granule particles.
- The possibility of using bead particles for possible immediate release dosage forms because of the improved flow properties of bead particles in comparison to granules.

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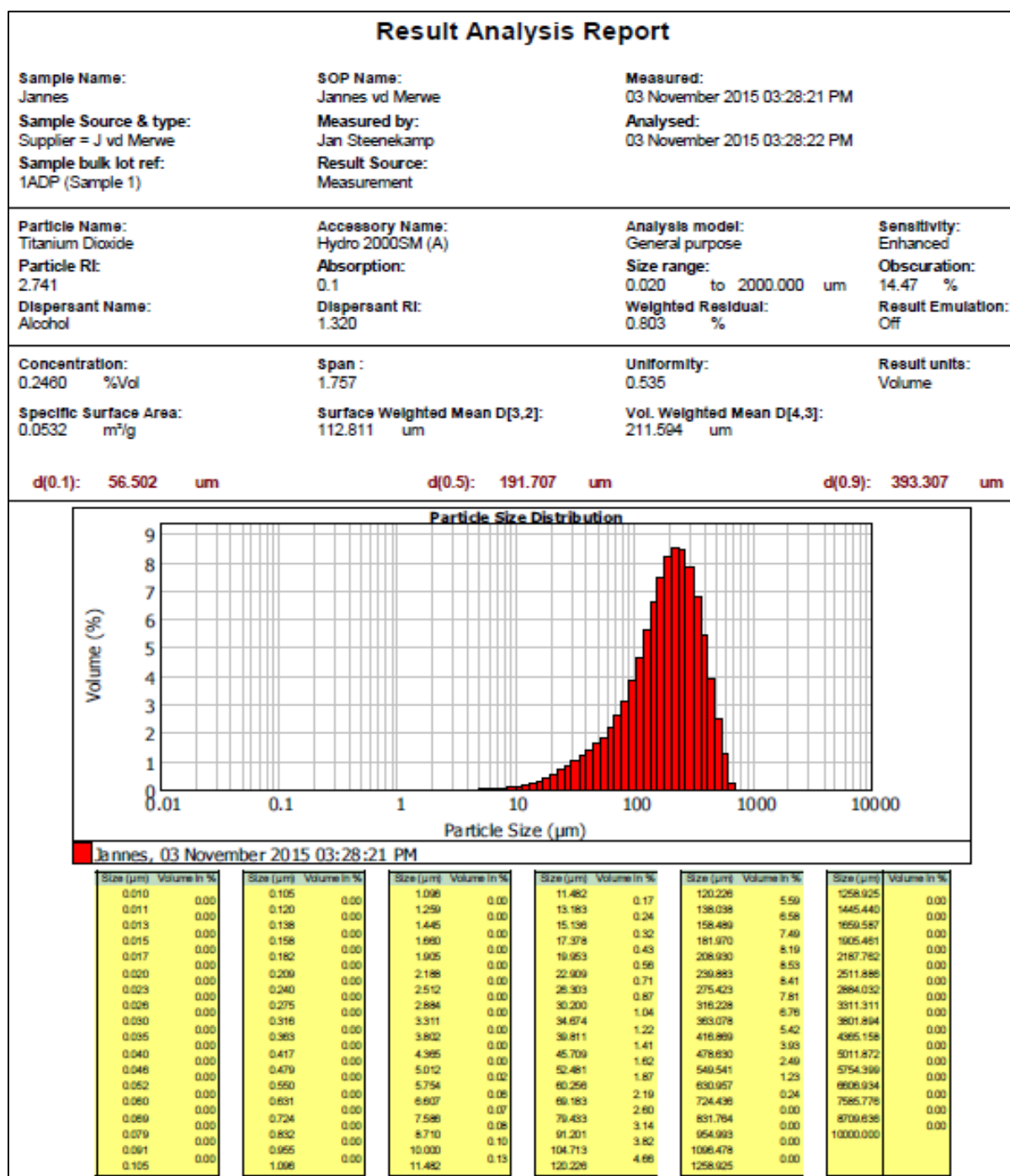
7 ANNEXURE A: PARTICLE SIZE DATA

7.1 AVICEL®-CONTAINING FORMULATIONS

7.1.1 AVICEL®-CONTAINING DRY POWDER FORMULATIONS

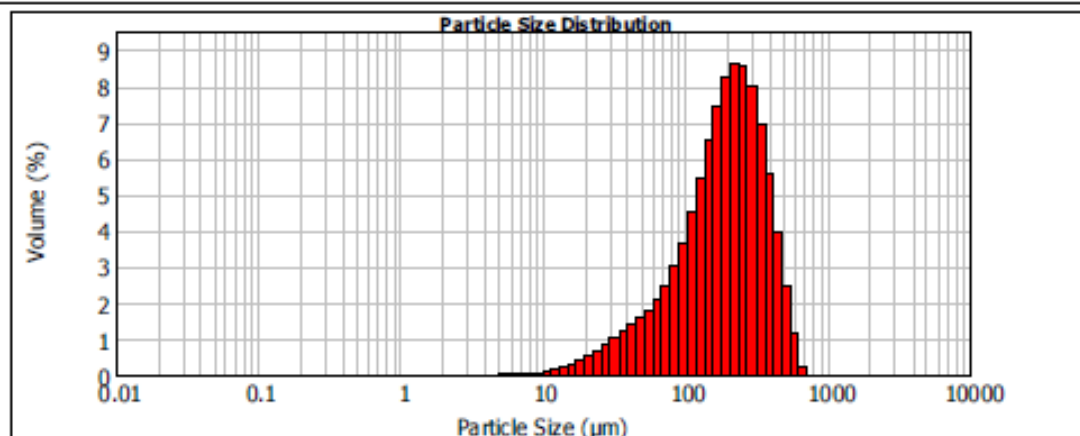
7.1.1.1 Formulation 1

In the following figures the particle size distribution data for Avicel®-containing dry powder formulation 1 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:29:01 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:29:02 PM	
Sample bulk lot ref: 1ADP (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 μm	Obscuration: 14.45 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.733 %	Result Emulation: Off
Concentration: 0.2488 %Vol	Span : 1.729	Uniformity: 0.527	Result units: Volume
Specific Surface Area: 0.0525 m^2/g	Surface Weighted Mean D[3,2]: 114.255 μm	Vol. Weighted Mean D[4,3]: 213.554 μm	
d[0.1]: 57.219 μm	d[0.5]: 194.832 μm	d[0.9]: 394.071 μm	



Jannes, 03 November 2015 03:29:01 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	1.098	0.00	11.482	0.17	120.228	5.48	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.23	138.038	6.52	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.32	158.489	7.49	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.42	181.970	8.27	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.55	208.930	8.67	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.70	239.883	8.61	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.86	275.423	8.02	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.03	316.228	6.96	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.20	363.078	5.99	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.38	416.869	4.01	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.58	478.630	2.50	5011.672	0.00
0.046	0.00	0.479	0.00	5.012	0.02	52.481	1.81	549.541	1.19	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.08	60.256	2.10	630.957	0.22	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.07	69.183	2.49	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.08	79.433	3.01	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.10	91.201	3.68	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.12	104.713	4.52	1096.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.12	120.228	4.52	1258.925	0.00		

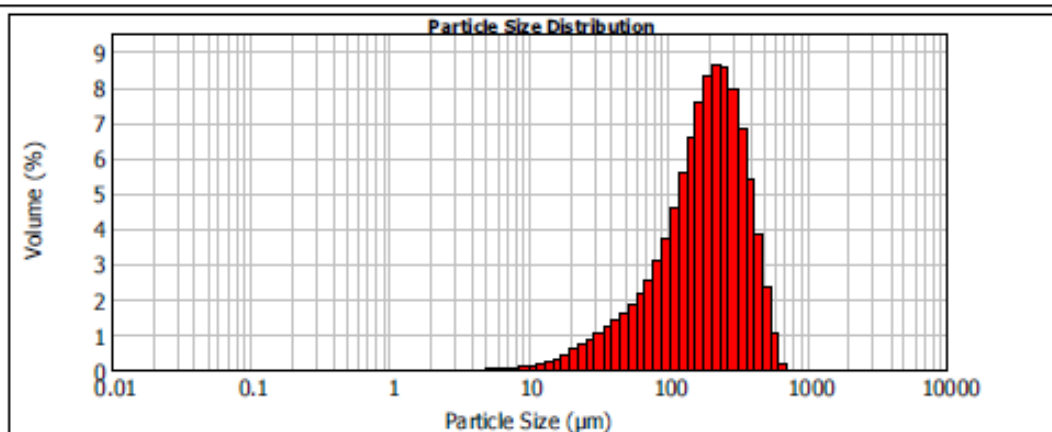
Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:29:40 PM
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:29:41 PM
Sample bulk lot ref: 1ADP (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: 14.09 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.791 %	Result Emulation: Off

Concentration: 0.2377 %Vol	Span : 1.733	Uniformity: 0.527	Result units: Volume
Specific Surface Area: 0.0535 m ² /g	Surface Weighted Mean D[3,2]: 112.214 um	Vol. Weighted Mean D[4,3]: 210.283 um	

d(0.1): 55.941 um **d(0.5):** 191.873 um **d(0.9):** 388.464 um

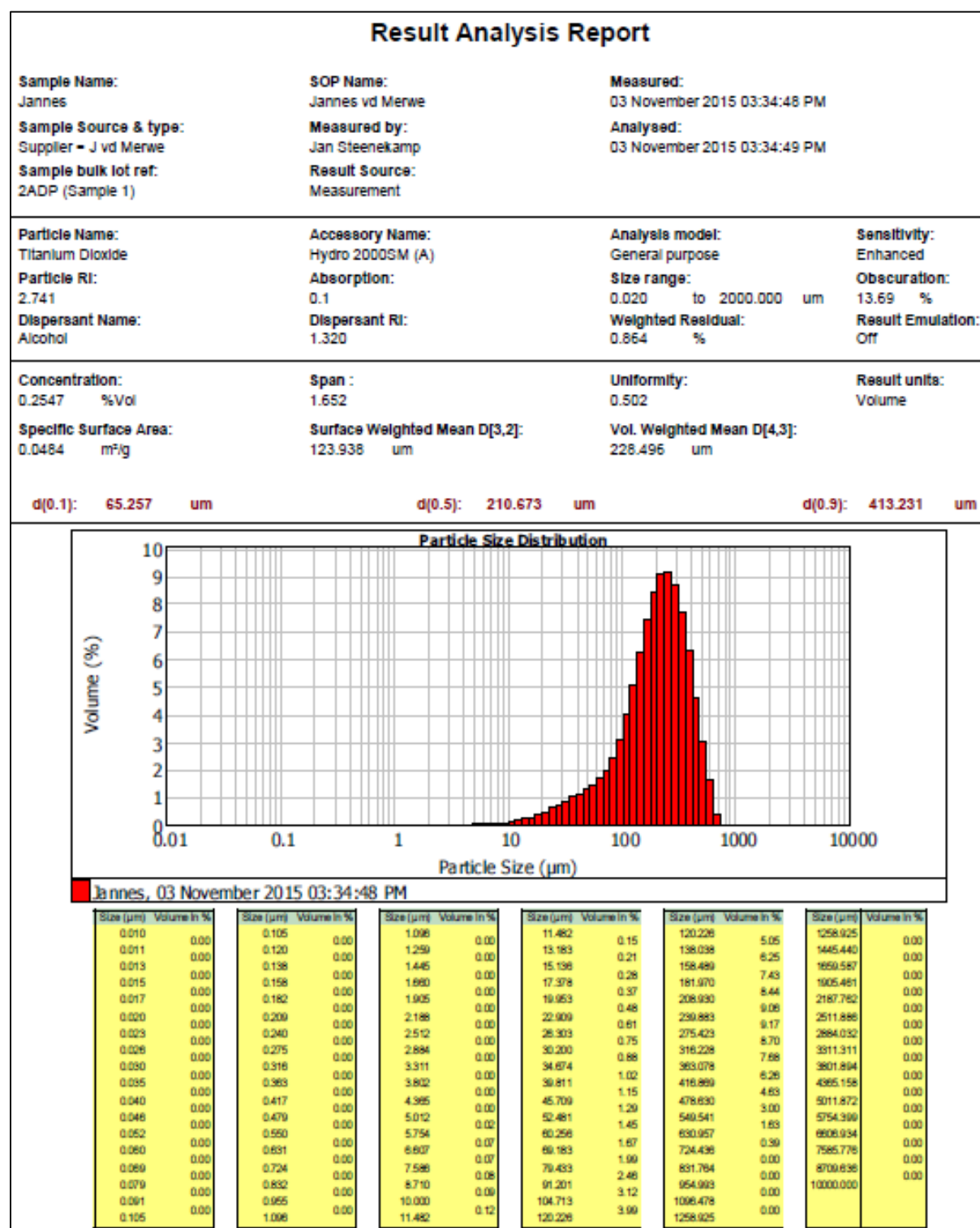


Jannes, 03 November 2015 03:29:40 PM

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	0.18	120.226	5.57	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.24	138.038	6.60	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.196	0.33	158.489	7.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.690	0.00	17.378	0.44	181.970	8.30	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.58	208.930	8.87	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.73	239.883	8.87	2511.888	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.89	275.423	7.92	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.08	316.228	6.83	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.24	363.078	5.42	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.42	416.869	3.88	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.62	478.630	2.37	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.85	549.541	1.05	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	2.15	630.957	0.15	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.54	724.436	0.00	7585.778	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.07	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.10	91.201	3.78	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.13	104.713	4.60	1098.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.13	120.226	4.60	1258.925	0.00		

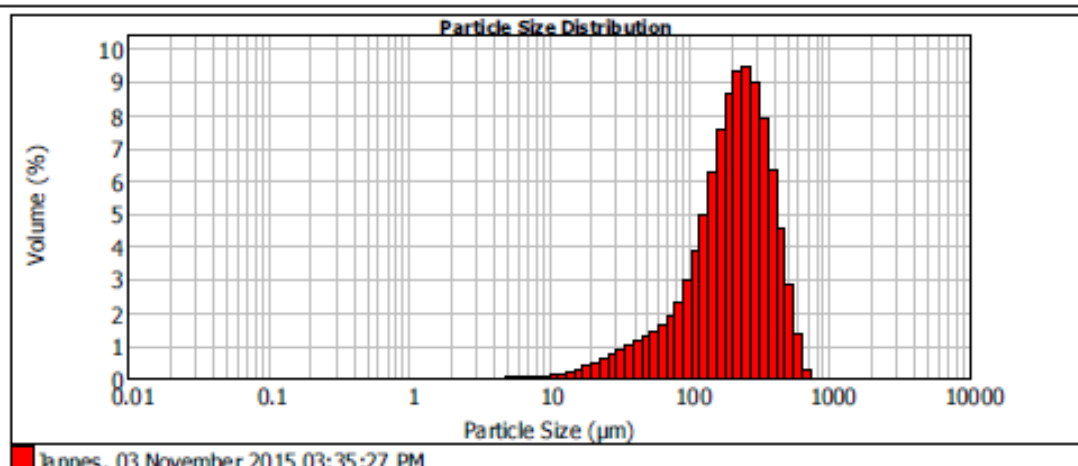
7.1.1.2 Formulation 2

In the following figures the particle size distribution data for Avicel®-containing dry powder formulation 2 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:35:27 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:35:28 PM	
Sample bulk lot ref: 2ADP (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 μm	Obscuration: 13.33 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.944 %	Result Emulation: Off
Concentration: 0.2494 %Vol	Span : 1.602	Uniformity: 0.486	Result units: Volume
Specific Surface Area: 0.048 m^2/g	Surface Weighted Mean D[3,2]: 124.899 μm	Vol. Weighted Mean D[4,3]: 227.614 μm	
d[0.1]: 66.349 μm d[0.5]: 212.078 μm d[0.9]: 406.170 μm			



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	1.098	0.00	11.482	0.15	120.228	4.99	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.20	138.038	6.26	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.27	158.489	7.52	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.37	181.970	8.83	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.963	0.48	208.930	9.33	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.61	239.883	9.48	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.74	275.423	8.99	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.88	316.228	7.89	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.01	363.078	6.35	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.13	416.869	4.57	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.25	478.630	2.83	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.02	52.481	1.40	549.541	1.31	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.07	60.256	1.59	630.957	0.22	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.07	69.183	1.89	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.08	79.433	2.34	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	2.99	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.12	104.713	3.89	1096.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.12	120.228	3.89	1258.925	0.00		

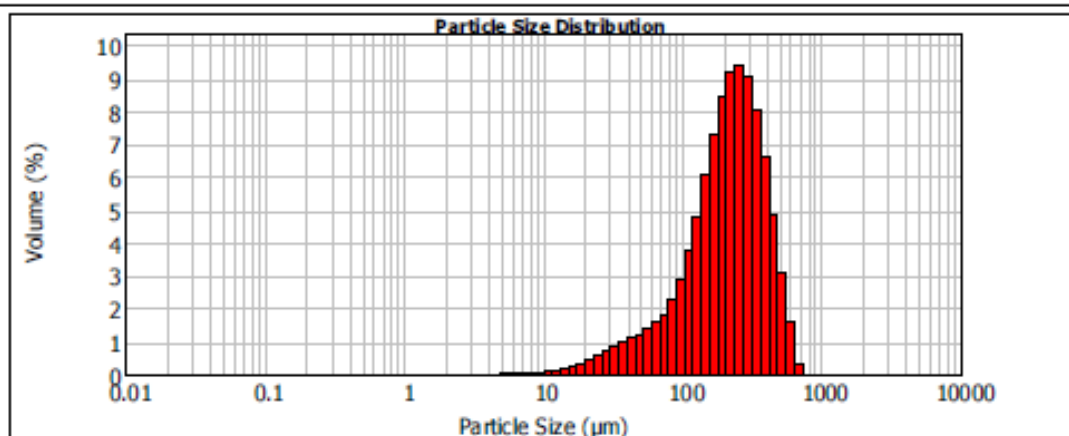
Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:36:06 PM
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analyzed: 03 November 2015 03:36:08 PM
Sample bulk lot ref: 2ADP (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 μm	Obscuration: 13.22 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.933 %	Result Emulation: Off

Concentration: 0.2510 %Vol	Span : 1.610	Uniformity: 0.487	Result units: Volume
Specific Surface Area: 0.0473 m^2/g	Surface Weighted Mean D[3,2]: 126.749 μm	Vol. Weighted Mean D[4,3]: 232.438 μm	

d(0.1): 67.205 μm
d(0.5): 216.406 μm
d(0.9): 415.725 μm

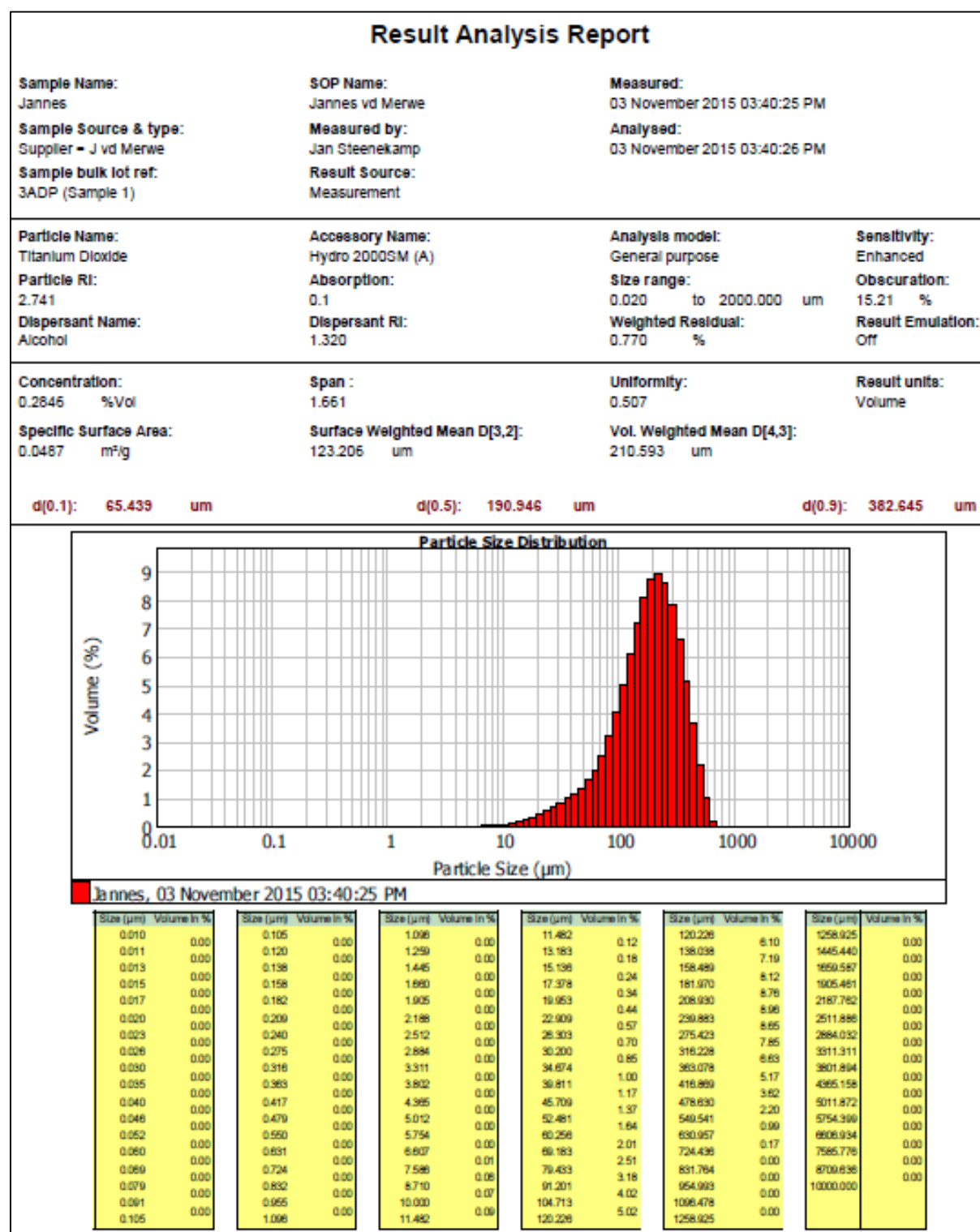


■ Jannes, 03 November 2015 03:36:06 PM

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	0.15	120.226	4.81	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.20	138.038	6.06	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.27	158.489	7.32	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.36	181.970	8.44	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.47	208.930	9.20	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.59	239.883	9.44	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.73	275.423	9.07	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.88	316.228	8.08	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.99	363.078	6.82	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.12	418.869	4.88	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.24	478.630	3.12	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.02	52.481	1.37	549.541	1.57	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.05	60.256	1.56	630.957	0.32	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.07	69.183	1.84	724.436	0.00	7585.778	0.00
0.069	0.00	0.724	0.00	7.586	0.08	79.433	2.27	831.794	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	2.89	954.993	0.00	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.09	104.713	3.74	1098.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.11	120.226		1258.925	0.00		

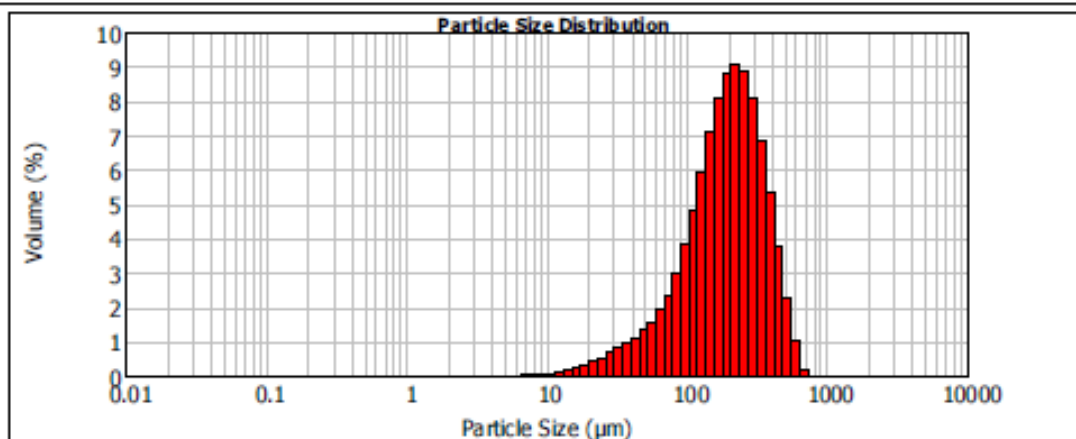
7.1.1.3 Formulation 3

In the following figures the particle size distribution data for Avicel®-containing dry powder formulation 3 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:41:04 PM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:41:05 PM	
Sample bulk lot ref: 3ADP (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 μm	Obscuration: 14.83 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.778 %	Result Emulation: Off
Concentration: 0.2826 %Vol	Span : 1.637	Uniformity: 0.5	Result units: Volume
Specific Surface Area: 0.0477 m^2/g	Surface Weighted Mean D[3,2]: 125.747 μm	Vol. Weighted Mean D[4,3]: 214.065 μm	
d[0.1]: 67.173 μm d[0.5]: 195.134 μm d[0.9]: 386.601 μm			

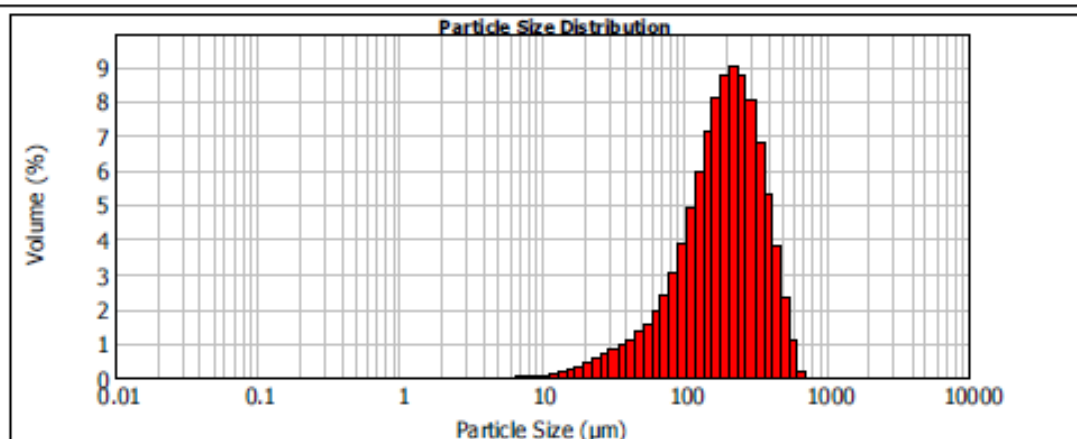


Jannes, 03 November 2015 03:41:04 PM

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	0.12	120.226	5.94	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.17	138.038	7.08	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.23	158.480	8.08	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.32	181.970	8.81	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.43	208.930	9.10	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.55	239.883	8.86	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.68	275.423	8.10	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.82	316.228	6.88	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.97	363.078	5.38	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.13	418.869	3.78	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.32	478.630	2.29	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.57	549.541	1.03	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.91	630.957	0.17	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.01	69.183	2.38	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.06	79.433	3.02	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	3.84	954.993	0.00	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.09	104.713	4.84	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.12	120.226	5.94	1258.925	0.00		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:41:44 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:41:45 PM	
Sample bulk lot ref: 3ADP (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 μm	Obscuration: 14.45 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.842 %	Result Emulation: Off
Concentration: 0.2739 %Vol	Span : 1.649	Uniformity: 0.504	Result units: Volume
Specific Surface Area: 0.0479 m^2/g	Surface Weighted Mean D[3,2]: 125.326 μm	Vol. Weighted Mean D[4,3]: 213.840 μm	
d(0.1): 67.219 μm	d(0.5): 194.246 μm	d(0.9): 387.452 μm	

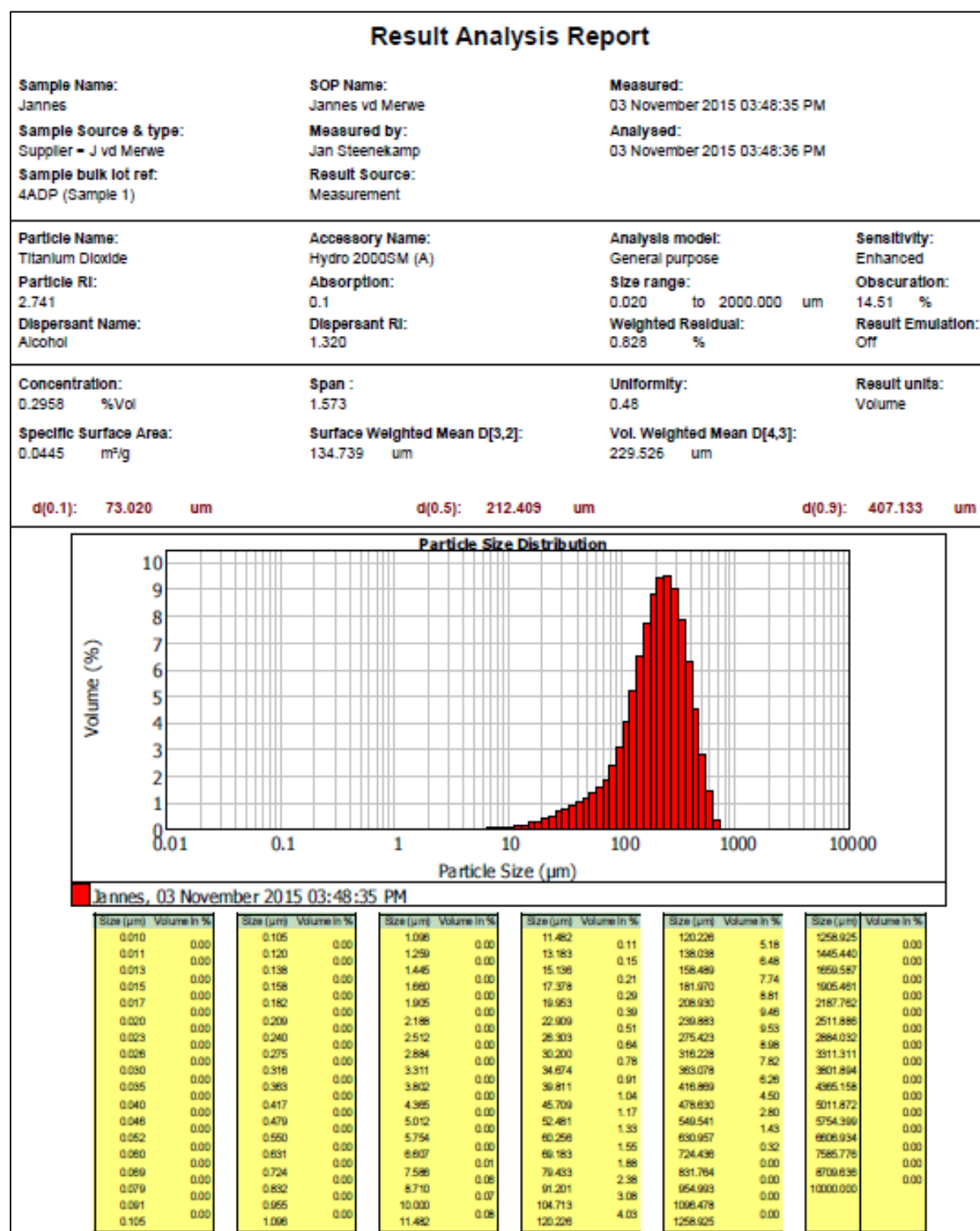


Jannes, 03 November 2015 03:41:44 PM

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	1.098	0.00	11.482	0.13	120.226	6.00	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.17	138.038	7.11	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.24	158.489	8.08	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.33	181.970	8.77	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.43	208.930	9.02	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.55	239.883	8.77	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.68	275.423	8.01	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.81	316.228	6.81	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.95	363.078	5.35	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.11	416.869	3.79	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	1.31	478.630	2.33	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.56	549.541	1.07	5754.369	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.92	630.957	0.18	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.01	69.183	2.41	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.06	79.433	3.07	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	3.90	954.993	0.00	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.09	104.713	4.91	1098.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.09	120.226		1258.925	0.00		

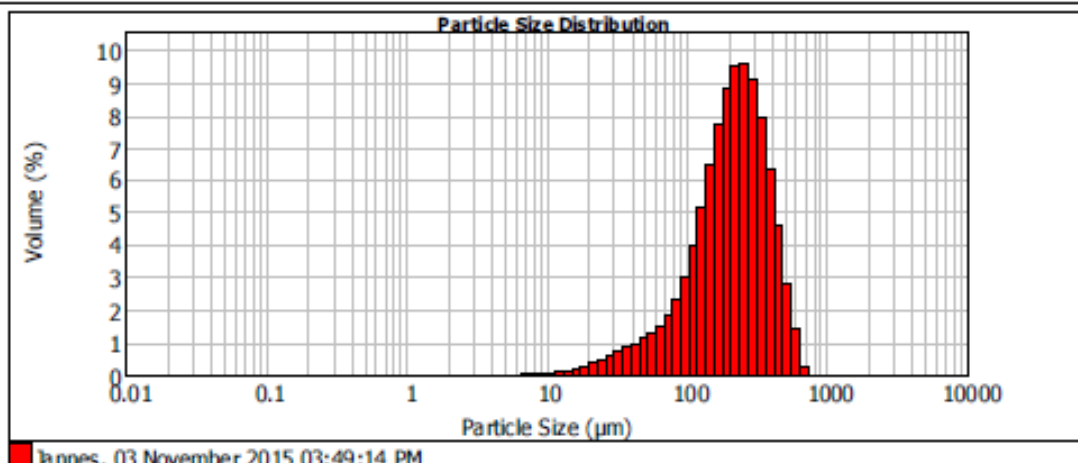
7.1.1.4 Formulation 4

In the following figures the particle size distribution data for Avicel®-containing dry powder formulation 4 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:49:14 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:49:16 PM	
Sample bulk lot ref: 4ADP (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 μm	Obscuration: 14.12 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.865 %	Result Emulation: Off
Concentration: 0.2908 %Vol	Span : 1.558	Uniformity: 0.475	Result units: Volume
Specific Surface Area: 0.044 m^2/g	Surface Weighted Mean D[3,2]: 136.332 μm	Vol. Weighted Mean D[4,3]: 230.727 μm	
d[0.1]: 74.797 μm d[0.5]: 213.768 μm d[0.9]: 407.932 μm			

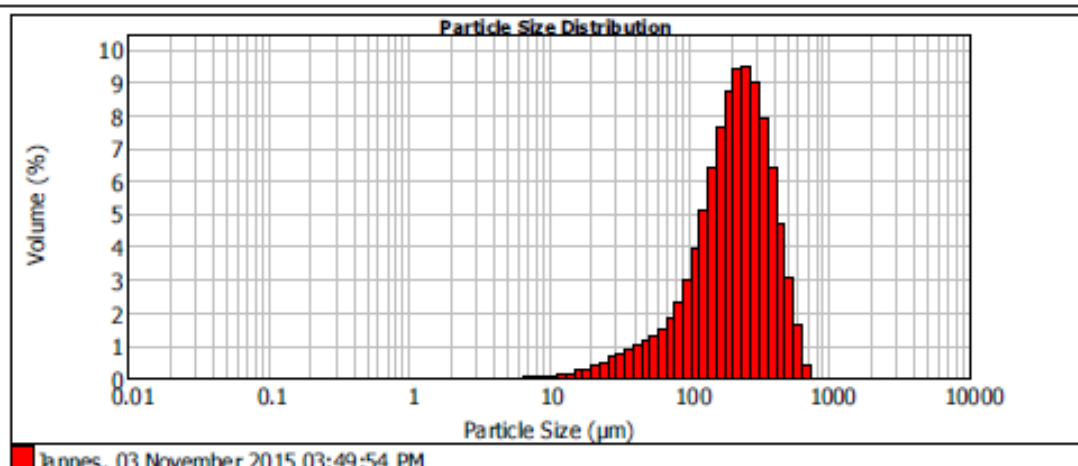


Jannes, 03 November 2015 03:49:14 PM

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	1.098	0.00	11.482	0.11	120.228	5.16	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.15	138.038	6.48	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.21	158.480	7.77	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.29	181.970	8.86	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.963	0.39	208.930	9.52	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.50	239.883	9.61	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.63	275.423	9.06	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.75	316.228	7.90	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.88	363.078	6.33	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.00	416.869	4.59	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.13	478.630	2.85	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.28	549.541	1.42	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.49	630.957	0.90	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.01	69.183	1.82	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.06	79.433	2.32	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	3.03	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.07	104.713	3.99	1096.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.08	120.228		1258.925	0.00		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:49:54 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:49:55 PM	
Sample bulk lot ref: 4ADP (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 μm	Obscuration: 13.79 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.858 %	Result Emulation: Off
Concentration: 0.2842 %Vol	Span : 1.579	Uniformity: 0.481	Result units: Volume
Specific Surface Area: 0.0439 m^2/g	Surface Weighted Mean D[3,2]: 136.730 μm	Vol. Weighted Mean D[4,3]: 233.316 μm	
d[0.1]: 74.876 μm d[0.5]: 215.341 μm d[0.9]: 414.835 μm			



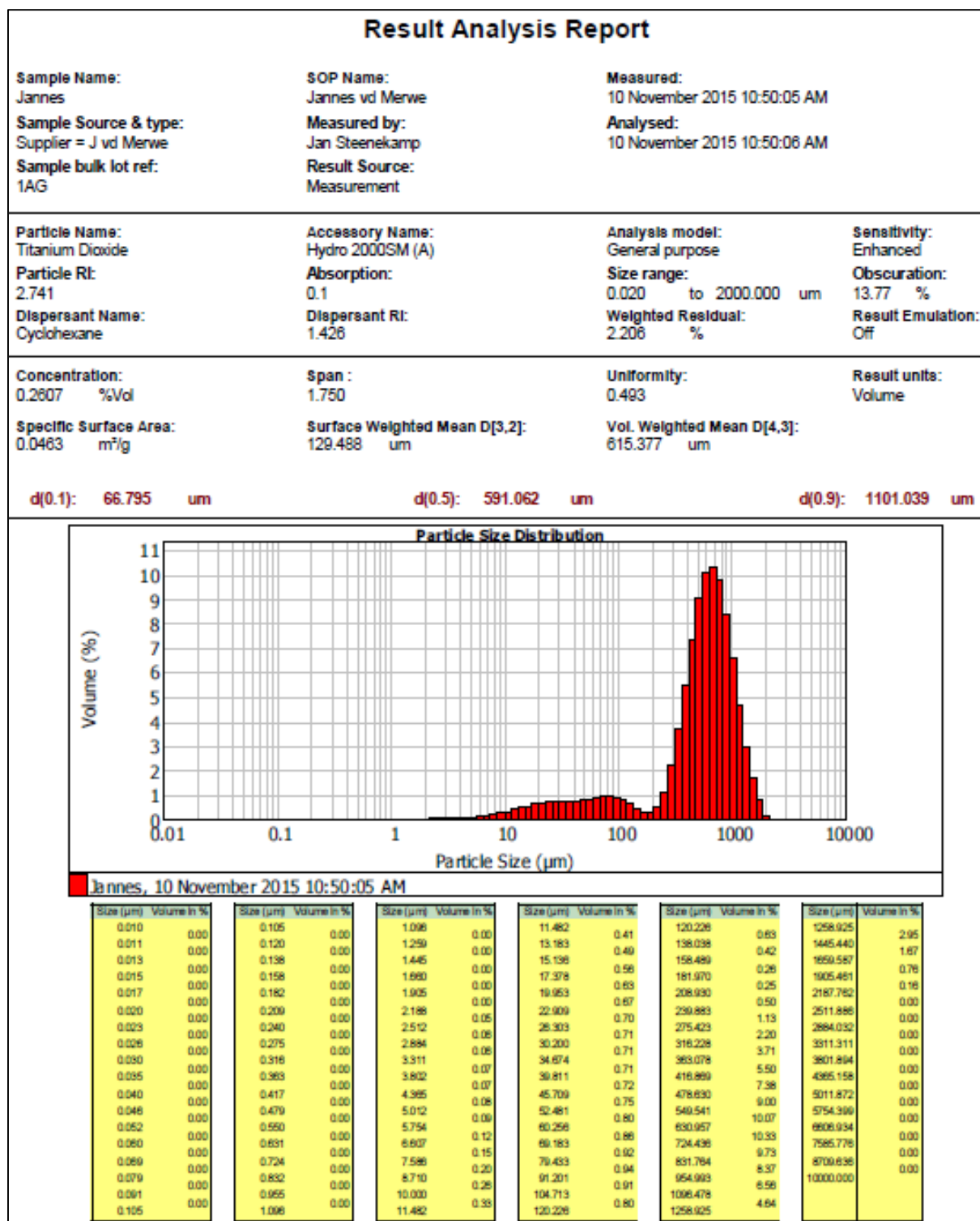
Jannes, 03 November 2015 03:49:54 PM

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	1.098	0.00	11.482	0.11	120.228	5.11	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.15	138.038	6.41	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.21	158.489	7.87	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.29	181.970	8.75	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.963	0.39	208.930	9.40	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.51	239.883	9.51	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.63	275.423	8.99	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.78	316.228	7.91	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.88	363.078	6.41	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.00	416.869	4.72	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.12	478.630	3.04	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.27	549.541	1.65	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.47	630.957	0.40	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	1.79	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.01	79.433	2.29	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	3.00	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.07	104.713	3.95	1096.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.08	120.228		1258.925	0.00		

7.1.2 AVICEL®-CONTAINING GRANULE FORMULATIONS

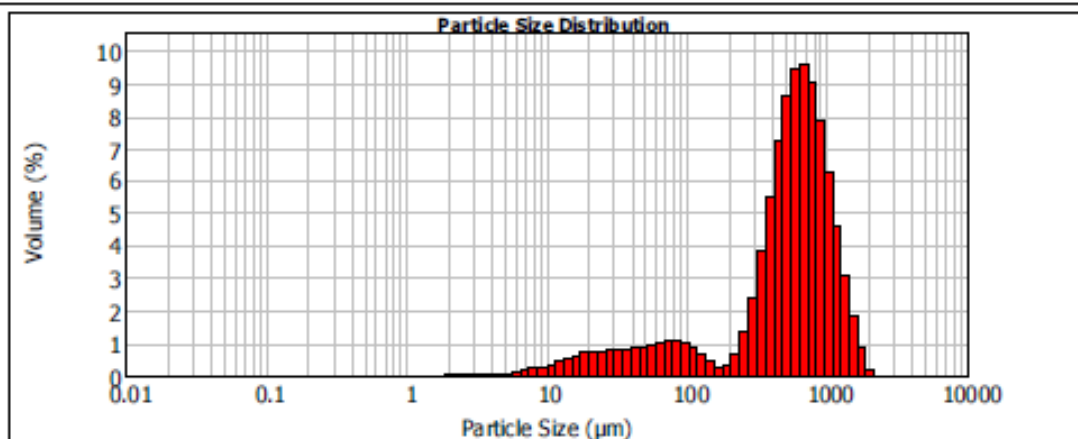
7.1.2.1 Formulation 1

In the following figures the particle size distribution data for Avicel®-containing granule formulation 1 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 10:50:46 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 10:50:46 AM	
Sample bulk lot ref: 1AG	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 μm	Obscuration: 14.66 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.836 %	Result Emulation: Off
Concentration: 0.2419 %Vol	Span : 1.852	Uniformity: 0.531	Result units: Volume
Specific Surface Area: 0.0532 m^2/g	Surface Weighted Mean D[3,2]: 112.832 μm	Vol. Weighted Mean D[4,3]: 601.766 μm	
d(0.1): 53.519 μm	d(0.5): 573.233 μm	d(0.9): 1114.987 μm	

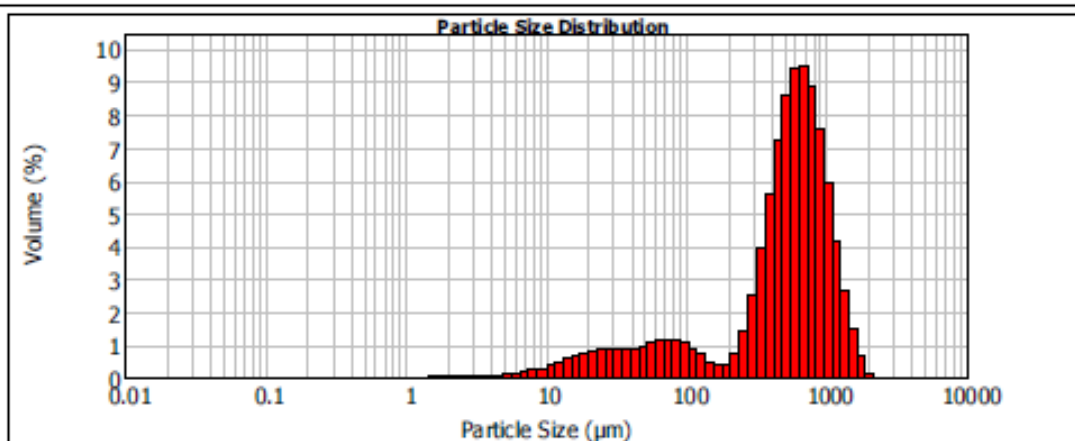


Jannes, 10 November 2015 10:50:46 AM

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	0.45	120.226	0.86	1258.925	3.08
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.54	138.038	0.44	1445.440	1.87
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.63	158.480	0.30	1659.587	0.91
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.70	181.970	0.33	1905.481	0.20
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.75	208.930	0.64	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.79	239.883	1.33	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.81	275.423	2.40	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.82	316.228	3.86	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.83	363.078	5.52	3601.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.86	418.869	7.20	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.90	478.630	8.59	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.97	549.541	9.45	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	1.03	630.957	9.61	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	1.08	724.436	9.03	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	1.08	831.764	7.83	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	1.01	954.993	6.26	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.00	104.713	0.86	1096.478	4.59		
0.105	0.00	1.096	0.00	11.482	0.37	120.226		1258.925			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 10:51:26 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 10:51:27 AM	
Sample bulk lot ref: 1AG	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 μm	Obscuration: 15.51 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.920 %	Result Emulation: Off
Concentration: 0.2323 %Vol	Span : 1.848	Uniformity: 0.535	Result units: Volume
Specific Surface Area: 0.0586 m^2/g	Surface Weighted Mean D[3,2]: 102.450 μm	Vol. Weighted Mean D[4,3]: 576.121 μm	
d(0.1): 47.934 μm d(0.5): 553.912 μm d(0.9): 1071.642 μm			

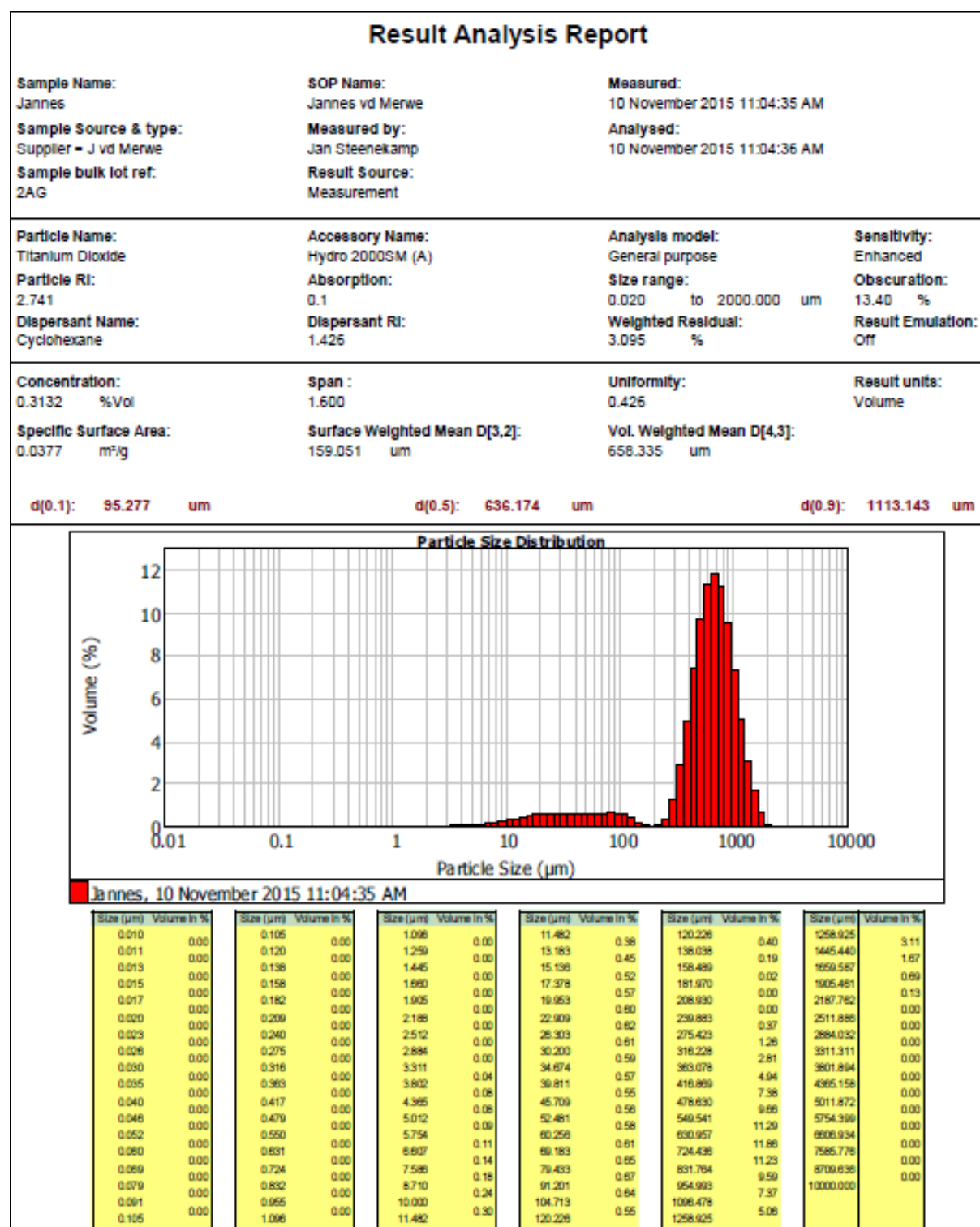


Jannes, 10 November 2015 10:51:26 AM

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	1.098	0.00	11.482	0.48	120.226	0.73	1258.925	2.66
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.58	138.038	0.51	1445.440	1.49
0.013	0.00	0.138	0.00	1.446	0.00	15.139	0.67	158.489	0.37	1659.587	0.67
0.015	0.00	0.158	0.00	1.660	0.01	17.378	0.67	181.970	0.42	1905.481	0.14
0.017	0.00	0.182	0.00	1.905	0.06	19.953	0.75	208.930	0.74	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.07	22.909	0.84	239.883	1.44	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.07	26.303	0.86	275.423	2.52	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	0.88	316.228	3.98	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	0.88	363.078	5.63	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	0.94	416.969	7.28	4385.158	0.00
0.040	0.00	0.417	0.00	4.385	0.09	45.709	0.99	478.630	8.63	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.11	52.481	1.06	549.541	9.44	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.14	60.258	1.13	630.957	9.54	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.18	69.183	1.18	724.436	8.88	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.23	79.433	1.17	831.784	7.59	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.30	91.201	1.09	954.993	5.93	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.39	104.713	0.94	1096.478	4.19		
0.105	0.00	1.098	0.00	11.482		120.226		1258.925			

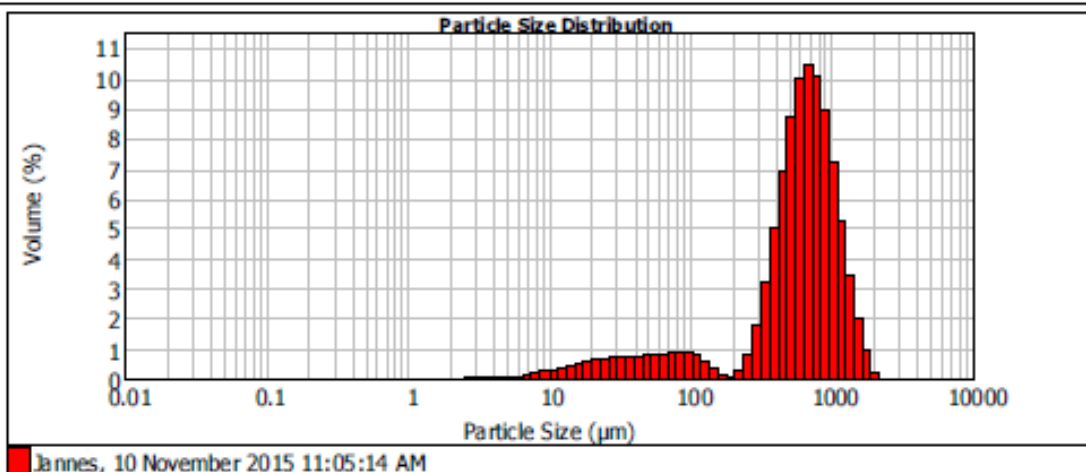
7.1.2.2 Formulation 2

In the following figures the particle size distribution data for Avicel®-containing granule formulation 2 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:05:14 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analyzed: 10 November 2015 11:05:16 AM	
Sample bulk lot ref: 2AG	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: 15.25 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 2.703 %	Result Emulation: Off
Concentration: 0.3157 %Vol	Span : 1.742	Uniformity: 0.483	Result units: Volume
Specific Surface Area: 0.0429 m ² /g	Surface Weighted Mean D[3,2]: 139.922 um	Vol. Weighted Mean D[4,3]: 645.886 um	
d(0.1): 69.940 um	d(0.5): 620.072 um	d(0.9): 1149.938 um	

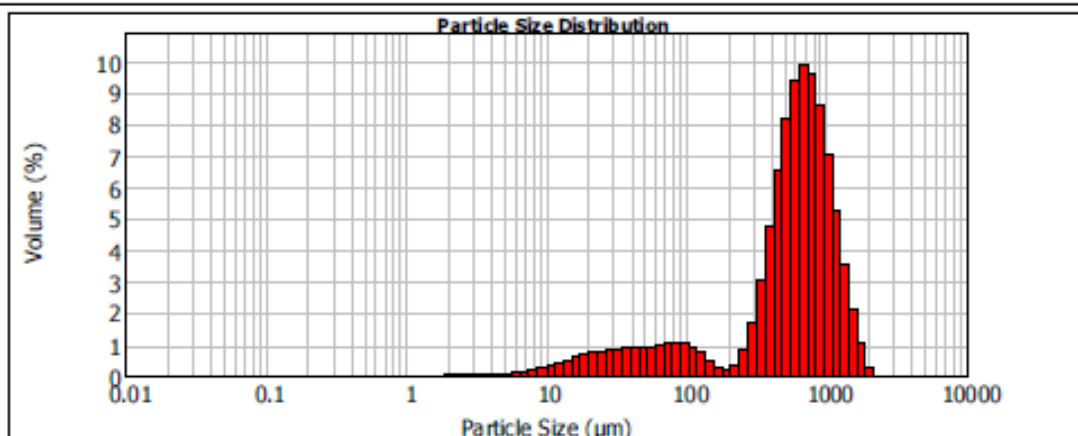


Jannes, 10 November 2015 11:05:14 AM

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	1.098	0.00	11.482	0.38	120.226	0.59	1258.925	3.49
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.46	138.038	0.36	1445.440	2.08
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.53	158.489	0.15	1659.587	0.99
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.60	181.970	0.07	1905.481	0.21
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.65	208.930	0.24	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.69	239.883	0.77	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.05	26.303	0.70	275.423	1.78	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.08	30.200	0.71	316.228	3.22	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	0.71	363.078	5.02	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.07	39.811	0.73	416.969	6.97	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.08	45.709	0.75	478.630	8.73	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.09	52.481	0.80	549.541	9.99	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.09	60.256	0.85	630.957	10.48	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.14	69.183	0.90	724.436	10.09	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.18	79.433	0.92	831.764	8.91	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.24	91.201	0.89	954.993	7.19	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.30	104.713	0.77	1098.478	5.27		
0.105	0.00	1.098	0.00	11.482		120.226		1258.925			

Result Analysis Report

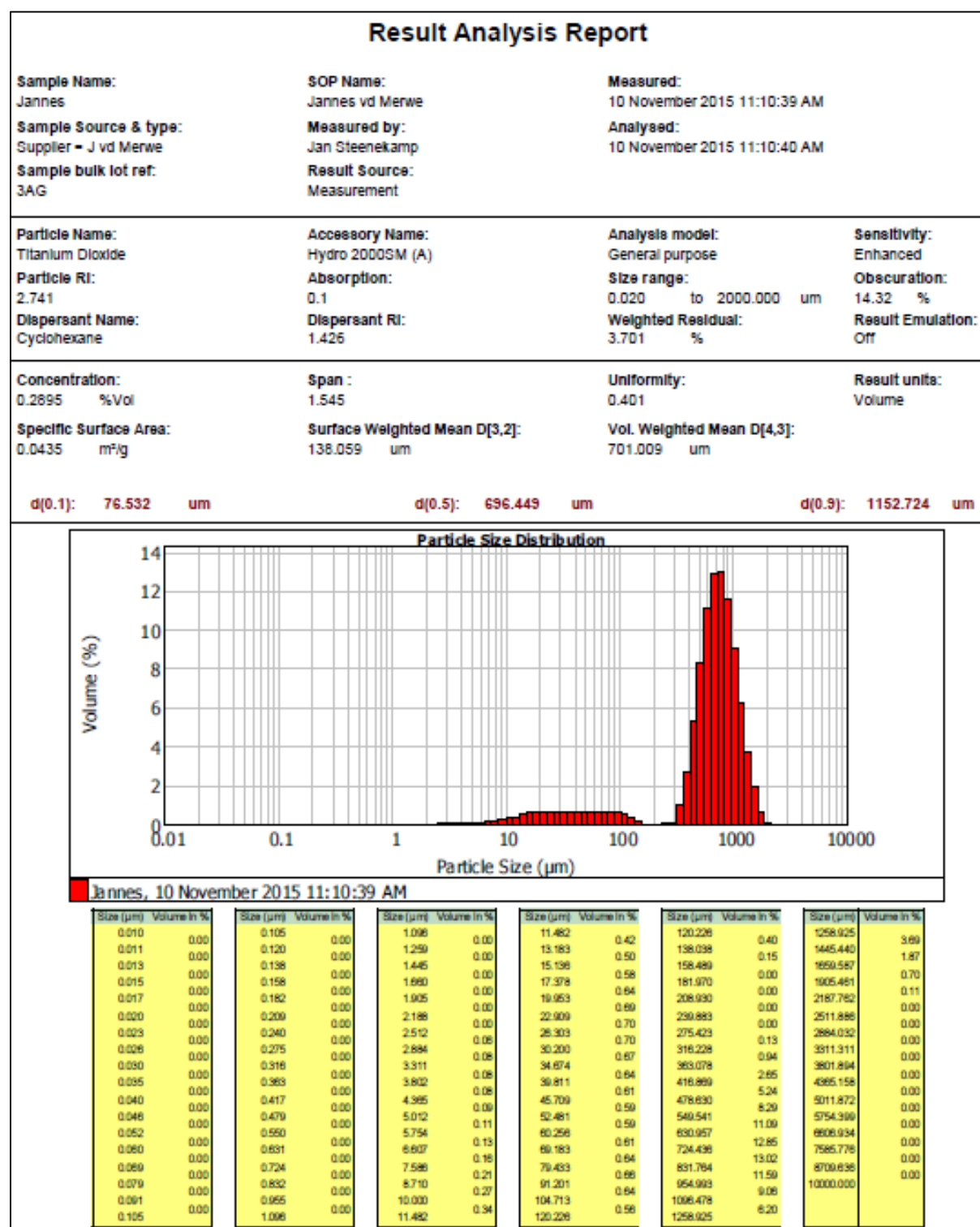
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:05:54 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:05:55 AM	
Sample bulk lot ref: 2AG	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 um	Obscuration: 16.34 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 2.661 %	Result Emulation: Off
Concentration: 0.2780 %Vol	Span : 1.813	Uniformity: 0.518	Result units: Volume
Specific Surface Area: 0.0521 m ² /g	Surface Weighted Mean D[3,2]: 115.179 um	Vol. Weighted Mean D[4,3]: 629.860 um	
d(0.1): 53.068 um d(0.5): 608.459 um d(0.9): 1156.376 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	1.098	0.00	11.482	0.43	120.226	0.74	1258.925	3.98
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.52	138.038	0.51	1445.440	2.15
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.61	158.489	0.30	1659.587	1.04
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.69	181.970	0.21	1905.461	0.22
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.76	208.930	0.35	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.05	22.909	0.81	239.883	0.82	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.07	26.303	0.84	275.423	1.71	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	0.86	316.228	3.05	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.07	34.674	0.88	363.078	4.71	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.08	39.811	0.90	416.869	6.52	4395.158	0.00
0.040	0.00	0.417	0.00	4.385	0.09	45.709	0.93	478.630	8.18	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	0.98	549.541	9.39	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.13	60.256	1.03	630.957	9.92	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.16	69.183	1.08	724.436	9.64	7585.778	0.00
0.069	0.00	0.724	0.00	7.586	0.21	79.433	1.09	831.784	8.61	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.27	91.201	1.04	954.993	7.05	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.34	104.713	0.92	1096.478	5.26		
0.105	0.00	1.098	0.00	11.482		120.226		1258.925			

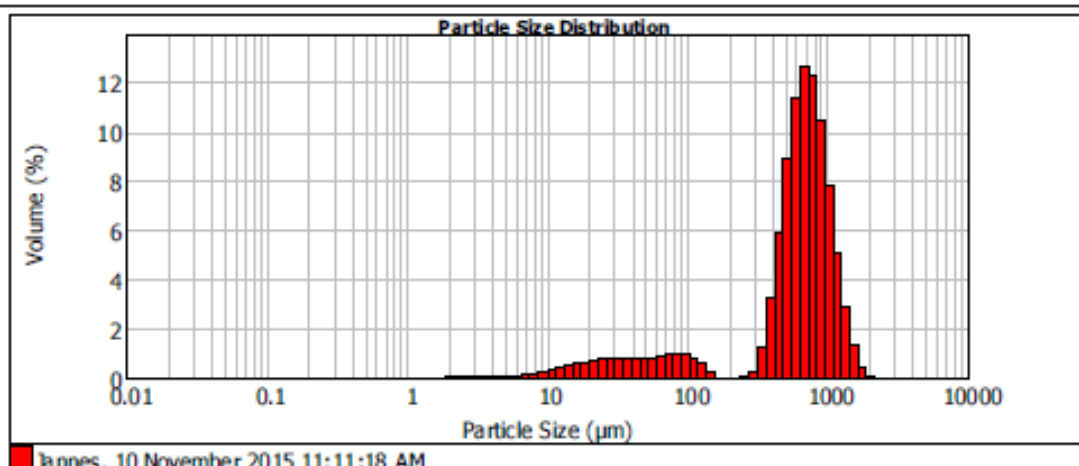
7.1.2.3 Formulation 3

In the following figures the particle size distribution data for Avicel®-containing granule formulation 3 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:11:18 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:11:19 AM	
Sample bulk lot ref: 3AG	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 μm	Obscuration: 16.72 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 3.488 %	Result Emulation: Off
Concentration: 0.2995 %Vol	Span : 1.582	Uniformity: 0.422	Result units: Volume
Specific Surface Area: 0.0495 m^2/g	Surface Weighted Mean D[3,2]: 121.148 μm	Vol. Weighted Mean D[4,3]: 650.610 μm	
d(0.1): 58.080 μm d(0.5): 654.540 μm d(0.9): 1093.531 μm			

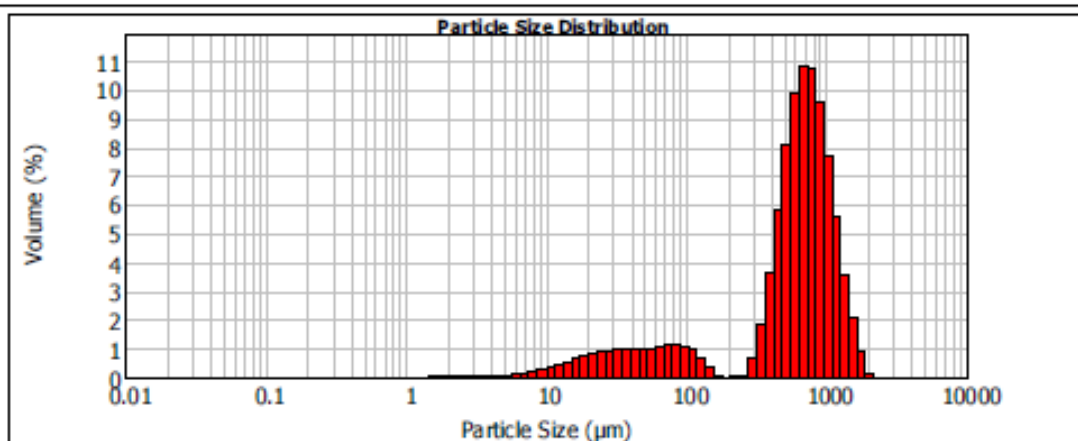


Jannes, 10 November 2015 11:11:18 AM

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	0.42	120.226	0.61	1258.925	2.86
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.51	138.038	0.24	1445.440	1.36
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.60	158.480	0.00	1650.587	0.48
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.68	181.970	0.00	1805.461	0.07
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.74	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.78	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.80	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.80	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.79	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.79	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.80	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.84	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.89	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.94	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.97	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.94	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.82	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.00	120.226		1258.925	5.09		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:12:01 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:12:02 AM	
Sample bulk lot ref: 3AG	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 μm	Obscuration: 18.48 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 2.697 %	Result Emulation: Off
Concentration: 0.2833 %Vol	Span : 1.731	Uniformity: 0.486	Result units: Volume
Specific Surface Area: 0.0582 m^2/g	Surface Weighted Mean D[3,2]: 103.181 μm	Vol. Weighted Mean D[4,3]: 643.901 μm	
d(0.1): 45.283 μm	d(0.5): 640.354 μm	d(0.9): 1153.675 μm	

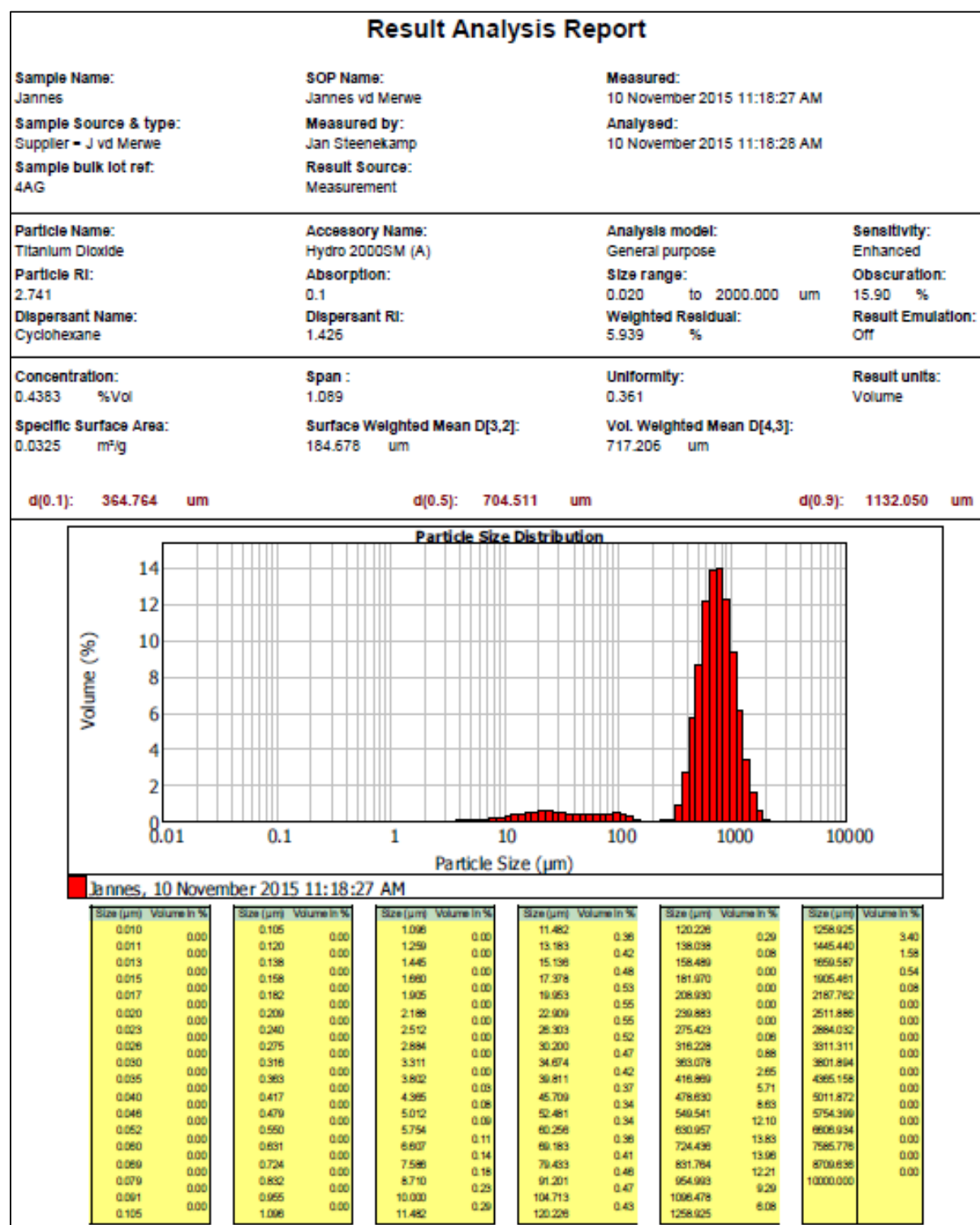


Jannes, 10 November 2015 11:12:01 AM

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	0.47	120.226	0.71	1258.925	3.80
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.58	138.038	0.38	1445.440	2.05
0.013	0.00	0.138	0.00	1.445	0.01	15.136	0.68	158.480	0.38	1659.587	0.90
0.015	0.00	0.158	0.00	1.660	0.01	17.378	0.77	181.970	0.08	1905.461	0.17
0.017	0.00	0.182	0.00	1.905	0.05	19.953	0.85	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.07	22.909	0.91	239.883	0.09	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.07	26.303	0.94	275.423	0.68	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.08	30.200	0.96	316.228	1.87	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	0.97	363.078	3.84	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	0.98	416.869	5.83	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.10	45.709	1.01	478.630	8.06	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.11	52.481	1.06	549.541	9.88	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.14	60.256	1.11	630.957	10.84	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.17	69.183	1.16	724.436	10.72	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.23	79.433	1.17	831.764	9.57	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.29	91.201	1.11	954.993	7.70	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.38	104.713	0.96	1096.478	5.57		
0.105	0.00	1.096		11.482		120.226		1258.925			

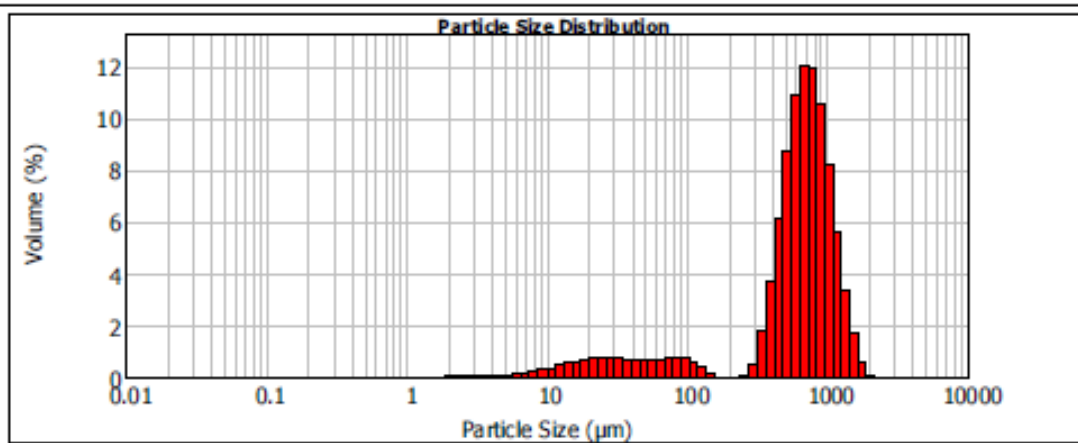
7.1.2.4 Formulation 4

In the following figures the particle size distribution data for Avicel®-containing granule formulation 4 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:19:07 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:19:10 AM	
Sample bulk lot ref: 4AG	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 μm	Obscuration: 18.43 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 4.713 %	Result Emulation: Off
Concentration: 0.3125 %Vol	Span : 1.617	Uniformity: 0.431	Result units: Volume
Specific Surface Area: 0.0526 m^2/g	Surface Weighted Mean D[3,2]: 114.061 μm	Vol. Weighted Mean D[4,3]: 666.188 μm	
d(0.1): 58.928 μm d(0.5): 661.348 μm d(0.9): 1128.514 μm			

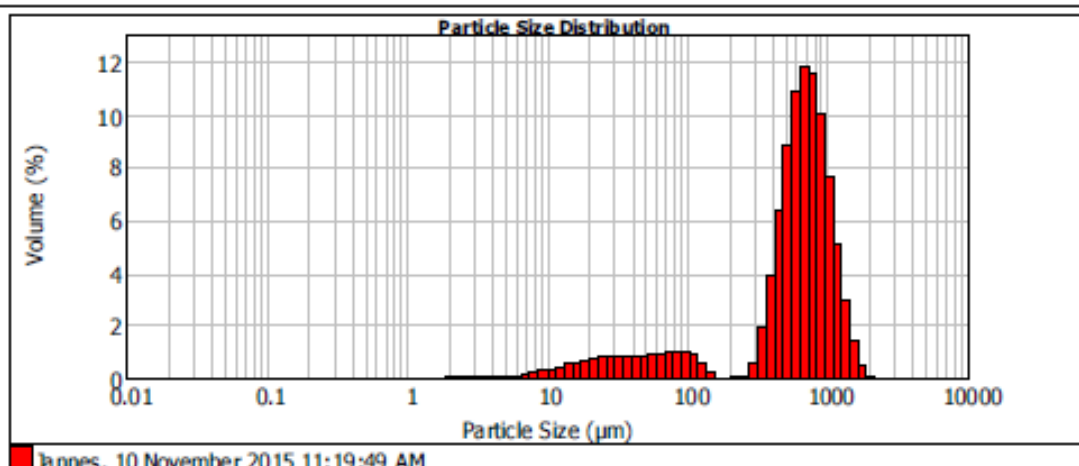


Jannes, 10 November 2015 11:19:07 AM

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	0.47	120.226	0.45	1258.025	3.33
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.56	138.038	0.17	1445.440	1.67
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.64	158.489	0.00	1650.587	0.64
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.71	181.970	0.00	1905.461	0.11
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.75	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.77	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.76	275.423	0.50	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.74	316.228	1.75	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.70	363.078	3.67	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.67	416.869	6.14	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.66	478.630	8.71	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.11	52.481	0.67	540.541	10.86	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.15	60.256	0.71	630.957	12.04	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.19	69.183	0.75	724.436	11.91	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.24	79.433	0.77	831.764	10.50	8700.636	0.00
0.079	0.00	0.832	0.00	8.710	0.31	91.201	0.74	954.993	8.21	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.39	104.713	0.64	1096.478	5.62		
0.105	0.00	1.096	0.00	11.482	0.47	120.226	0.45	1258.025			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:19:49 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:19:50 AM	
Sample bulk lot ref: 4AG	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 μm	Obscuration: 21.37 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 4.427 %	Result Emulation: Off
Concentration: 0.3784 %Vol	Span : 1.631	Uniformity: 0.443	Result units: Volume
Specific Surface Area: 0.0515 m^2/g	Surface Weighted Mean D[3,2]: 116.544 μm	Vol. Weighted Mean D[4,3]: 640.217 μm	
d(0.1): 54.741 μm d(0.5): 640.273 μm d(0.9): 1099.284 μm			



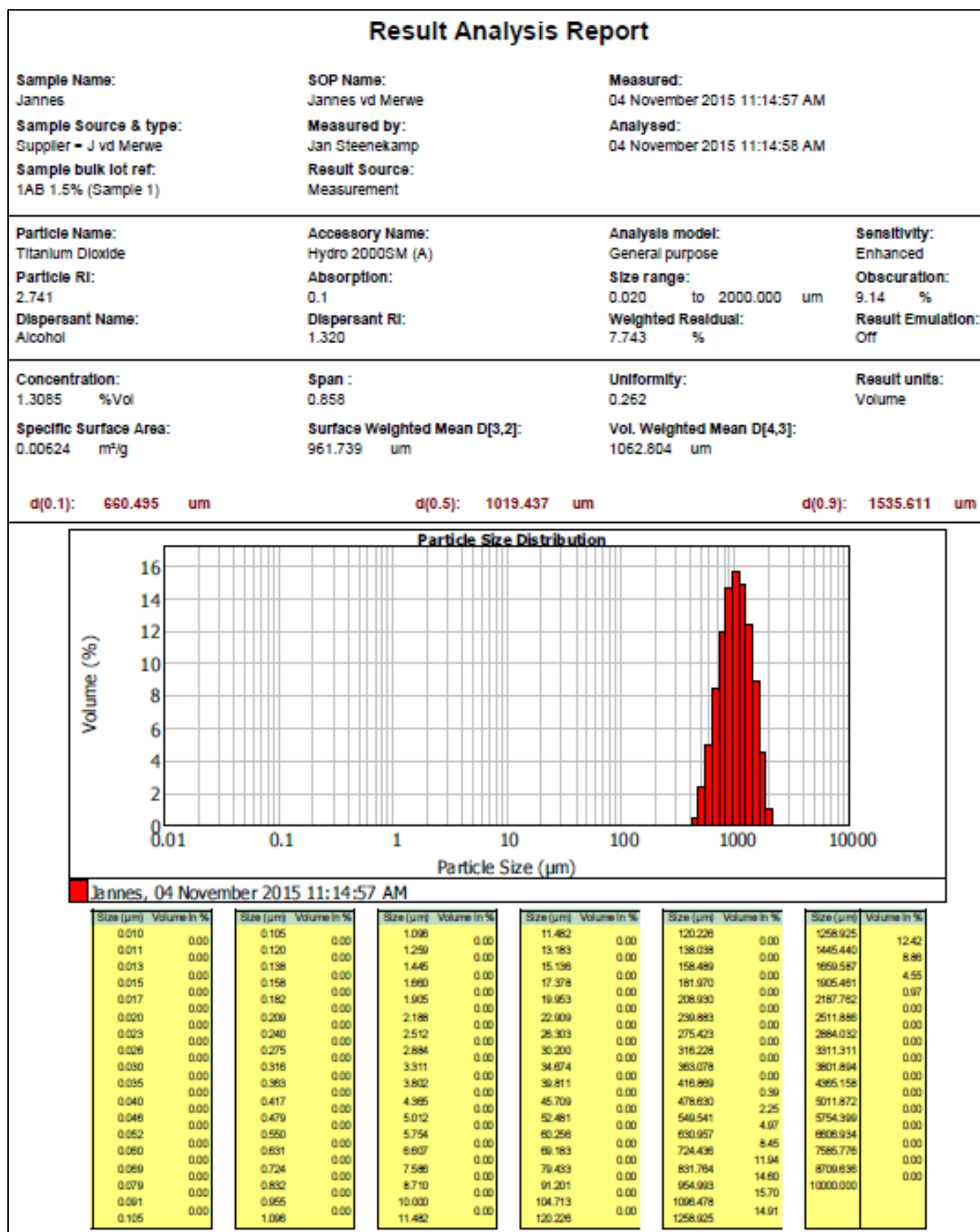
Jannes, 10 November 2015 11:19:49 AM

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	0.44	120.226	0.63	1258.925	2.95
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.53	138.038	0.25	1445.440	1.42
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.62	158.480	0.00	1650.587	0.52
0.015	0.00	0.158	0.00	1.660	0.00	17.379	0.70	181.970	0.00	1905.461	0.09
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.76	208.930	0.01	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.80	239.883	0.02	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.82	275.423	0.03	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.82	316.228	1.02	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.82	363.078	3.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.83	416.869	6.33	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.85	478.630	8.84	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.11	52.481	0.89	549.541	10.86	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.13	60.256	0.94	630.957	11.86	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.16	69.183	1.00	724.436	11.55	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.21	79.433	1.02	831.764	10.02	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.27	91.201	0.99	954.993	7.68	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.35	104.713	0.85	1096.478	5.13		
0.105	0.00	1.096	0.00	11.482	0.35	120.226	0.85	1258.925	5.13		

7.1.3 AVICEL®-CONTAINING BEADS FORMULATIONS

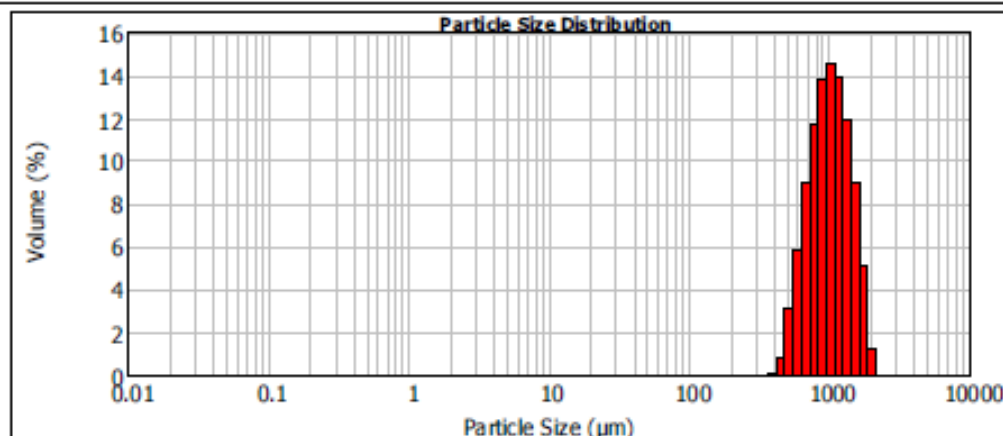
7.1.3.1 Formulation 1

In the following figures the particle size distribution data for Avicel®-containing bead formulation 1 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 11:15:36 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 04 November 2015 11:15:37 AM	
Sample bulk lot ref: 1AB 1.5% (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 μm	Obscuration: 10.62 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 8.024 %	Result Emulation: Off
Concentration: 1.5347 %Vol	Span : 0.916	Uniformity: 0.279	Result units: Volume
Specific Surface Area: 0.00636 m^2/g	Surface Weighted Mean D[3,2]: 943.779 μm	Vol. Weighted Mean D[4,3]: 1055.580 μm	
d[0.1]: 633.293 μm	d[0.5]: 1008.068 μm	d[0.9]: 1556.993 μm	

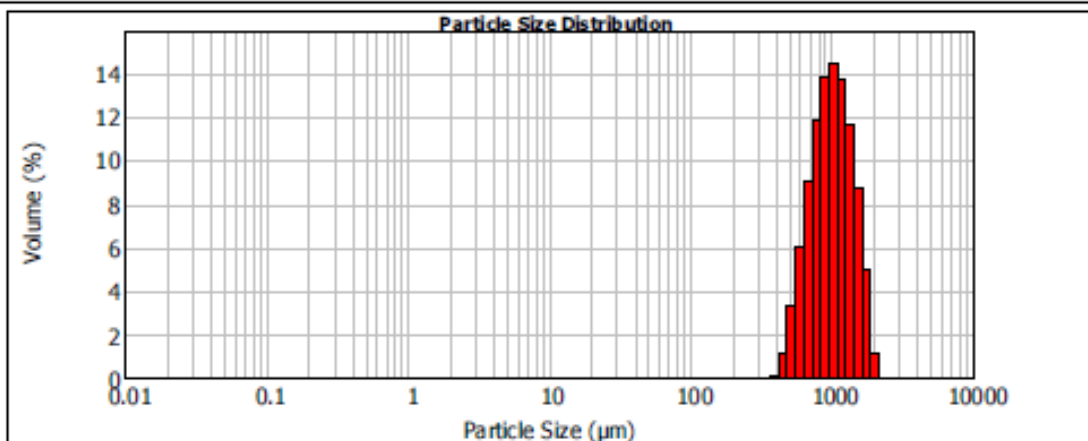


Jannes, 04 November 2015 11:15:36 AM

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	1.098	0.00	11.482	0.00	120.228	0.00	1258.925	11.91
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.97
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.00	158.480	0.00	1659.587	5.09
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	1.21
0.017	0.00	0.182	0.00	1.905	0.00	19.963	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	0.01	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.01	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.00	478.630	0.01	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	3.17	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	5.82	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	8.92	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	11.76	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	13.82	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	14.60		
0.105	0.00	1.098	0.00	11.482	0.00	120.228	0.00	1258.925	13.92		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 11:16:15 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 04 November 2015 11:16:17 AM	
Sample bulk lot ref: 1AB 1.5% (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 μm	Obscuration: 12.76 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 8.178 %	Result Emulation: Off
Concentration: 1.8099 %Vol	Span : 0.926	Uniformity: 0.263	Result units: Volume
Specific Surface Area: 0.00642 m^2/g	Surface Weighted Mean D[3,2]: 933.970 μm	Vol. Weighted Mean D[4,3]: 1047.431 μm	
d(0.1): 624.671 μm d(0.5): 999.373 μm d(0.9): 1550.468 μm			

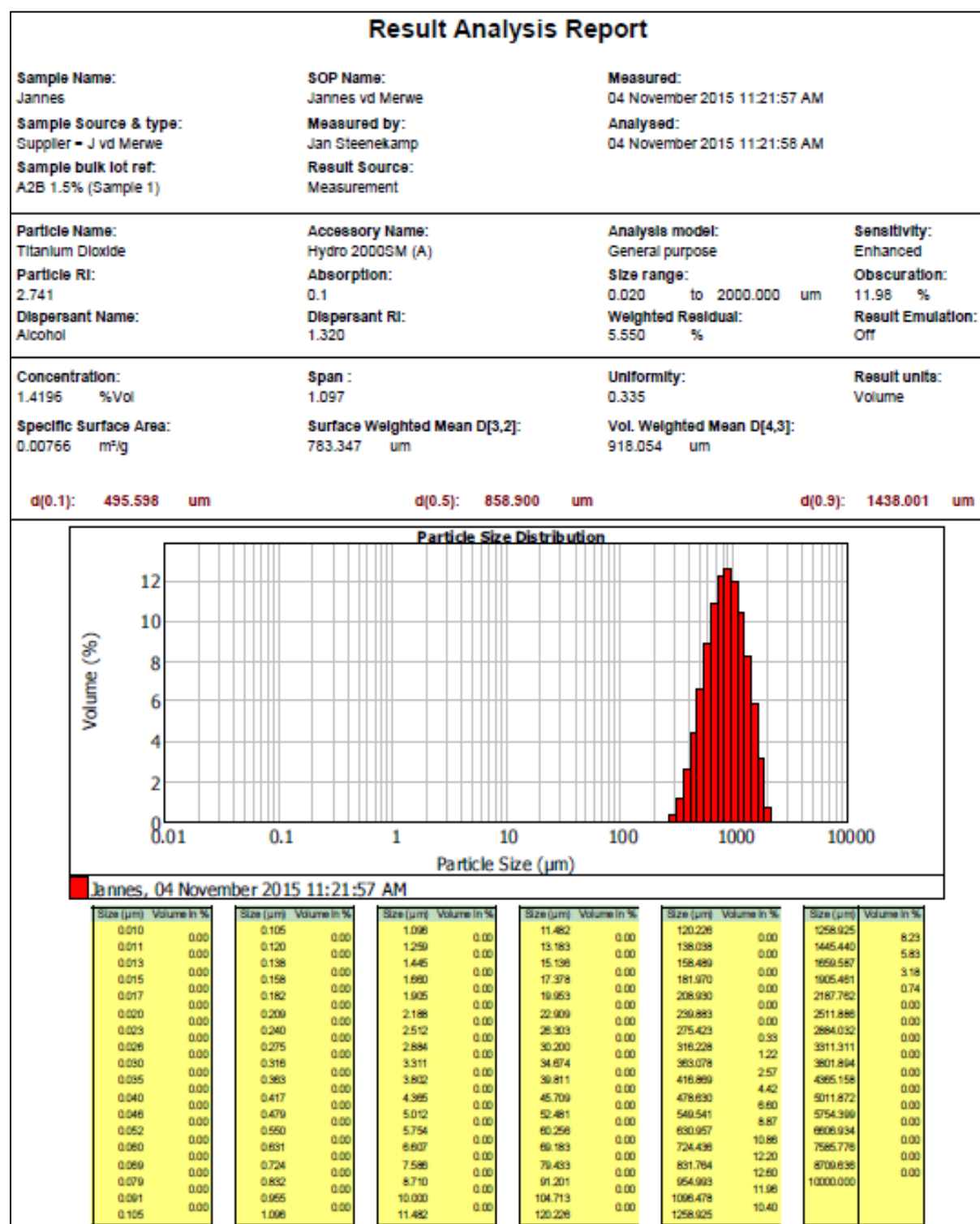


Jannes, 04 November 2015 11:16:15 AM

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	11.67
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	8.76
0.013	0.00	0.138	0.00	1.446	0.00	15.139	0.00	158.489	0.00	1659.587	4.95
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	1.17
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	0.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	416.869	0.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.00	45.709	0.00	478.630	1.14	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	3.32	5754.999	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	0.00	630.957	8.05	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	9.07	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.784	11.84	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	13.79	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.00	104.713	0.00	1098.478	14.47		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	13.72		

7.1.3.2 Formulation 2

In the following figures the particle size distribution data for Avicel®-containing bead formulation 2 is given.



Result Analysis Report

Sample Name: Jannes

SOP Name:
Jannes vd Merwe

Measured:
04 November 2015 11:22:37 AM

Sample Source & type:
Supplier = J vd Merwe

Measured by:
Jan Steenekamp

Analysed:
04 November 2015 11:22:38 AM

Sample bulk lot ref:
A2B 1.5% (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 μm

Obscuration:
12.93 %

Dispersant Name:
Alcohol

Dispersant RI:
1.320

Weighted Residual:
5.421 %

Result Emulation:
Off

Concentration:
1.5123 %Vol

Span :
1.113

Uniformity:
0.341

Result units:
Volume

Specific Surface Area:
0.0078 m²/g

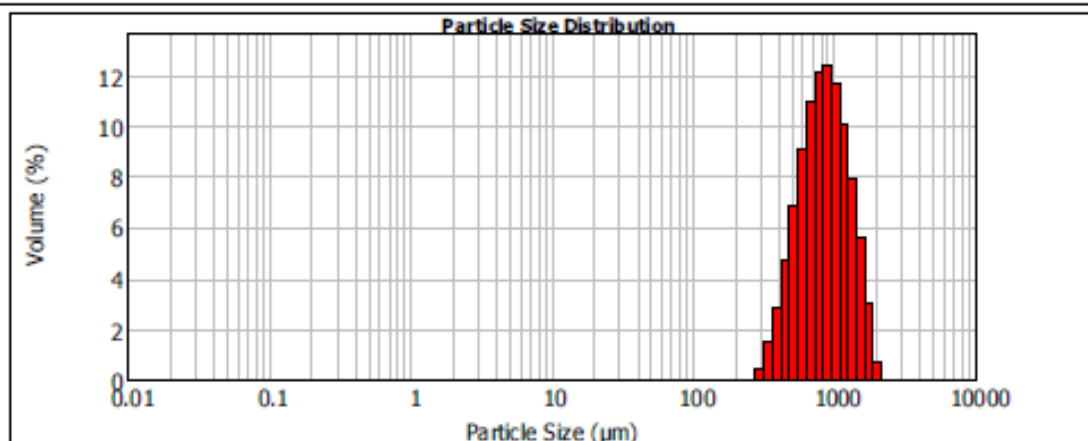
Surface Weighted Mean D[3,2]:
769.319 μm

Vol. Weighted Mean D[4,3]:
904.982 μm

d(0.1): 484.614 um

d(0.5): 844.707 um

d(0.9): 1424.401 um

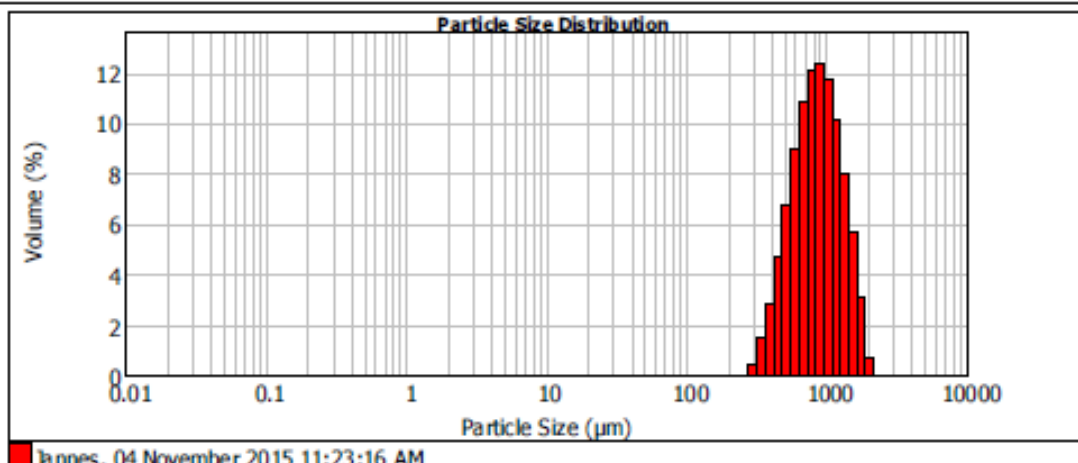


Jannes, 04 November 2015 11:22:37 AM

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	0.00	120.226	0.00	1258.925	7.90
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.00	158.469	0.00	1659.587	3.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.70
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.00	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.00	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.00	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.00	316.228	0.00	3311.331	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	416.969	2.84	4365.156	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.72	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	6.88	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	9.09	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	10.97	7585.778	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	12.19	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	12.45	10000.000	0.00
0.091	0.00	0.955	0.00	10.003	0.00	104.713	0.00	1086.478	11.70		
0.105	0.00	1.096	0.00	11.482	0.00	120.226	0.00	1258.925	10.08		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 11:23:16 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 04 November 2015 11:23:17 AM	
Sample bulk lot ref: A2B 1.5% (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 μm	Obscuration: 14.79 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 5.313 %	Result Emulation: Off
Concentration: 1.7537 %Vol	Span : 1.114	Uniformity: 0.341	Result units: Volume
Specific Surface Area: 0.00777 m^2/g	Surface Weighted Mean D[3,2]: 771.981 μm	Vol. Weighted Mean D[4,3]: 908.925 μm	
d(0.1): 485.435 μm	d(0.5): 848.892 μm	d(0.9): 1431.363 μm	



Jannes, 04 November 2015 11:23:16 AM

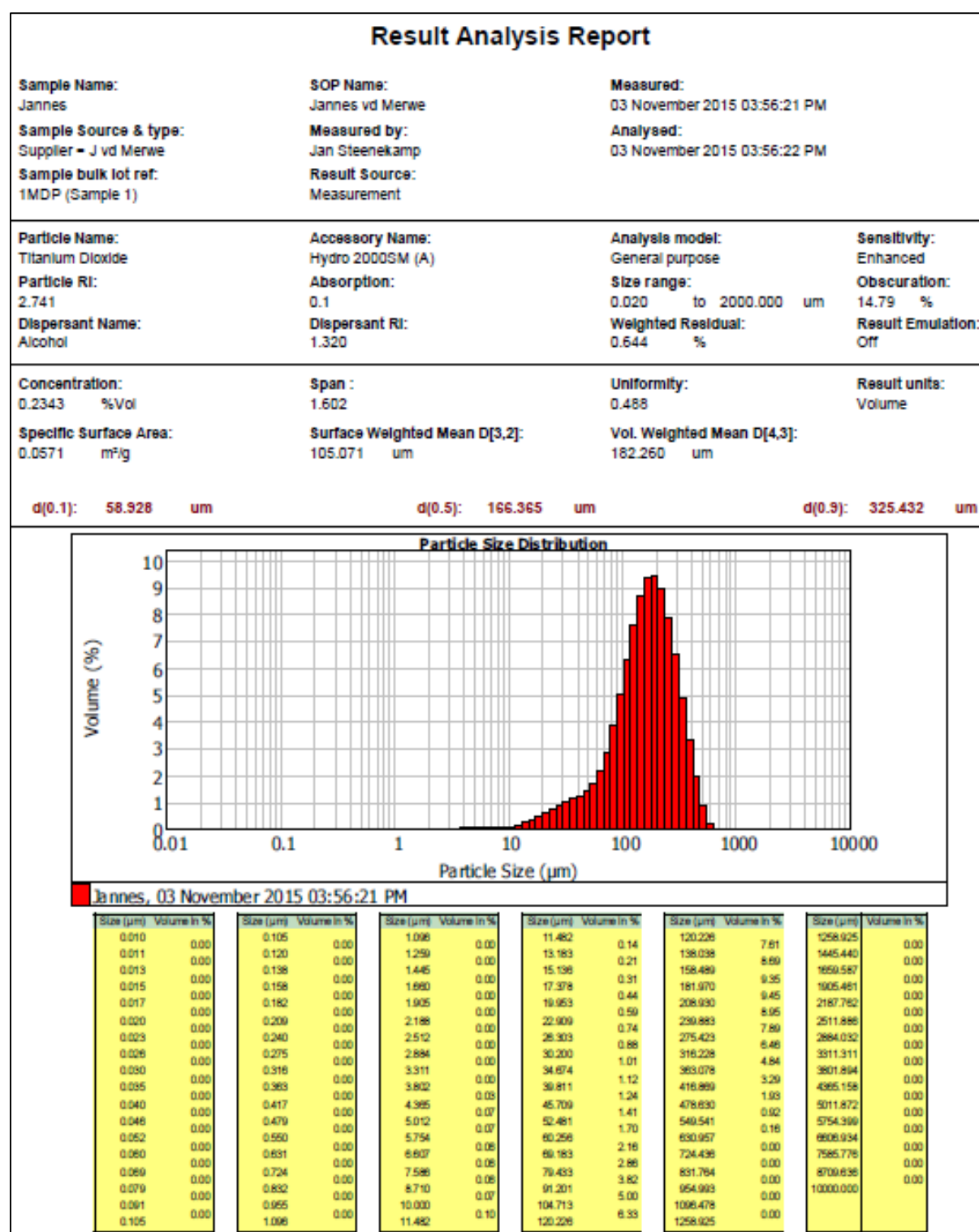
Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %
0.010	0.00	0.105	0.00	1.098	0.00	11.482	0.00	120.228	0.00	1258.925	8.03
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.00	138.038	0.00	1445.440	5.68
0.013	0.00	0.138	0.00	1.445	0.00	15.138	0.00	158.489	0.00	1650.587	3.10
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.00	181.970	0.00	1905.461	0.72
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	0.47	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.00	363.078	1.45	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.00	418.889	2.82	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.00	478.630	4.87	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.00	549.541	8.80	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.00	630.957	8.99	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.00	724.436	10.87	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.00	831.764	12.10	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.00	954.993	12.41	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.00	1096.478	11.72		
0.105	0.00	1.098	0.00	11.482	0.00	120.228	0.00	1258.925	10.17		

7.2 MICROCELAC®-CONTAINING FORMULATIONS

7.2.1 MICROCELAC®-CONTAINING DRY POWDER FORMULATIONS

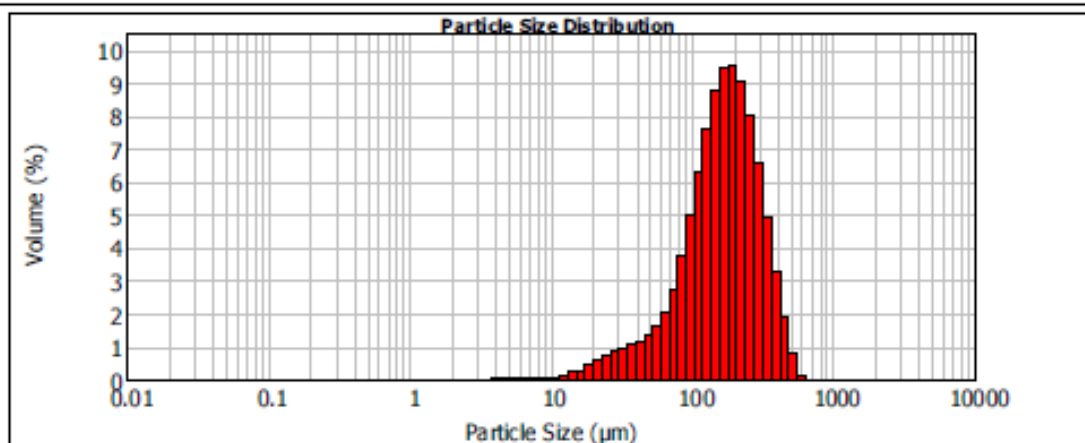
7.2.1.1 Formulation 1

In the following figures the particle size distribution data for MicroceLac®-containing dry powder formulation 1 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:57:00 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 03 November 2015 03:57:01 PM	
Sample bulk lot ref: 1MDP (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 μm	Obscuration: 14.30 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.657 %	Result Emulation: Off
Concentration: 0.2273 %Vol	Span : 1.581	Uniformity: 0.482	Result units: Volume
Specific Surface Area: 0.0568 m^2/g	Surface Weighted Mean D[3,2]: 105.654 μm	Vol. Weighted Mean D[4,3]: 182.652 μm	
d(0.1): 59.868 μm d(0.5): 167.417 μm d(0.9): 324.485 μm			

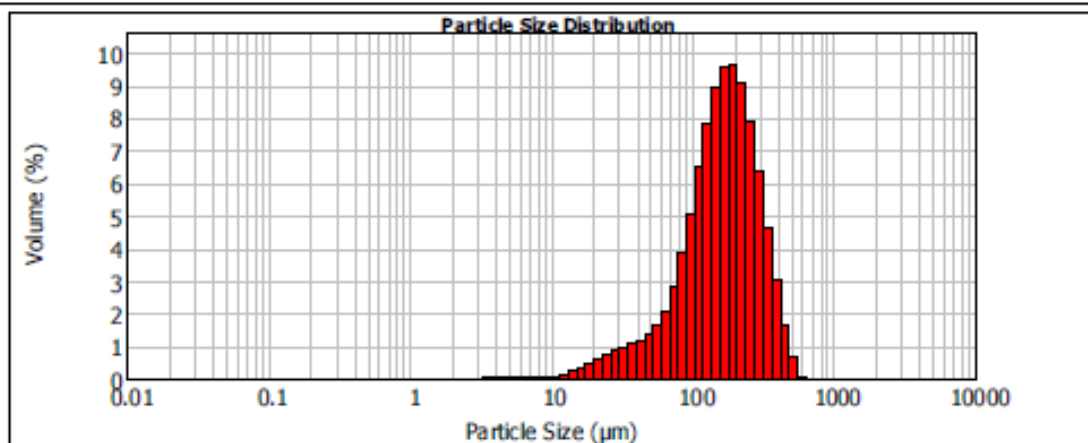


Jannes, 03 November 2015 03:57:00 PM

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	0.14	120.226	7.63	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.21	138.038	8.75	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.198	0.31	158.489	9.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.44	181.970	9.57	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.59	208.930	9.07	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.74	239.883	8.01	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.87	275.423	6.56	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.99	316.228	4.90	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.09	363.078	3.30	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.20	416.869	1.90	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.00	45.709	1.36	478.630	0.82	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.62	549.541	0.12	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	2.08	630.957	0.00	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.77	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.75	831.784	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.95	954.993	0.00	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.00	104.713	6.30	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.10	120.226		1258.925	0.00		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 03:57:39 PM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 03:57:40 PM	
Sample bulk lot ref: 1MDP (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: 13.83 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.656 %	Result Emulation: Off
Concentration: 0.2121 %Vol	Span : 1.566	Uniformity: 0.476	Result units: Volume
Specific Surface Area: 0.0586 m ² /g	Surface Weighted Mean D[3,2]: 102.412 um	Vol. Weighted Mean D[4,3]: 179.175 um	
d(0.1): 59.097 um	d(0.5): 164.649 um	d(0.9): 316.907 um	

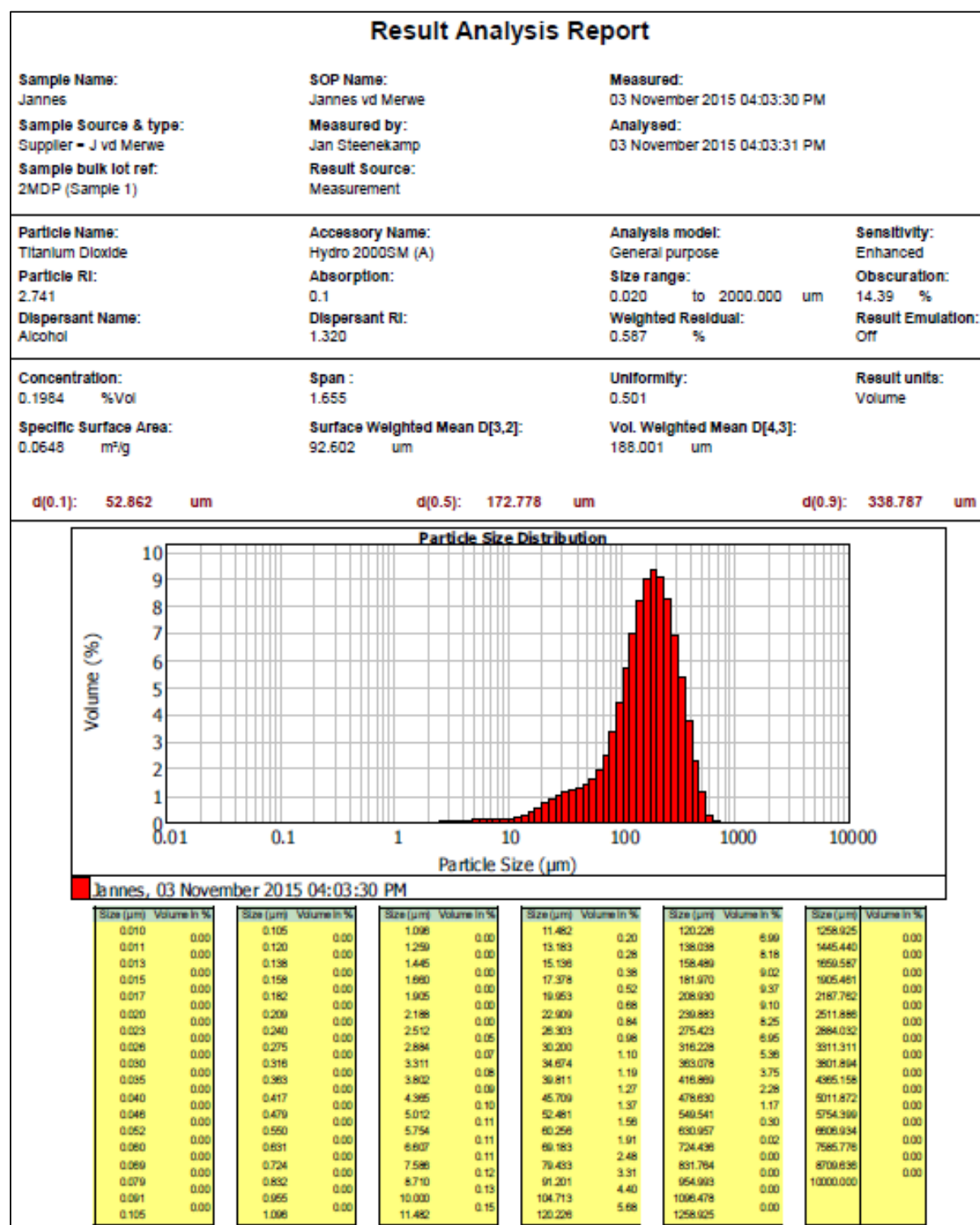


Jannes, 03 November 2015 03:57:39 PM

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	1.098	0.00	11.482	0.15	120.226	7.85	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.22	138.038	8.06	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.33	158.489	9.61	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.48	181.970	9.65	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.60	208.930	9.05	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.75	239.883	7.87	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.89	275.423	6.33	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.00	316.228	4.63	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.09	363.078	3.02	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.03	39.811	1.19	416.999	1.68	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.07	45.709	1.35	478.630	0.88	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.07	52.481	1.62	549.541	0.08	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.07	60.256	2.09	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.06	69.183	2.82	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.07	79.433	3.84	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.07	91.201	5.09	954.993	0.00	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.10	104.713	6.49	1098.478	0.00		
0.105	0.00	1.098	0.00	11.482		120.226		1258.925			

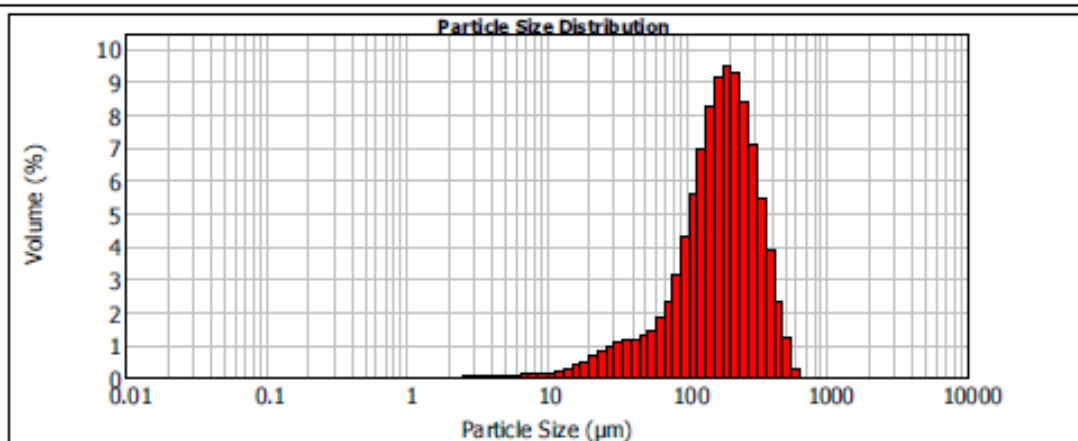
7.2.1.2 Formulation 2

In the following figures the particle size distribution data for MicroceLac®-containing dry powder formulation 2 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:04:09 PM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 04:04:11 PM	
Sample bulk lot ref: 2MDP (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 μm	Obscuration: 14.05 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.674 %	Result Emulation: Off
Concentration: 0.1983 %Vol	Span : 1.626	Uniformity: 0.492	Result units: Volume
Specific Surface Area: 0.0632 m^2/g	Surface Weighted Mean D[3,2]: 94.933 μm	Vol. Weighted Mean D[4,3]: 190.202 μm	
d(0.1): 55.403 μm d(0.5): 175.384 μm d(0.9): 340.648 μm			

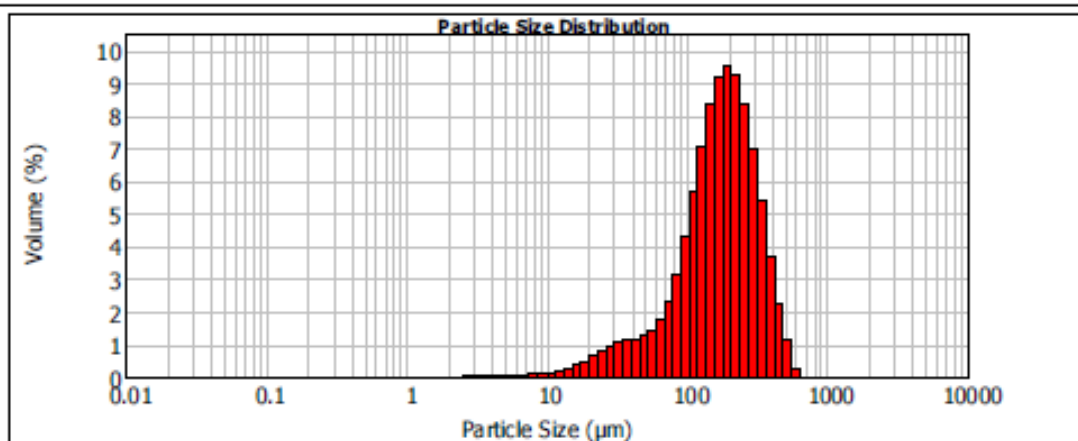


Jannes, 03 November 2015 04:04:09 PM

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	1.098	0.00	11.482	0.19	120.226	6.98	1258.025	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.26	138.038	8.23	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.37	158.489	9.13	1650.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.50	181.970	9.52	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.65	208.930	9.28	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.80	239.883	8.43	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.05	26.303	0.94	275.423	7.10	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	1.13	316.228	5.49	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	1.20	363.078	3.86	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	1.29	418.889	2.35	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.10	45.709	1.46	478.630	1.23	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	1.79	549.541	0.24	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.10	60.256	2.35	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.11	69.183	3.19	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.11	79.433	4.29	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.12	91.201	5.61	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.14	104.713		1096.478	0.00		
0.105	0.00	1.098	0.00	11.482		120.226		1258.025	0.00		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:04:49 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analyzed: 03 November 2015 04:04:50 PM	
Sample bulk lot ref: 2MDP (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 μm	Obscuration: 13.76 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 0.618 %	Result Emulation: Off
Concentration: 0.1930 %Vol	Span : 1.621	Uniformity: 0.49	Result units: Volume
Specific Surface Area: 0.0635 m^2/g	Surface Weighted Mean D[3,2]: 94.504 μm	Vol. Weighted Mean D[4,3]: 188.704 μm	
d(0.1): 55.059 μm d(0.5): 174.131 μm d(0.9): 337.298 μm			

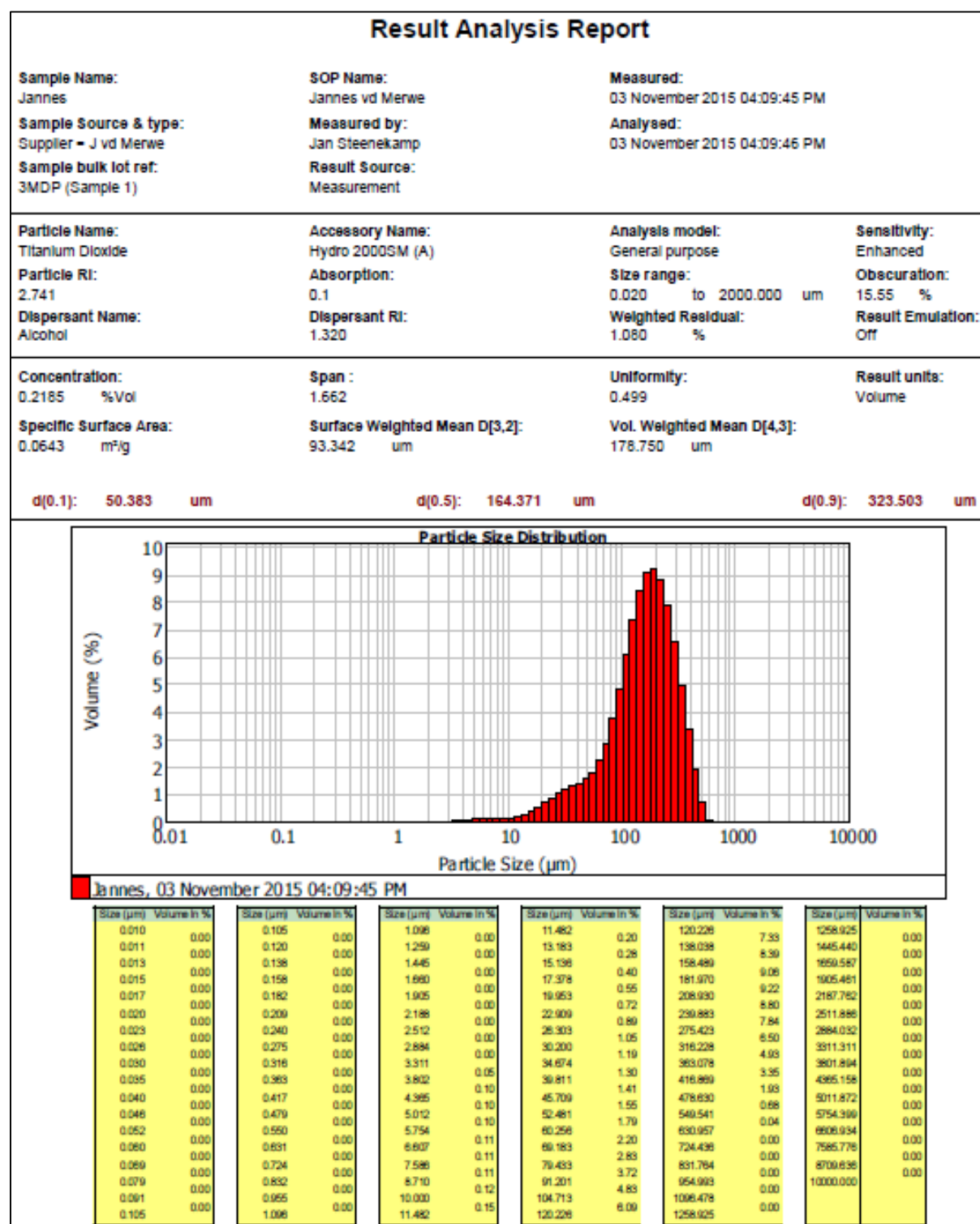


Jannes, 03 November 2015 04:04:49 PM

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	1.098	0.00	11.482	0.19	120.226	7.08	1258.025	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.26	138.038	8.34	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.37	158.489	9.23	1650.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.51	181.970	9.58	1905.481	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.963	0.66	208.930	9.58	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.82	230.883	8.39	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.05	26.303	0.98	275.423	7.02	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.07	30.200	1.07	316.228	5.38	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.08	34.674	1.14	363.078	3.73	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	1.20	416.869	2.24	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.10	45.709	1.28	478.630	1.14	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	1.45	549.541	0.22	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.10	60.256	1.78	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	2.35	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.11	79.433	3.21	831.784	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.12	91.201	4.35	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.14	104.713	5.69	1096.478	0.00		
0.105	0.00	1.098	0.00	11.482	0.14	120.226	5.69	1258.025	0.00		

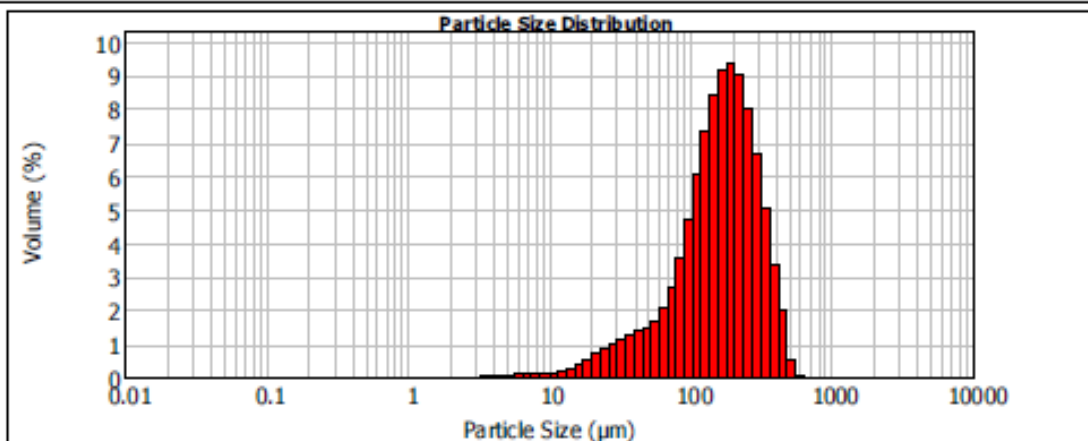
7.2.1.3 Formulation 3

In the following figures the particle size distribution data for MicroceLac®-containing dry powder formulation 3 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:10:24 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 03 November 2015 04:10:26 PM	
Sample bulk lot ref: 3MDP (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 μm	Obscuration: 14.84 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 1.181 %	Result Emulation: Off
Concentration: 0.2112 %Vol	Span : 1.633	Uniformity: 0.491	Result units: Volume
Specific Surface Area: 0.0632 m^2/g	Surface Weighted Mean D[3,2]: 94.924 μm	Vol. Weighted Mean D[4,3]: 180.496 μm	
d(0.1): 51.807 μm	d(0.5): 166.838 μm	d(0.9): 324.302 μm	

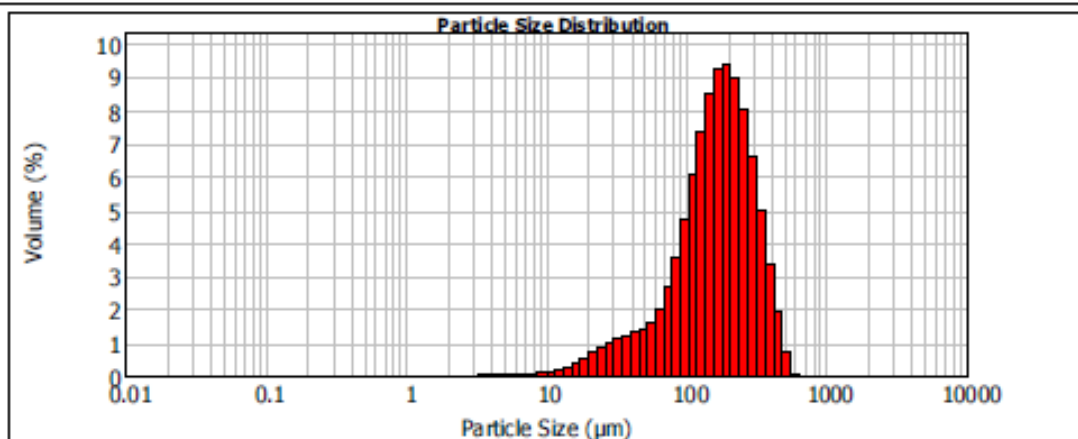


Jannes, 03 November 2015 04:10:24 PM

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	0.19	120.226	7.31	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.27	138.038	8.44	1445.440	0.00
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.39	158.489	9.18	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.53	181.970	9.40	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.70	208.930	9.01	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.87	239.883	8.05	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.03	275.423	6.67	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.16	316.228	5.05	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.28	363.078	3.40	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	1.35	416.869	1.99	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	1.47	478.630	0.54	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	1.68	549.541	0.06	5754.369	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	2.07	630.957	0.00	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	2.69	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	3.58	831.784	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	4.71	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	6.01	1098.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.14	120.226		1258.925			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:11:04 PM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 04:11:05 PM	
Sample bulk lot ref: 3MDP (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 μm	Obscuration: 14.52 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 1.201 %	Result Emulation: Off
Concentration: 0.2076 %Vol	Span : 1.629	Uniformity: 0.49	Result units: Volume
Specific Surface Area: 0.0628 m^2/g	Surface Weighted Mean D[3,2]: 95.479 μm	Vol. Weighted Mean D[4,3]: 180.823 μm	
d(0.1): 52.687 μm d(0.5): 166.834 μm d(0.9): 324.489 μm			

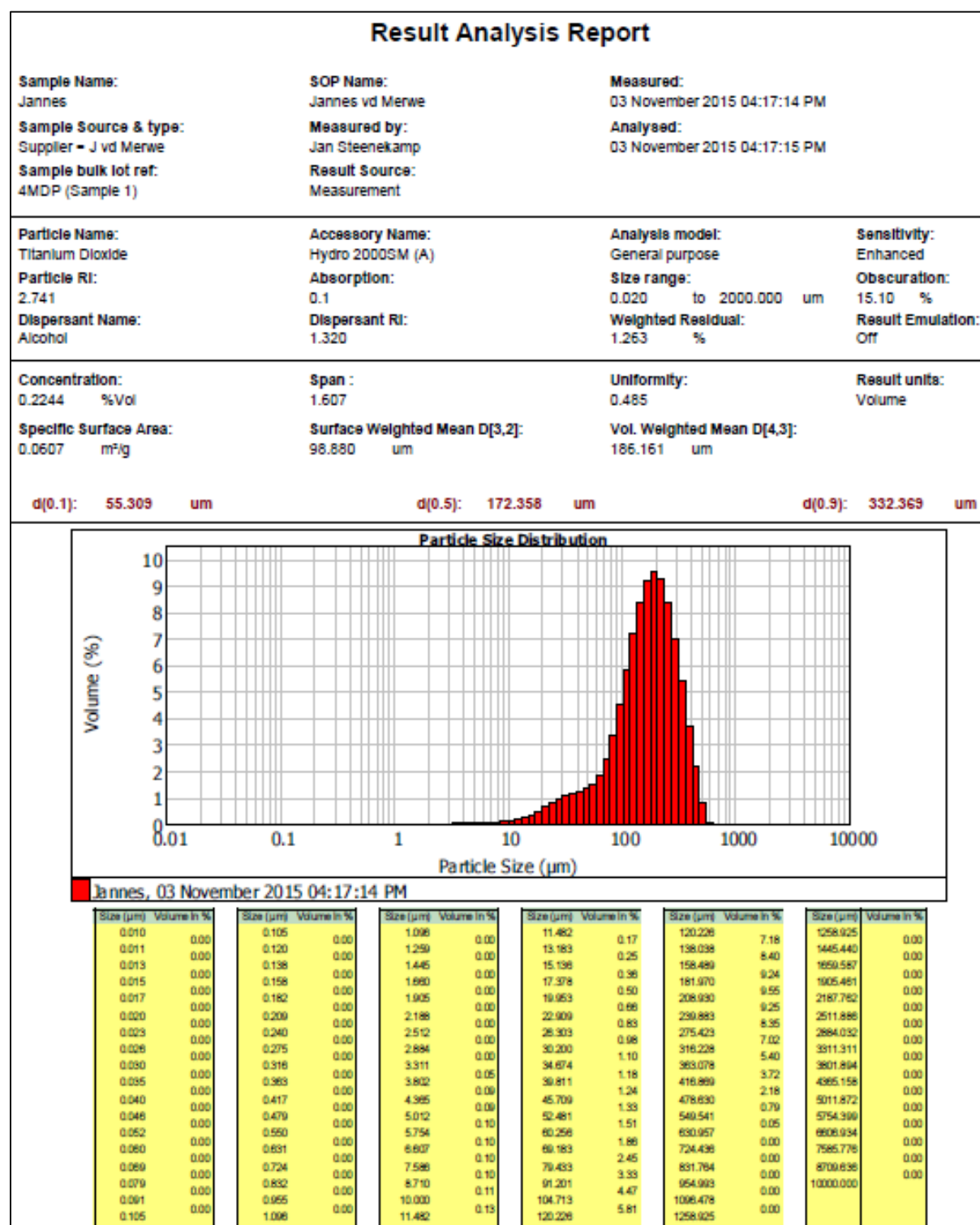


Jannes, 03 November 2015 04:11:04 PM

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	0.19	120.226	7.39	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.27	138.038	8.52	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.39	158.489	9.25	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.54	181.970	9.43	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.70	208.930	9.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.87	239.883	8.01	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	1.02	275.423	6.82	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.14	316.228	5.01	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.05	34.674	1.22	363.078	3.39	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	1.30	418.869	1.95	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.10	45.709	1.42	478.630	0.88	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	1.64	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.10	60.256	2.03	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	2.67	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	3.59	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.11	91.201	4.75	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.14	104.713	6.08	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.19	120.226	7.39	1258.925	0.00		

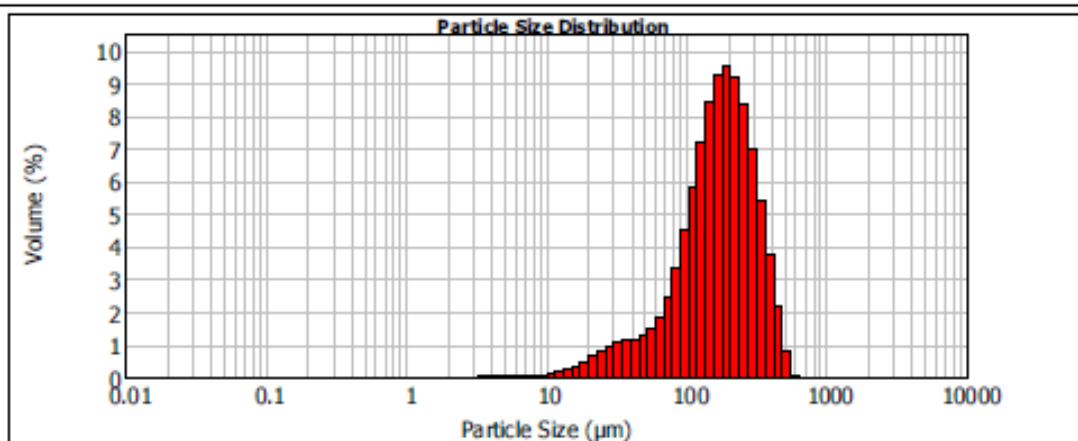
7.2.1.4 Formulation 4

In the following figures the particle size distribution data for MicroceLac®-containing dry powder formulation 4 is given.



Result Analysis Report

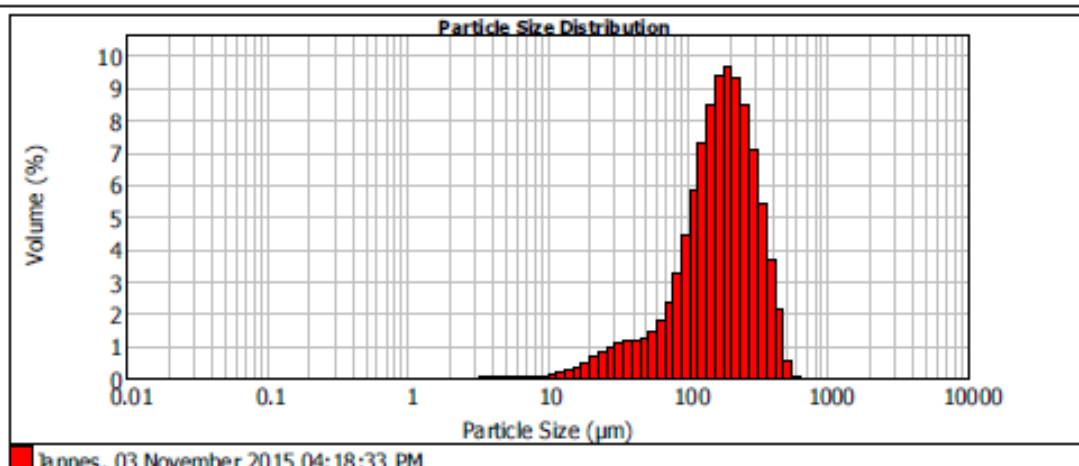
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:17:54 PM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 04:17:55 PM	
Sample bulk lot ref: 4MDP (Sample 1)	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory 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: 14.44 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 1.468 %	Result Emulation: Off
Concentration: 0.2150 %Vol	Span : 1.601	Uniformity: 0.484	Result units: Volume
Specific Surface Area: 0.0603 m ² /g	Surface Weighted Mean D[3,2]: 99.456 um	Vol. Weighted Mean D[4,3]: 186.623 um	
d(0.1): 56.301 um	d(0.5): 172.696 um	d(0.9): 332.829 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	0.17	120.226	7.21	1258.025	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.25	138.038	8.43	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.36	158.489	9.27	1650.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.50	181.970	9.58	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.66	208.930	9.26	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.82	239.893	8.36	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.98	275.423	7.02	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.07	316.228	5.41	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.05	34.674	1.15	363.078	3.74	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	1.21	418.889	2.21	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.09	45.709	1.29	478.630	0.80	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	1.48	549.541	0.04	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.10	60.256	1.83	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	2.43	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	3.33	831.764	0.00	8709.638	0.00
0.079	0.00	0.832	0.00	8.710	0.10	91.201	4.48	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.12	104.713	5.84	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482		120.226		1258.025	0.00		

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 03 November 2015 04:18:33 PM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 03 November 2015 04:18:34 PM	
Sample bulk lot ref: 4MDP (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 μm	Obscuration: 14.06 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 1.524 %	Result Emulation: Off
Concentration: 0.2096 %Vol	Span : 1.582	Uniformity: 0.477	Result units: Volume
Specific Surface Area: 0.0602 m^2/g	Surface Weighted Mean D[3,2]: 99.715 μm	Vol. Weighted Mean D[4,3]: 185.802 μm	
d(0.1): 56.670 μm d(0.5): 172.645 μm d(0.9): 329.760 μm			



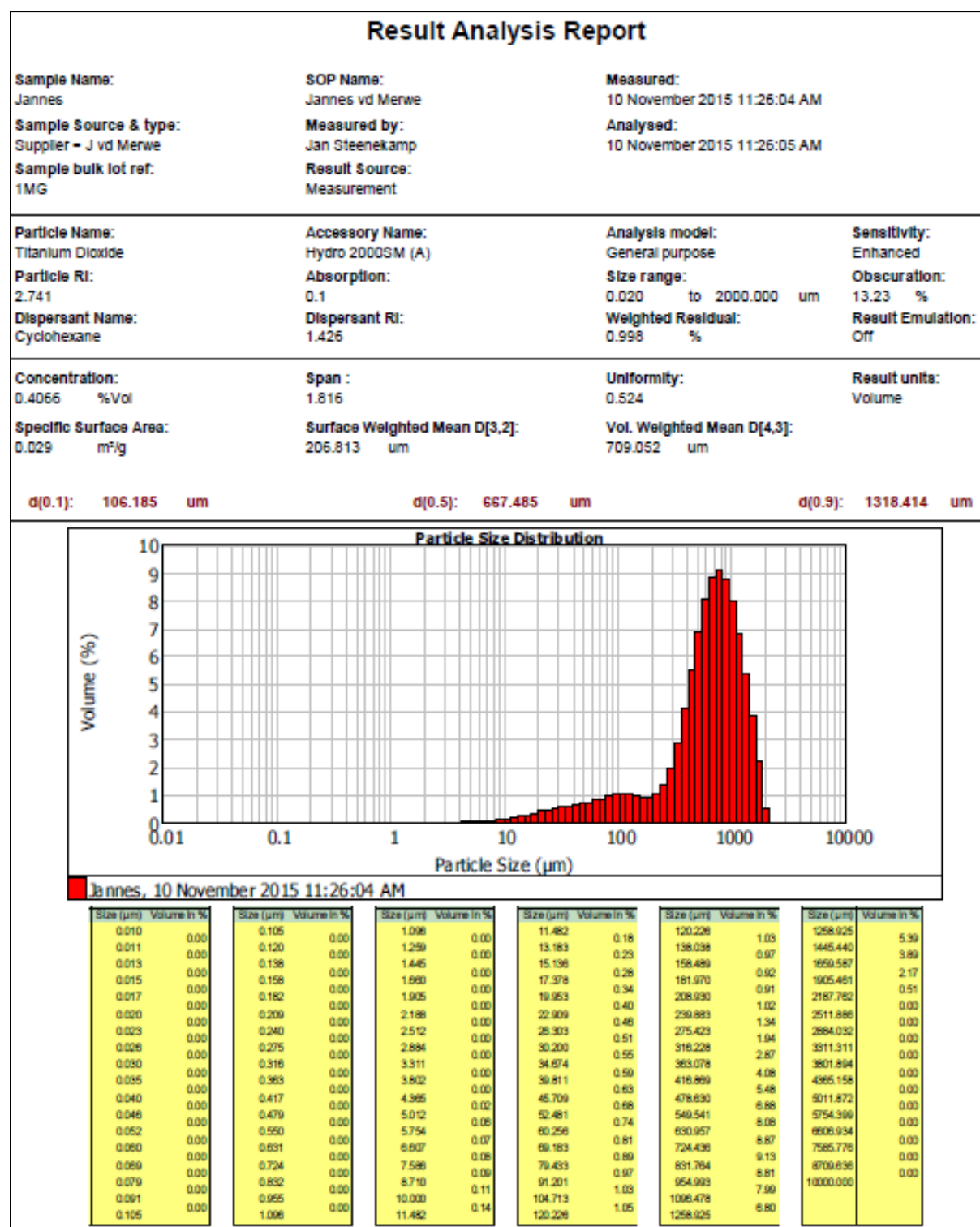
Jannes, 03 November 2015 04:18:33 PM

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	0.16	120.226	7.27	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.24	138.038	8.53	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.35	158.480	9.39	1650.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.50	181.970	9.99	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.66	208.930	9.37	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.83	239.883	8.43	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.97	275.423	7.05	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	1.08	316.228	5.39	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	1.15	363.078	3.66	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.05	39.811	1.19	416.869	2.17	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.09	45.709	1.27	478.630	0.55	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.10	52.481	1.43	549.541	0.04	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.10	60.256	1.78	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	2.38	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.09	79.433	3.29	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.10	91.201	4.47	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.12	104.713	5.86	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.16	120.226	7.27	1258.925	0.00		

7.2.2 MICROCELAC®-CONTAINING GRANULE FORMULATIONS

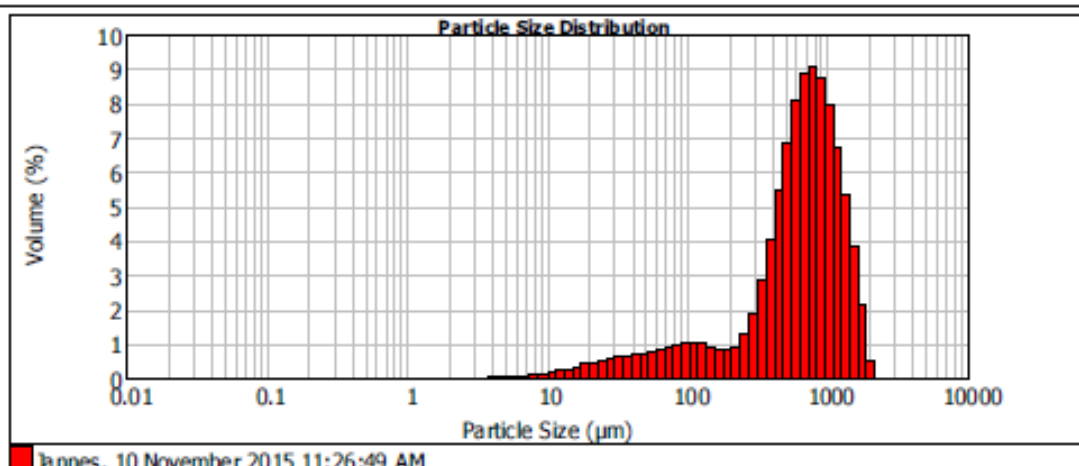
7.2.2.1 Formulation 1

In the following figures the particle size distribution data for MicroceLac®-containing granule formulation 1 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:26:49 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:26:51 AM	
Sample bulk lot ref: 1MG	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 μm	Obscuration: 13.54 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 0.922 %	Result Emulation: Off
Concentration: 0.3708 %Vol	Span : 1.838	Uniformity: 0.529	Result units: Volume
Specific Surface Area: 0.0325 m^2/g	Surface Weighted Mean D[3,2]: 184.685 μm	Vol. Weighted Mean D[4,3]: 703.693 μm	
d(0.1): 94.061 μm d(0.5): 663.880 μm d(0.9): 1314.424 μm			

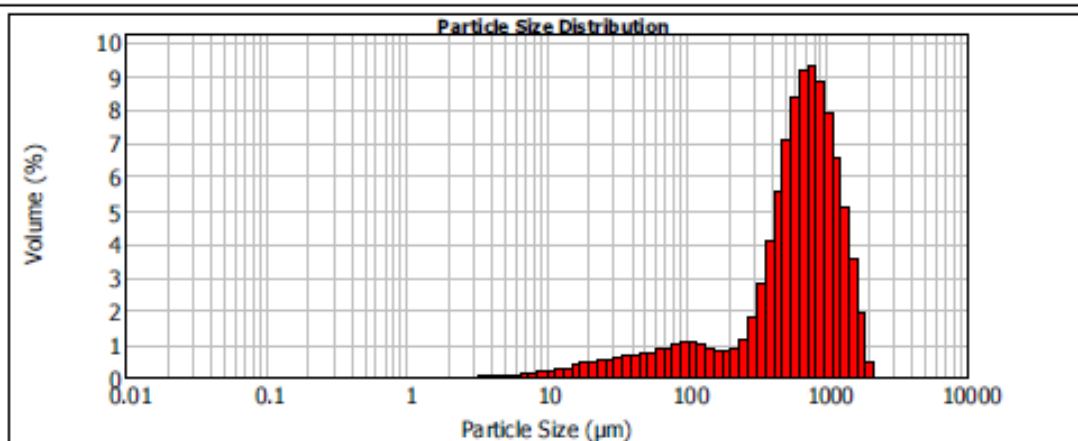


Jannes, 10 November 2015 11:26:49 AM

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	1.098	0.00	11.482	0.22	120.228	1.00	1258.925	5.33
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.28	138.038	0.92	1445.440	3.84
0.013	0.00	0.138	0.00	1.445	0.00	15.138	0.34	158.489	0.82	1650.587	2.14
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.40	181.970	0.85	1905.461	0.50
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.46	208.930	0.94	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.52	239.883	1.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.57	275.423	1.88	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.61	316.228	2.82	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.64	363.078	4.04	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.68	418.889	5.46	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.03	45.709	0.72	478.630	6.87	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.07	52.481	0.77	549.541	8.07	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.08	60.256	0.85	630.957	9.88	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	0.92	724.436	11.10	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.12	79.433	1.00	831.764	12.76	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.14	91.201	1.04	954.993	14.73	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.16	104.713	1.05	1096.478	16.74		
0.105	0.00	1.098	0.00	11.482	0.18	120.228	1.05	1258.925	18.74		

Result Analysis Report

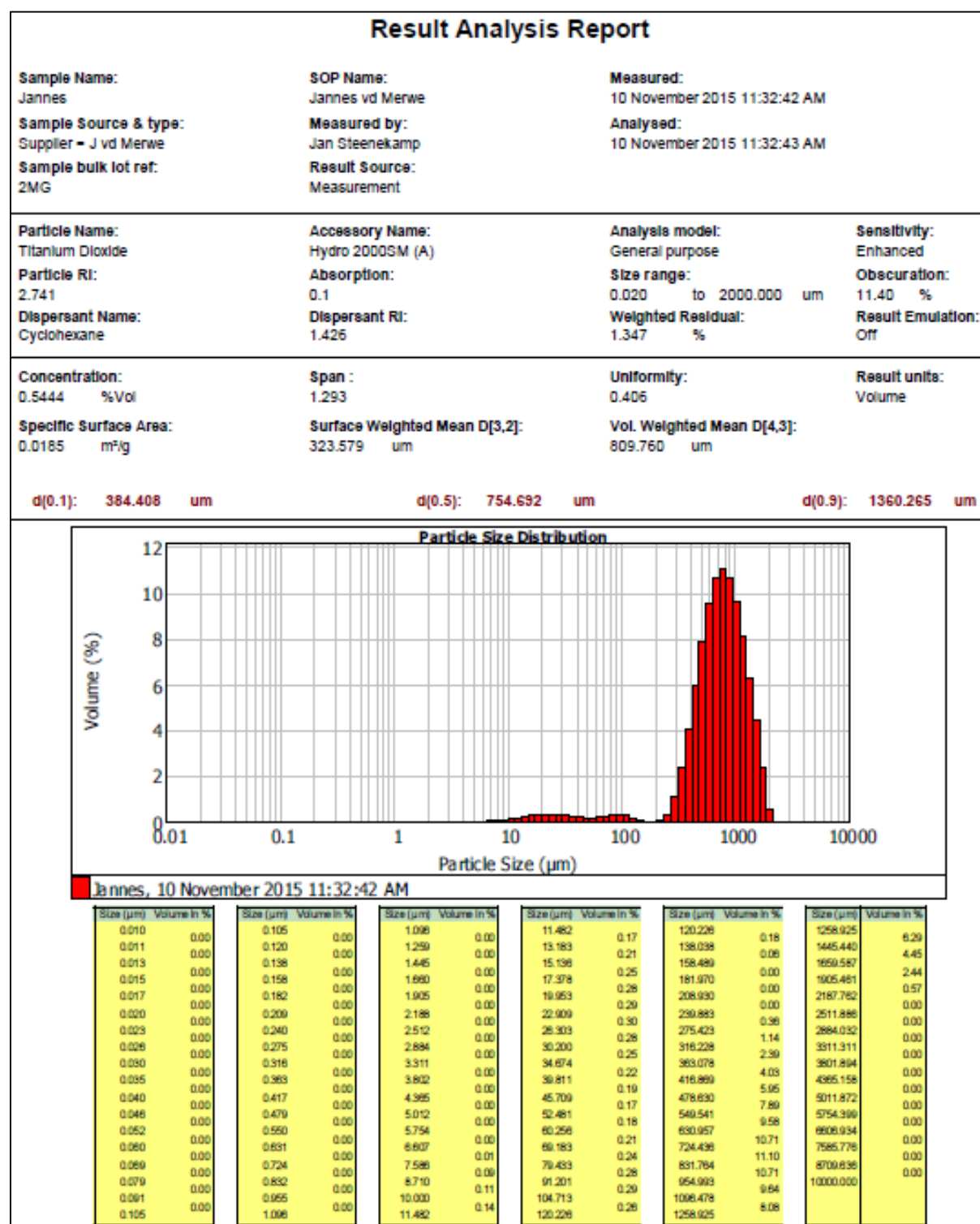
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:27:29 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:27:30 AM	
Sample bulk lot ref: 1MG	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 um	Obscuration: 13.54 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.042 %	Result Emulation: Off
Concentration: 0.3487 %Vol	Span : 1.817	Uniformity: 0.52	Result units: Volume
Specific Surface Area: 0.0344 m ² /g	Surface Weighted Mean D[3,2]: 174.299 um	Vol. Weighted Mean D[4,3]: 695.327 um	
d(0.1): 92.395 um d(0.5): 658.554 um d(0.9): 1288.929 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	0.25	120.226	1.00	1258.925	5.04
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.31	138.038	0.91	1445.440	3.54
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.37	158.489	0.82	1659.587	1.94
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.42	181.970	0.77	1905.461	0.45
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.48	208.930	0.66	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.52	239.883	1.18	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.56	275.423	1.80	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.59	316.228	2.78	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.62	363.078	4.08	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.65	416.889	5.59	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.70	478.630	7.10	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.461	0.76	549.541	8.37	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.84	630.957	9.16	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.92	724.436	9.34	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.11	79.433	0.99	831.764	8.88	8709.638	0.00
0.079	0.00	0.832	0.00	8.710	0.15	91.201	1.03	954.993	7.80	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.20	104.713	1.04	1096.478	6.54		
0.105	0.00	1.096	0.00	11.482	0.25	120.226		1258.925			

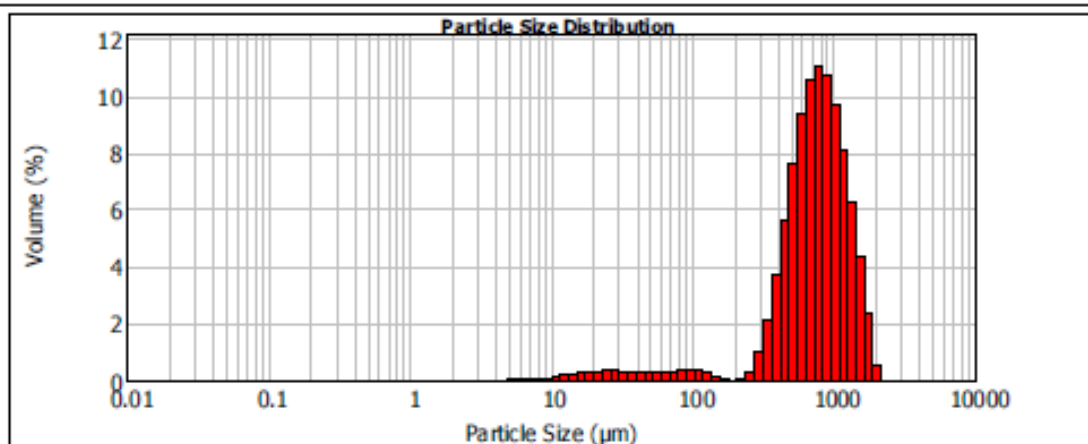
7.2.2.2 Formulation 2

In the following figures the particle size distribution data for MicroceLac®-containing granule formulation 2 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:33:21 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 10 November 2015 11:33:23 AM	
Sample bulk lot ref: 2MG	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: 12.07 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.563 %	Result Emulation: Off
Concentration: 0.4818 %Vol	Span : 1.319	Uniformity: 0.416	Result units: Volume
Specific Surface Area: 0.0222 m ² /g	Surface Weighted Mean D[3,2]: 270.654 um	Vol. Weighted Mean D[4,3]: 799.197 um	
d(0.1): 361.456 um d(0.5): 752.344 um d(0.9): 1354.044 um			

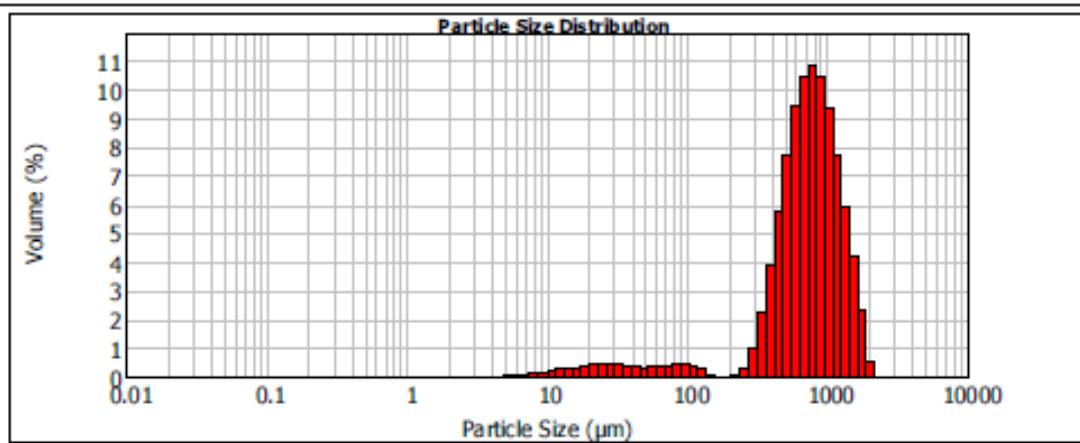


Jannes, 10 November 2015 11:33:21 AM

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	1.098	0.00	11.482	0.19	120.226	0.32	1258.925	6.22
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.24	138.038	0.17	1445.440	4.36
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.20	158.489	0.17	1659.587	4.36
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.28	181.970	0.09	1905.481	2.38
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.33	208.930	0.00	2187.762	0.55
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.36	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.38	275.423	0.28	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.38	316.228	0.98	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.36	363.078	2.14	3801.894	0.00
0.035	0.00	0.363	0.00	3.892	0.00	39.811	0.34	416.989	3.72	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.31	478.830	5.62	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.30	549.541	7.60	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.02	60.256	0.30	630.957	9.36	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.08	69.183	0.32	724.436	10.59	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.07	79.433	0.36	831.764	11.07	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	0.41	954.993	10.73	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.12	104.713	0.42	1098.478	9.65		
0.105	0.00	1.098	0.00	11.482	0.15	120.226	0.40	1258.925	8.08		

Result Analysis Report

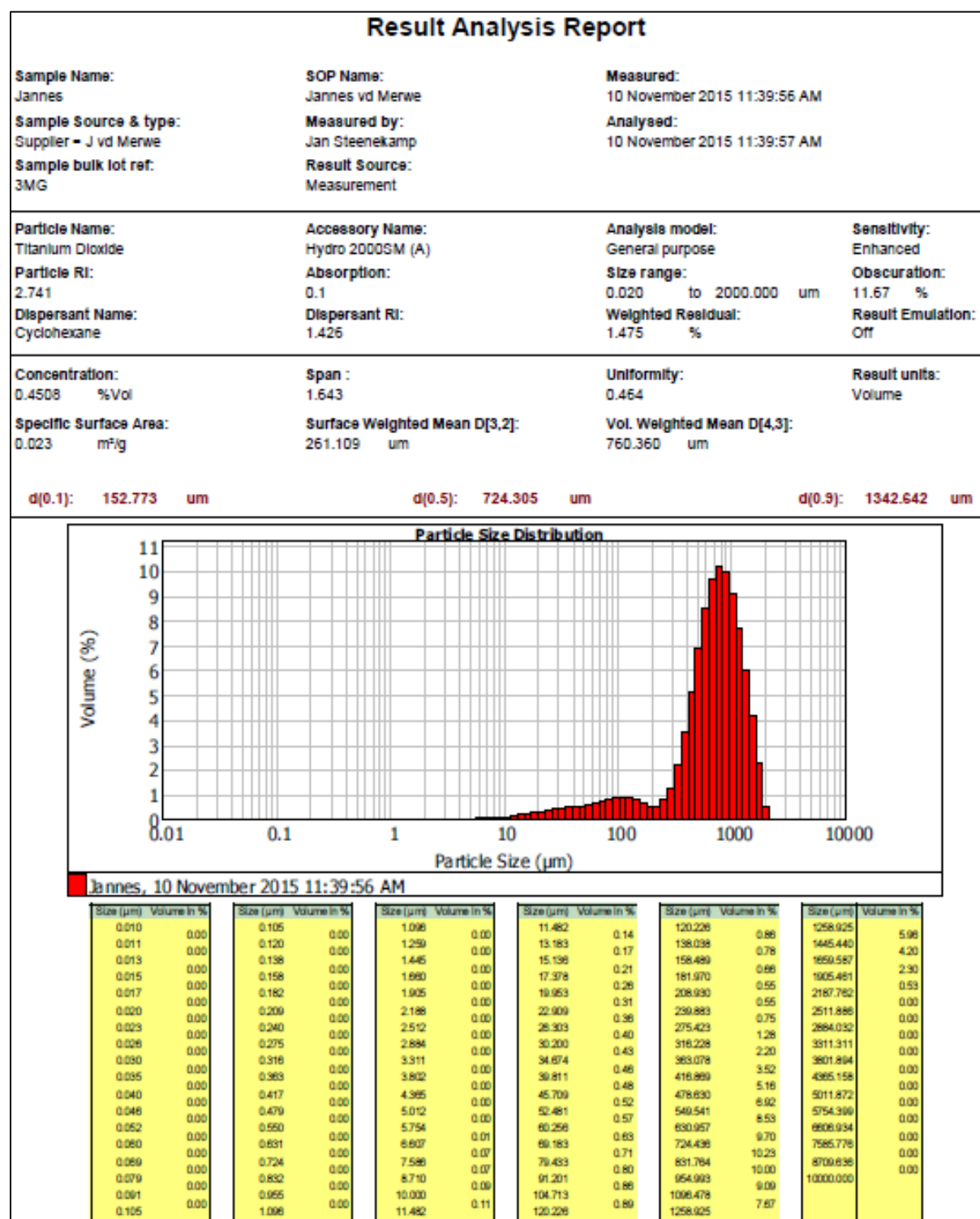
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:34:01 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 10 November 2015 11:34:02 AM	
Sample bulk lot ref: 2MG	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 μm	Obscuration: 12.98 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.349 %	Result Emulation: Off
Concentration: 0.4507 %Vol	Span : 1.359	Uniformity: 0.428	Result units: Volume
Specific Surface Area: 0.0256 m^2/g	Surface Weighted Mean D[3,2]: 234.745 μm	Vol. Weighted Mean D[4,3]: 783.475 μm	
d(0.1): 339.863 μm	d(0.5): 737.772 μm	d(0.9): 1342.159 μm	



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	0.25	120.226	0.28	1258.925	5.98
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.30	138.038	0.11	1445.440	4.19
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.35	158.489	0.00	1659.587	2.29
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.40	181.970	0.00	1905.461	0.53
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.43	208.930	0.00	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.45	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.44	275.423	1.06	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.43	316.228	2.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.40	363.078	3.88	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.37	416.869	5.79	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.00	45.709	0.36	478.630	7.72	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.02	52.481	0.36	549.541	9.40	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.09	60.256	0.38	630.957	10.52	6608.934	0.00
0.060	0.00	0.631	0.00	6.637	0.10	69.183	0.40	724.436	10.88	7585.775	0.00
0.069	0.00	0.724	0.00	7.586	0.12	79.433	0.42	831.764	10.45	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.16	91.201	0.42	954.993	9.34	10000.000	0.00
0.091	0.00	0.955	0.00	10.030	0.20	104.713	0.37	1095.478	7.77		
0.105	0.00	1.096	0.00	11.482	0.25	120.226	0.37	1258.925	7.77		

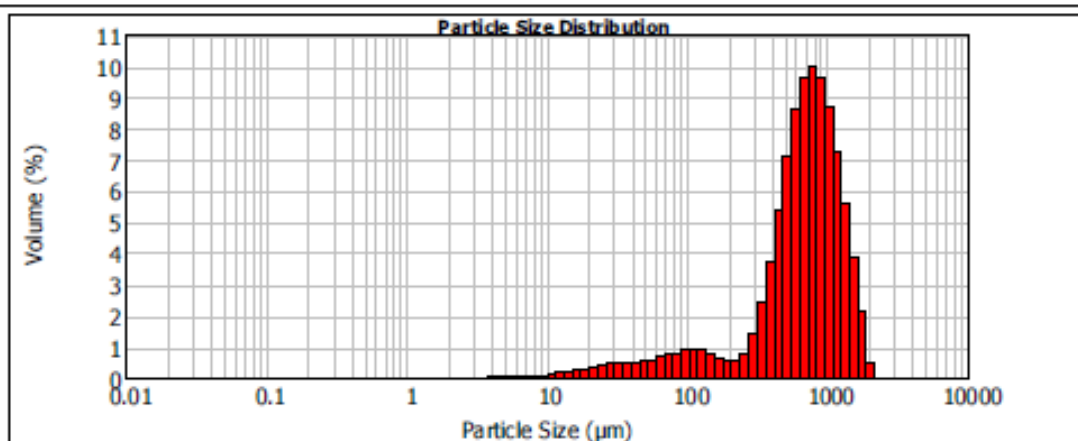
7.2.2.3 Formulation 3

In the following figures the particle size distribution data for MicroceLac®-containing granule formulation 3 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:40:36 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 10 November 2015 11:40:37 AM	
Sample bulk lot ref: 3MG	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 μm	Obscuration: 12.15 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.279 %	Result Emulation: Off
Concentration: 0.3853 %Vol	Span : 1.701	Uniformity: 0.48	Result units: Volume
Specific Surface Area: 0.0279 m^2/g	Surface Weighted Mean D[3,2]: 215.411 μm	Vol. Weighted Mean D[4,3]: 738.420 μm	
d(0.1): 126.632 μm d(0.5): 702.382 μm d(0.9): 1321.035 μm			

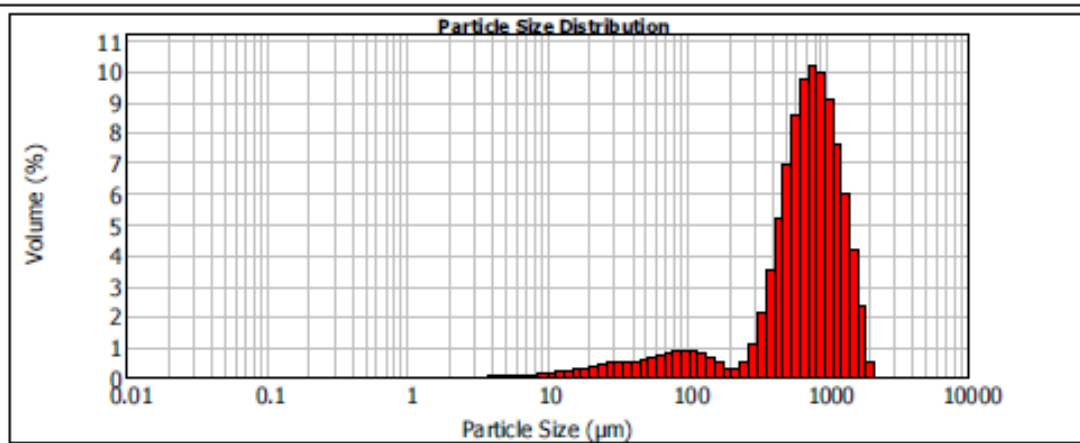


Jannes, 10 November 2015 11:40:36 AM

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	0.17	120.226	0.88	1258.925	5.59
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.21	138.038	0.79	1445.440	3.92
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.26	158.480	0.66	1659.587	2.13
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.32	181.970	0.56	1905.461	0.50
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.37	208.930	0.57	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.43	239.883	0.81	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.47	275.423	1.39	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.50	316.228	2.38	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.52	363.078	3.74	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.03	39.811	0.54	418.869	5.40	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.08	45.709	0.57	478.630	7.11	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.07	52.481	0.61	549.541	8.62	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.07	60.256	0.67	630.957	9.66	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.08	69.183	0.74	724.436	10.03	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.09	79.433	0.83	831.764	9.68	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.11	91.201	0.89	954.993	8.69	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.13	104.713	0.92	1096.478	7.25		
0.105	0.00	1.096	0.00	11.482	0.17	120.226	0.92	1258.925	7.25		

Result Analysis Report

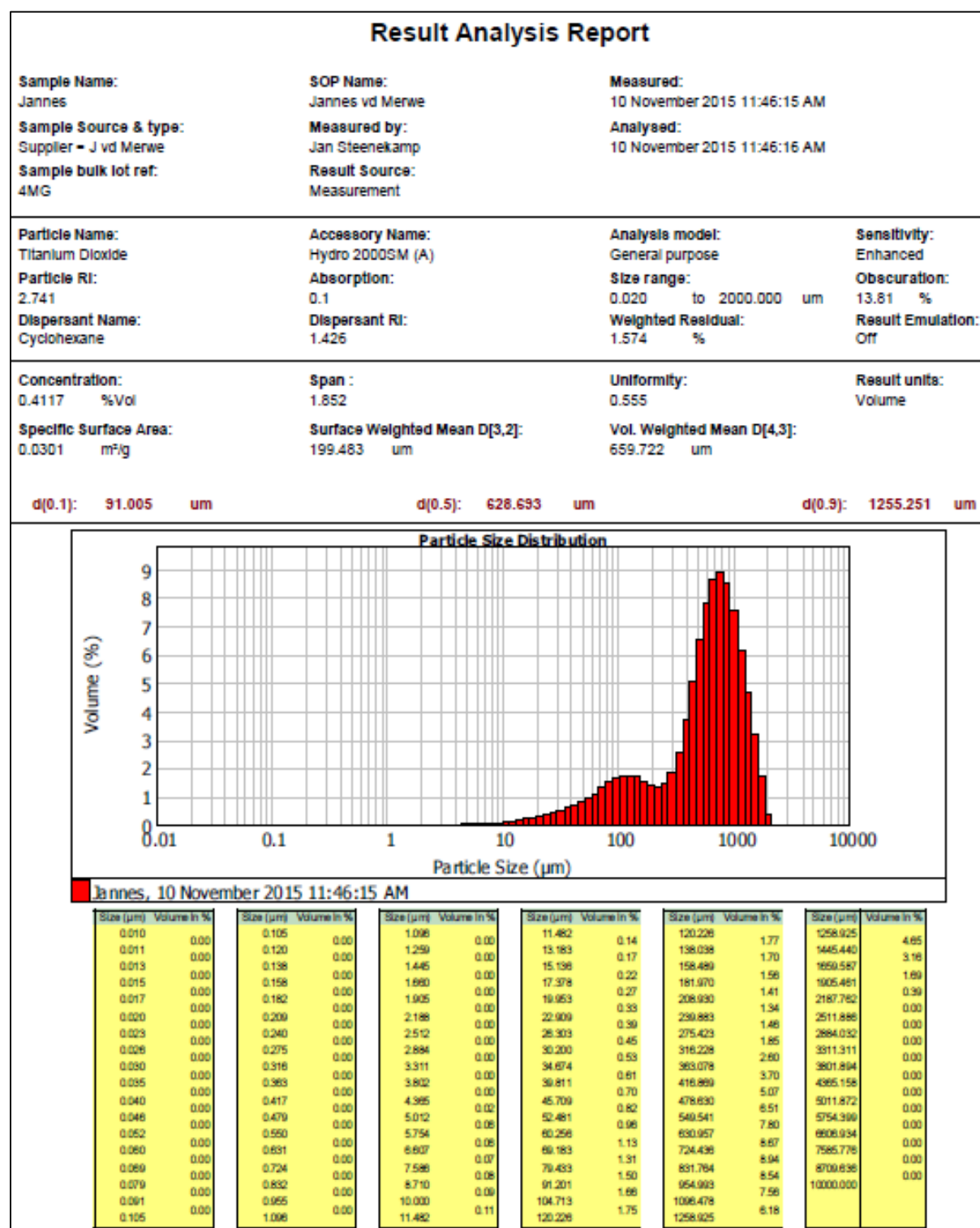
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:41:15 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:41:16 AM	
Sample bulk lot ref: 3MG	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 μm	Obscuration: 12.54 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.443 %	Result Emulation: Off
Concentration: 0.3939 %Vol	Span : 1.691	Uniformity: 0.469	Result units: Volume
Specific Surface Area: 0.0282 m^2/g	Surface Weighted Mean D[3,2]: 212.998 μm	Vol. Weighted Mean D[4,3]: 757.015 μm	
d(0.1): 120.908 μm d(0.5): 722.861 μm d(0.9): 1343.280 μm			



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	0.18	120.226	0.79	1258.925	5.95
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.22	138.038	0.64	1445.440	4.21
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.27	158.489	0.46	1659.587	2.31
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.33	181.970	0.32	1905.461	0.54
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.39	208.930	0.31	2187.782	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.44	239.883	0.54	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.48	275.423	1.12	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.51	316.228	2.10	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.53	363.078	3.48	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.03	39.811	0.56	416.869	5.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.385	0.07	45.709	0.59	478.630	6.96	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.07	52.481	0.64	540.541	8.57	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.08	60.256	0.71	630.957	9.72	6608.934	0.00
0.060	0.00	0.631	0.00	6.637	0.08	69.183	0.79	724.436	10.21	7585.775	0.00
0.069	0.00	0.724	0.00	7.586	0.10	79.433	0.86	831.764	9.96	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.12	91.201	0.90	954.993	9.04	10000.000	0.00
0.091	0.00	0.955	0.00	10.030	0.15	104.713	0.88	1098.478	7.83		
0.105	0.00	1.096	0.00	11.482	0.15	120.226		1258.925			

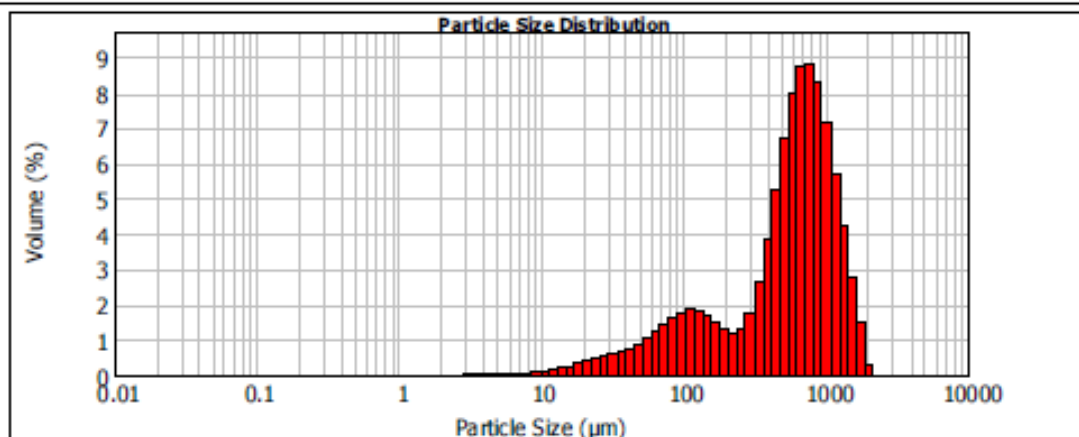
7.2.2.4 Formulation 4

In the following figures the particle size distribution data for MicroceLac®-containing granule formulation 4 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:46:55 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenkamp	Analysed: 10 November 2015 11:46:56 AM	
Sample bulk lot ref: 4MG	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: 13.51 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.538 %	Result Emulation: Off
Concentration: 0.3274 %Vol	Span : 1.879	Uniformity: 0.569	Result units: Volume
Specific Surface Area: 0.0366 m ² /g	Surface Weighted Mean D[3,2]: 163.913 um	Vol. Weighted Mean D[4,3]: 635.190 um	
d(0.1): 79.770 um	d(0.5): 606.210 um	d(0.9): 1219.105 um	

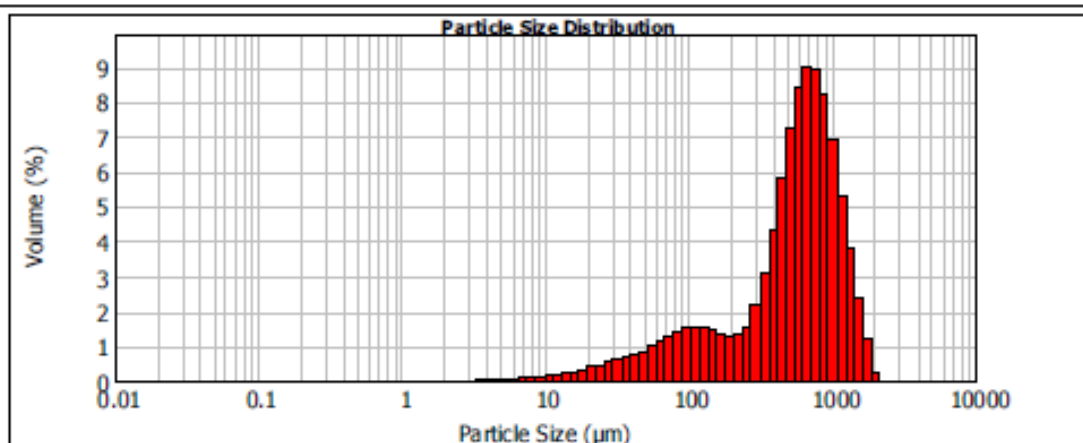


Jannes, 10 November 2015 11:46:55 AM

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	0.00	11.482	0.18	120.226	1.84	1258.925	4.20
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.23	138.038	1.70	1445.440	2.80
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.29	158.489	1.48	1659.587	1.47
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.35	181.970	1.28	1905.461	0.33
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.42	208.930	1.32	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.49	239.883	1.32	2511.888	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.55	275.423	1.70	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.04	30.200	0.62	316.228	2.65	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.05	34.674	0.68	363.078	3.86	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.05	39.811	0.77	416.869	5.30	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.07	45.709	0.88	478.630	6.77	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.07	52.481	1.03	549.541	8.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.08	60.256	1.22	630.957	8.75	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.08	69.183	1.43	724.436	8.85	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.09	79.433	1.63	831.764	8.28	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.11	91.201	1.79	954.993	7.17	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.14	104.713	1.87	1096.478	5.72		
0.105	0.00	1.096	0.00	11.482		120.226		1258.925			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 10 November 2015 11:47:34 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 10 November 2015 11:47:35 AM	
Sample bulk lot ref: 4MG	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 μm	Obscuration: 12.96 %
Dispersant Name: Cyclohexane	Dispersant RI: 1.426	Weighted Residual: 1.653 %	Result Emulation: Off
Concentration: 0.3211 %Vol	Span : 1.852	Uniformity: 0.555	Result units: Volume
Specific Surface Area: 0.0357 m^2/g	Surface Weighted Mean D[3,2]: 167.842 μm	Vol. Weighted Mean D[4,3]: 623.502 μm	
d(0.1): 81.230 μm d(0.5): 593.045 μm d(0.9): 1179.526 μm			



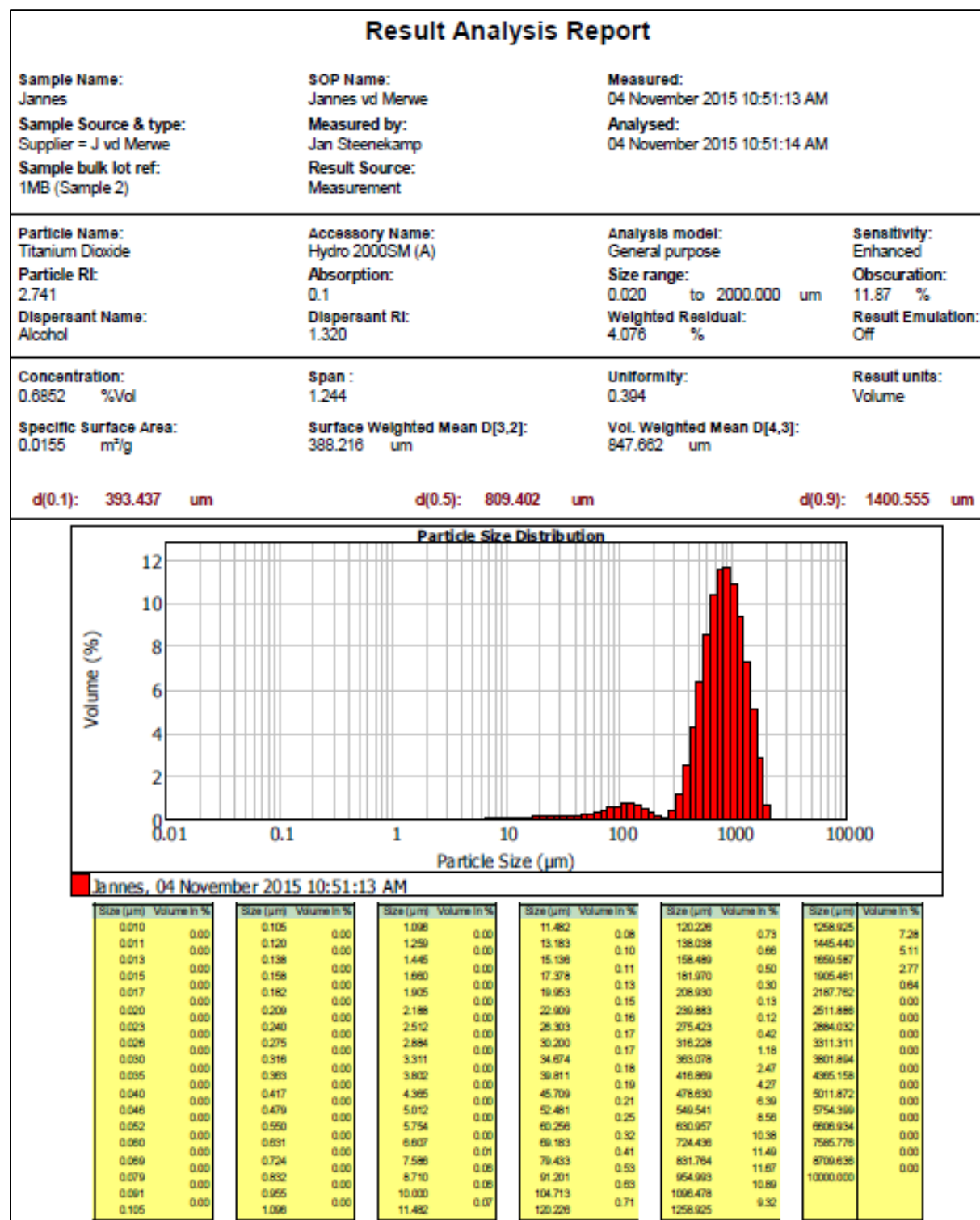
Jannes, 10 November 2015 11:47:34 AM

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	1.098	0.00	11.482	0.19	120.226	1.54	1258.925	3.78
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.23	138.038	1.45	1445.440	2.41
0.013	0.00	0.138	0.00	1.446	0.00	15.136	0.28	158.480	1.33	1659.587	1.22
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.34	181.970	1.25	1905.461	0.27
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.40	208.930	1.30	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.48	239.883	1.58	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.55	275.423	2.16	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.63	316.228	3.11	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.04	34.674	0.71	363.078	4.37	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.07	39.811	0.79	416.869	5.82	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.07	45.709	0.80	478.630	7.25	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.08	52.481	1.01	549.541	8.40	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.09	60.256	1.14	630.957	9.02	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.10	69.183	1.29	724.438	8.95	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.12	79.433	1.43	831.764	8.20	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.14	91.201	1.53	954.993	6.91	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.16	104.713	1.57	1098.478	5.34		
0.105	0.00	1.098	0.00	11.482	0.19	120.226		1258.925			

7.2.3 MICROCELAC®-CONTAINING BEAD FORMULATIONS

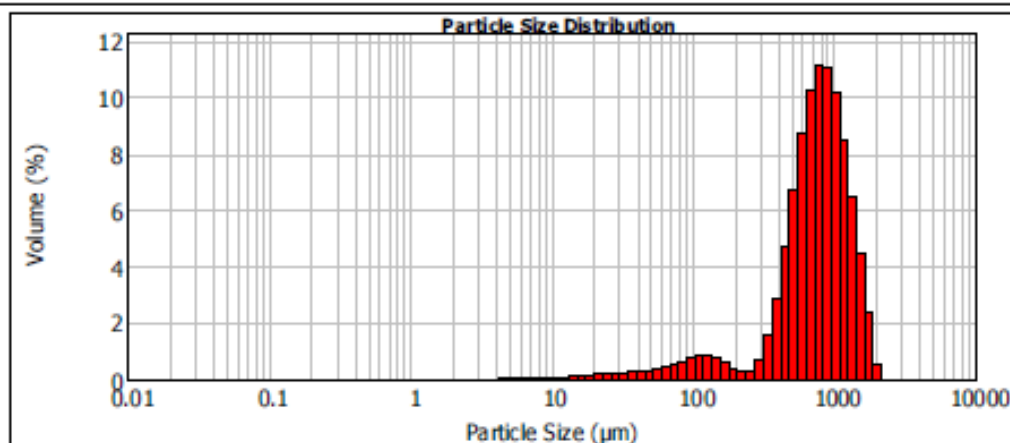
7.2.3.1 Formulation 1

In the following figures the particle size distribution data for Microcelac®-containing bead formulation 1 is given.



Result Analysis Report

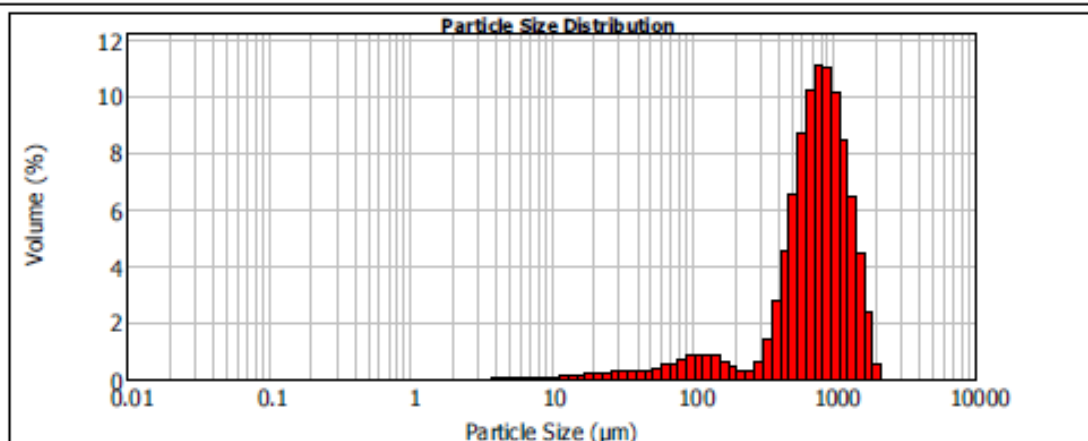
Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 10:51:53 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 04 November 2015 10:51:54 AM	
Sample bulk lot ref: 1MB (Sample 2)	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 μm	Obscuration: 17.61 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 3.646 %	Result Emulation: Off
Concentration: 0.7877 %Vol	Span : 1.387	Uniformity: 0.419	Result units: Volume
Specific Surface Area: 0.0204 m^2/g	Surface Weighted Mean D[3,2]: 293.706 μm	Vol. Weighted Mean D[4,3]: 802.105 μm	
d(0.1): 293.044 μm	d(0.5): 768.291 μm	d(0.9): 1358.529 μm	



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	1.098	0.00	11.482	0.11	120.226	0.85	1258.925	6.47
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.13	138.038	0.77	1445.440	4.44
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.15	158.489	0.62	1659.587	2.37
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.17	181.970	0.43	1905.481	0.54
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.19	208.930	0.30	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.21	239.883	0.35	2511.888	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.22	275.423	0.73	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.24	316.228	1.56	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.25	363.078	2.88	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.28	416.869	4.67	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.31	478.630	6.71	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.37	549.541	8.71	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.45	630.957	10.30	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.56	724.436	11.16	7585.778	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.67	831.764	11.10	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.78	954.993	10.14	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.85	1098.478	8.48		
0.105	0.00	1.098	0.00	11.482	0.10	120.226		1258.925			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 10:52:32 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 04 November 2015 10:52:33 AM	
Sample bulk lot ref: 1MB (Sample 2)	Result Source: Measurement		
Particle Name: Titanium Dioxide	Accessory Name: Hydro 2000SM (A)	Analysis model: General purpose	Sensitivity: Enhanced
Particle RI: 2.741	Absorption: 0.1	Size range: 0.020 to 2000.000 um	Obscuration: 22.78 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 3.734 %	Result Emulation: Off
Concentration: 0.9399 %Vol	Span : 1.492	Uniformity: 0.424	Result units: Volume
Specific Surface Area: 0.0228 m ² /g	Surface Weighted Mean D[3,2]: 263.637 um	Vol. Weighted Mean D[4,3]: 798.462 um	
d(0.1): 214.342 um d(0.5): 767.316 um d(0.9): 1358.936 um			

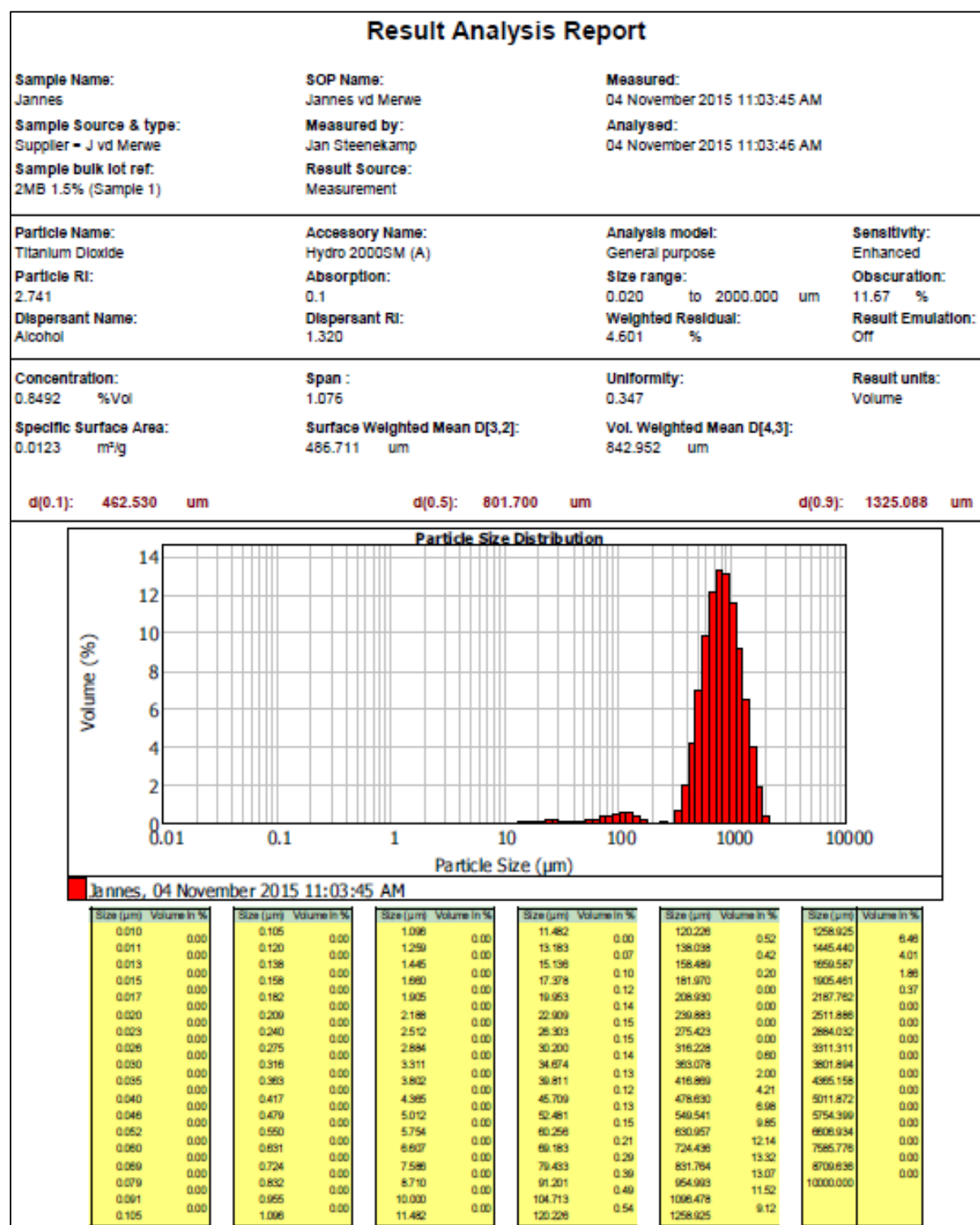


Jannes, 04 November 2015 10:52:32 AM

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	1.098	0.00	11.482	0.13	120.226	0.00	1258.925	6.46
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.15	138.038	0.82	1445.440	4.44
0.013	0.00	0.138	0.00	1.446	0.00	15.138	0.17	158.489	0.66	1659.587	2.38
0.015	0.00	0.158	0.00	1.680	0.00	17.378	0.19	181.970	0.45	1905.461	0.55
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.21	208.930	0.29	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.24	239.883	0.31	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.25	275.423	0.65	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.27	316.228	1.45	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.29	363.078	2.76	3801.864	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.31	416.889	4.55	4365.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.35	478.630	6.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.41	549.541	8.63	5754.369	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	0.49	630.957	10.24	6908.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.60	724.436	11.12	7585.778	0.00
0.069	0.00	0.724	0.00	7.589	0.00	79.433	0.71	831.764	11.06	8709.638	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.82	954.993	10.11	10000.000	0.00
0.091	0.00	0.965	0.00	10.000	0.00	104.713	0.90	1098.478	8.48		
0.105	0.00	1.098	0.00	11.482	0.11	120.226		1258.925			

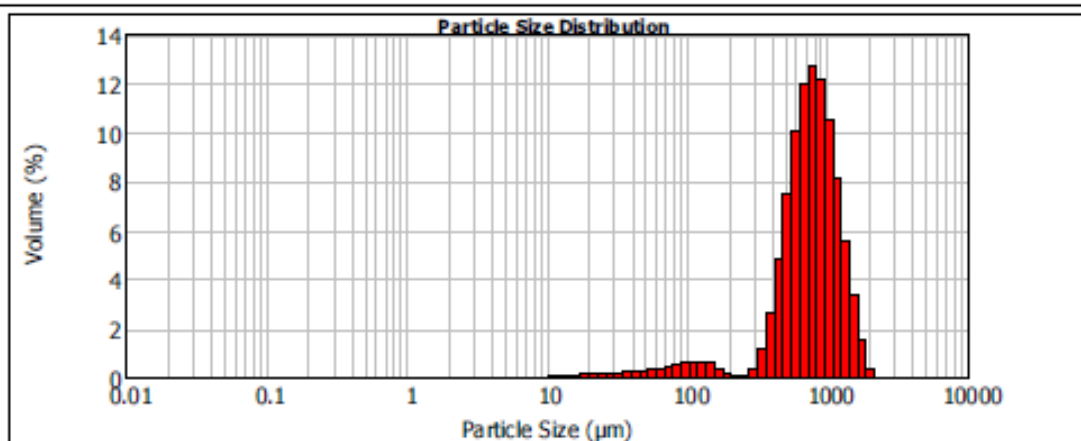
7.2.3.2 Formulation 2

In the following figures the particle size distribution data for MicroceLac®-containing granule formulation 2 is given.



Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 11:04:24 AM	
Sample Source & type: Supplier - J vd Merwe	Measured by: Jan Steenekamp	Analyzed: 04 November 2015 11:04:26 AM	
Sample bulk lot ref: 2MB 1.5% (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: 17.10 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 3.929 %	Result Emulation: Off
Concentration: 1.0087 %Vol	Span : 1.161	Uniformity: 0.371	Result units: Volume
Specific Surface Area: 0.0156 m ² /g	Surface Weighted Mean D[3,2]: 384.196 um	Vol. Weighted Mean D[4,3]: 795.558 um	
d(0.1): 400.086 um	d(0.5): 760.715 um	d(0.9): 1283.270 um	

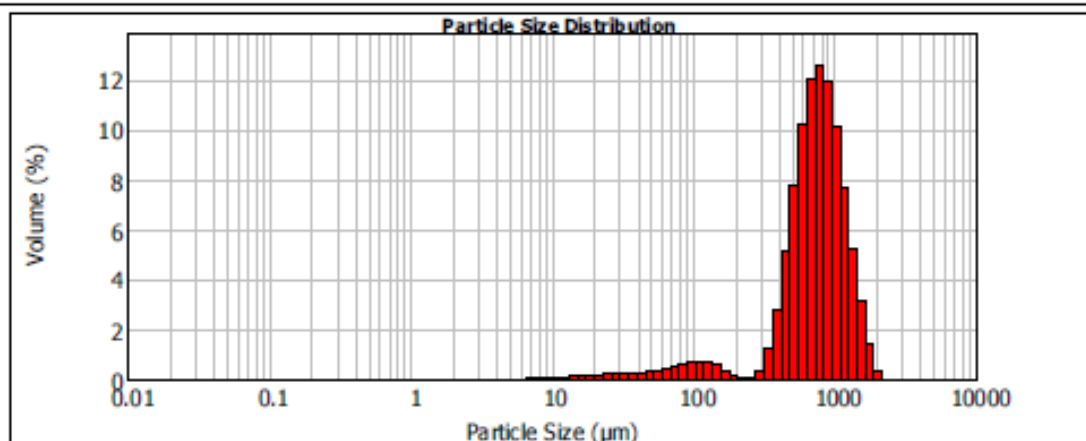


Jannes, 04 November 2015 11:04:24 AM

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	1.098	0.00	11.482	0.00	120.226	0.88	1258.025	5.82
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.11	138.038	0.57	1445.440	3.42
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.13	158.489	0.40	1650.587	1.57
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.16	181.970	0.31	1905.481	0.31
0.017	0.00	0.182	0.00	1.905	0.00	19.963	0.18	208.930	0.17	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.19	239.883	0.03	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.20	275.423	0.31	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.21	316.228	1.13	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.21	363.078	2.65	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.22	416.869	4.88	4395.158	0.00
0.040	0.00	0.417	0.00	4.395	0.00	45.709	0.24	478.630	7.52	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.29	549.541	10.10	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.256	0.36	630.957	12.01	6906.934	0.00
0.060	0.00	0.631	0.00	6.607	0.00	69.183	0.45	724.436	12.21	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.00	79.433	0.56	831.764	12.78	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.00	91.201	0.65	954.993	10.49	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.00	104.713	0.70	1096.478	8.10		
0.105	0.00	1.098	0.00	11.482	0.08	120.226		1258.025			

Result Analysis Report

Sample Name: Jannes	SOP Name: Jannes vd Merwe	Measured: 04 November 2015 11:05:04 AM	
Sample Source & type: Supplier = J vd Merwe	Measured by: Jan Steenekamp	Analysed: 04 November 2015 11:05:05 AM	
Sample bulk lot ref: 2MB 1.5% (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 μm	Obscuration: 22.38 %
Dispersant Name: Alcohol	Dispersant RI: 1.320	Weighted Residual: 3.851 %	Result Emulation: Off
Concentration: 1.1587 %Vol	Span : 1.194	Uniformity: 0.379	Result units: Volume
Specific Surface Area: 0.0183 m^2/g	Surface Weighted Mean D[3,2]: 328.262 μm	Vol. Weighted Mean D[4,3]: 775.944 μm	
d(0.1): 373.578 μm	d(0.5): 744.300 μm	d(0.9): 1261.985 μm	



Jannes, 04 November 2015 11:05:04 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	1.098	0.00	11.482	0.12	120.226	0.72	1258.925	5.25
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.14	138.038	0.59	1445.440	3.15
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.16	158.489	0.40	1659.587	1.43
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.19	181.970	0.17	1905.461	0.28
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	0.22	239.883	0.04	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.24	275.423	0.37	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.25	316.228	1.25	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.00	34.674	0.25	363.078	2.84	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.00	39.811	0.27	416.869	5.10	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.00	45.709	0.30	478.630	7.74	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.00	52.481	0.35	549.541	10.25	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.00	60.258	0.43	630.957	12.04	6608.934	0.00
0.060	0.00	0.631	0.00	6.607	0.01	69.183	0.52	724.436	12.64	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.08	79.433	0.63	831.764	11.92	8709.638	0.00
0.079	0.00	0.832	0.00	8.710	0.09	91.201	0.71	954.993	10.10	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.10	104.713	0.75	1096.478	7.69		
0.105	0.00	1.098	0.00	11.482		120.226		1258.925			

8 ANNEXURE B: FLOWABILITY DATA

8.1 AVICEL®-CONTAINING FORMULATIONS

8.1.1 AVICEL®-CONTAINING DRY POWDER FORMULATIONS

8.1.1.1 Formulation 1

In the following tables 8.1.1.1 A – G, flowability data and results are given regarding Avicel®-containing dry powder formulation 1.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	3.20	7.30	23.67
2	3.10	7.55	22.32
3	3.40	7.75	23.69
	Ave		23.23
	SD		0.785

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	216	194
2	210	196
3	212	194

B: COD (Critical orifice diameter)

	COD (mm)
	Orifice
1	1.50
2	1.50
3	1.50
Ave	1.50
SD	0

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.46	0.52
2	0.48	0.51
3	0.47	0.52
Ave	0.47	0.51
SD	0.007	0.003

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	4.90	12.70
2	4.60	12.20
3	4.70	12.30
Ave	4.73	12.40
SD	0.153	0.265

F: Hausner ratio's

	Hausner ratio
1	1.11
2	1.07
3	1.09
Ave	1.09
SD	0.021

G: Carr's indices

	Carr's index (%)
1	10.19
2	6.67
3	8.49
Ave	8.45
SD	1.760

8.1.1.2 Formulation 2

In the following tables 8.1.1.2 A – G, flowability data and results are given for Avicel®–containing dry powder formulation 2.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	3.40	7.55	24.24
2	3.30	7.35	24.18
3	3.20	7.35	23.53
		Ave	23.98
		SD	0.394

B: COD

	COD (mm)
	Orifice
1	1.50
2	1.50
3	1.50
Ave	1.50
SD	0

C: Flow rates

	Flow rate	
	Diameter size	
	10 mm	15 mm
1	4.20	11.60
2	4.00	11.50
3	4.00	11.10
Ave	4.07	11.40
SD	0.115	0.265

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	224.00	198.00
2	220.00	196.00
3	222.00	198.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.45	0.51
2	0.45	0.51
3	0.45	0.51
Ave	0.45	0.51
SD	0.004	0.003

F: Hausner ratio's

	Hausner ratio
1	1.13
2	1.12
3	1.12
Ave	1.12
SD	0.006

G: Carr's indices

	Carr's index (%)
1	11.61
2	10.91
3	10.81
Ave	11.11
SD	0.434

8.1.1.3 Formulation 3

In the following tables 8.1.1.3 A – G, flowability data and results are given regarding Avicel®–containing dry powder formulation 3.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	3.60	7.30	26.25
2	3.50	7.15	26.08
3	3.30	7.45	23.89
	Ave		25.41
	SD		1.316

B: COD

	COD (mm)
	Orifice
1	1.50
2	1.50
3	1.50
Ave	1.5
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.80	10.30
2	3.80	10.00
3	3.70	9.70
Ave	3.77	10.00
SD	0.058	0.300

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	228	196
2	228	195
3	226	196

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.44	0.51
2	0.44	0.51
3	0.44	0.51
Ave	0.44	0.51
SD	0.002	0.002

F: Hausner ratio's

	Hausner ratio
1	1.16
2	1.17
3	1.15
Ave	1.16
SD	0.008

G: Carr's Indices

	Carr's index
1	14.04
2	14.47
3	13.27
Ave	13.93
SD	0.607

8.1.1.4 Formulation 4

In the following tables 8.1.1.4 A – G, flowability data and results are given regarding Avicel®–containing dry powder formulation 4.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	3.70	7.45	26.41
2	3.50	7.50	25.02
3	3.70	7.45	26.41
		Ave	25.95
		SD	0.803

B: COD

	COD(mm)
	Gap size
1	1.50
2	1.50
3	1.50
Ave	1.50
SD	0

C: Flow rates

	Flow rate(g/s)	
	Diameter size	
	10 mm	15 mm
1	3.20	8.90
2	3.20	9.30
3	3.20	9.70
Ave	3.20	9.30
SD	0	0.4

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	225	195
2	227	196
3	226	195

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.44	0.51
2	0.44	0.51
3	0.44	0.51
Ave	0.44	0.51
SD	0.002	0.002

F: Hausner ratio's

	Hausner ratio
1	1.15
2	1.16
3	1.16
Ave	1.16
SD	0.003

G: Carr's indices

	Carr's index
1	13.33
2	13.66
3	13.72
Ave	13.57
SD	0.206

8.1.2 AVICEL®-CONTAINING GRANULE FORMULATIONS

8.1.2.1 Formulation 1

In the following tables 8.1.2.1 A – G, flowability data and results are given regarding Avicel®-containing granule formulation 1.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.50	9.00	26.57
2	4.80	8.40	29.73
3	5.00	8.60	30.16
	Ave		28.82
	SD		1.960

B: COD

	COD (mm)
	Orifice
1	8.00
2	8.00
3	8.00
Ave	8.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	11.60	35.70
2	11.80	35.70
3	11.60	35.70
Ave	11.67	35.70
SD	0.115	0.000

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	395	320
2	392	322
3	395	318

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.25	0.31
2	0.26	0.31
3	0.25	0.31
Ave	0.25	0.31
SD	0.001	0.002

F: Hausner ratio's

	Hausner ratio
1	1.23
2	1.22
3	1.24
Ave	1.23
SD	0.013

G: Carr's indices

	Carr's index (%)
1	18.99
2	17.86
3	19.49
Ave	18.78
SD	0.838

8.1.2.2 Formulation 2

In the following tables 8.1.2.2 A – G, flowability data and results are given regarding Avicel®– containing granule formulation 2.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.60	8.00	29.90
2	4.80	8.55	29.30
3	4.90	8.35	30.40
		Ave	29.87
		SD	0.551

B: COD

	COD (mm)
	Orifice
1	8.00
2	8.00
3	8.00
Ave	8.00
SD	0

C: Flow rates

	Flow rate (g/sec)	
	Diameter size	
	10 mm	15 mm
1	11.50	2.90
2	11.60	2.80
3	11.80	2.90
Ave	11.63	2.87
SD	0.153	0.058

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	380	310
2	370	305
3	390	315

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.26	0.32
2	0.27	0.33
3	0.26	0.32
Ave	0.26	0.32
SD	0.007	0.005

F: Hausner ratio's

	Hausner ratio
1	1.23
2	1.21
3	1.24
Ave	1.23
SD	0.012

G: Carr's indices

	Carr's index (%)
1	18.42
2	17.57
3	19.23
Ave	18.41
SD	0.832

8.1.2.3 Formulation 3

In the following tables 8.1.2.3 A – G, flowability data and results are given regarding Avicel®– containing granule formulation 3.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.70	8.40	29.30
2	4.90	8.55	29.80
3	4.90	8.40	30.24
		Ave	29.78
		SD	0.470

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	11.10	34.80
2	11.00	33.90
3	10.90	34.50
Ave	11.00	34.40
SD	0.100	0.458

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	392	317
2	385	312
3	390	310

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.26	0.32
2	0.26	0.32
3	0.26	0.32
Ave	0.26	0.32
SD	0.002	0.004

F: Hausner ratio's

	Hausner ratio
1	1.24
2	1.23
3	1.26
Ave	1.24
SD	0.013

G: Carr's indices

	Carr's index (%)
1	19.13
2	18.96
3	20.51
Ave	19.54
SD	0.851

8.1.2.4 Formulation 4

In the following tables 8.1.2.4 A – G, flowability data and results are given regarding Avicel® – containing granule formulation 4.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.85	8.10	31.00
2	4.90	7.75	32.30
3	4.90	8.40	30.20
		Ave	31.17
		SD	1.060

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	11.60	33.90
2	11.00	35.70
3	11.50	34.80
Ave	11.37	34.80
SD	0.321	0.900

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	387	310
2	390	315
3	380	305

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.26	0.32
2	0.26	0.32
3	0.26	0.33
Ave	0.26	0.32
SD	0.003	0.005

F: Hausner ratio's

	Hausner ratio
1	1.25
2	1.24
3	1.25
Ave	1.24
SD	0.005

G: Carr's indices

	Carr's index
1	19.90
2	19.23
3	19.74
Ave	19.62
SD	0.348

8.1.3 AVICEL®-CONTAINING BEADS FORMULATIONS

8.1.3.1 Formulation 1

In the following tables 8.1.3.1 A – G, flowability data and results are given regarding Avicel®–containing bead formulation 1.

A: Angle of repose

Angle of repose			
	Height (cm)	Radius (cm)	Degrees
1	2.40	6.85	19.30
2	2.20	6.85	17.80
3	2.30	6.60	19.20
		Ave	18.77
		SD	0.839

B: COD

COD (mm)	
	Orifice
1	8
2	8
3	8
Ave	8.00
SD	0

C: Flow rates

Flow rate (g/s)		
Diameter size		
	10mm	15mm
1	10.50	31.60
2	10.80	32.50
3	11.00	33.10
Ave	10.77	32.40
SD	0.252	0.755

D: Bulk and tapped volume

Volume		
	V _o (cm ³)	V _{tap} (cm ³)
1	131.00	110.00
2	130.00	105.00
3	131.00	110.00

E: Bulk and tapped densities

Densities		
	Bulk ρ	Tapped ρ
1	0.76	0.91
2	0.77	0.95
3	0.76	0.91
Ave	0.77	0.92
SD	0.003	0.025

F: Hausner ratio's

Hausner ratio	
1	1.19
2	1.24
3	1.19
Ave	1.21
SD	0.027

G: Carr's indices

Carr's index (%)	
1	16.03
2	19.23
3	16.03
Ave	17.10
SD	1.848

8.1.3.2 Formulation 2

In the following tables 8.1.3.2 A – G, flowability data and results are given regarding Avicel®–containing bead formulation 2.

A: Angle of repose

Angle of repose			
	Height (cm)	Radius (cm)	Degrees
1	2.35	6.55	19.70
2	2.20	6.50	18.70
3	2.20	6.75	18.10
		Ave	18.83
		SD	0.808

B: COD

COD (mm)	
	Orifice
1	8
2	8
3	8
Ave	8.00
SD	0

C: Flow rates

Flow rate (g/sec)		
Diameter size		
	10mm	15mm
1	10.2	30.7
2	10.3	31.5
3	10.2	32.3
Ave	10.23	31.50
SD	0.058	0.800

D: Bulk and tapped volume

Volume		
	V _o (cm ³)	V _{tap} (cm ³)
1	129	114
2	128	112
3	125	110

E: Bulk and tapped densities

Densities		
	Bulk ρ	Tapped ρ
1	0.78	0.88
2	0.78	0.89
3	0.80	0.91
Ave	0.79	0.89
SD	0.013	0.016

F: Hausner ratio's

Hausner ratio	
1	1.13
2	1.14
3	1.14
Ave	1.14
SD	0.006

G: Carr's indices

Carr's index (%)	
1	11.63
2	12.50
3	12.00
Ave	12.04
SD	0.438

8.2 MICROCELAC[®]-CONTAINING FORMULATIONS

8.2.1 MICROCELAC[®]-CONTAINING DRY POWDER FORMULATIONS

8.2.1.1 Formulation 1

In the following tables 8.2.1.1 A – G, flowability data and results are given regarding MicroceLac[®] – containing dry powder formulation 1.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	2.50	6.95	19.78
2	2.60	7.15	19.98
3	2.60	6.50	21.80
	Ave		20.52
	SD		1.113

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	180.00	146.00
2	175.00	144.00
3	175.00	144.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.56	0.68
2	0.57	0.69
3	0.57	0.69
Ave	0.57	0.69
SD	0.009	0.005

B: COD

	COD (mm)
	Orifice
1	3.00
2	3.00
3	3.00
Ave	3.00
SD	0

F: Hausner ratio's

	Hausner ratio
1	1.23
2	1.22
3	1.22
Ave	1.22
SD	0.010

C: Flow rates

	Flow rate(g/s)	
	Diameter size	
	10 mm	15 mm
1	3.80	11.00
2	3.80	10.30
3	3.90	10.50
Ave	3.83	10.60
SD	0.058	0.361

G: Carr's indices

	Carr's index (%)
1	18.89
2	17.71
3	17.71
Ave	18.11
SD	0.678

8.2.1.2 Formulation 2

In the following tables 8.2.1.2 A – G, flowability data and results are given regarding MicroceLac®-containing dry powder formulation 2.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	2.50	6.80	20.19
2	2.60	6.70	21.21
3	2.70	6.75	21.80
		Ave	21.07
		SD	0.815

B: COD

	COD (mm)
	Orifice
1	3.00
2	3.00
3	3.00
Ave	3.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.50	11.10
2	3.50	10.10
3	3.60	11.10
Ave	3.53	10.77
SD	0.058	0.577

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	172.00	142.00
2	170.00	141.00
3	171.00	140.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.58	0.70
2	0.59	0.71
3	0.58	0.71
Ave	0.58	0.71
SD	0.003	0.005

F: Hausner ratio's

	Hausner ratio
1	1.21
2	1.21
3	1.22
Ave	1.21
SD	0.008

G: Carr's indices

	Carr's index (%)
1	17.44
2	17.06
3	18.13
Ave	17.54
SD	0.542

8.2.1.3 Formulation 3

In the following tables 8.2.1.3 A – G, flowability data and results are given regarding MicroceLac®-containing dry powder formulation 3.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	2.80	6.95	21.94
2	2.80	6.65	22.83
3	2.80	6.85	22.23
		Ave	22.33
		SD	0.45

B: COD

	COD (mm)
	Orifice
1	3.00
2	3.00
3	3.00
Ave	3.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.30	9.40
2	3.10	9.30
3	3.10	9.00
Ave	3.17	9.23
SD	0.12	0.21

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	180.00	150.00
2	180.00	151.00
3	178.00	148.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.56	0.67
2	0.56	0.66
3	0.56	0.68
Ave	0.56	0.67
SD	0.00	0.01

F: Hausner ratio's

	Hausner ratio
1	1.20
2	1.19
3	1.20
Ave	1.20
SD	0.01

G: Carr's indices

	Carr's index (%)
1	16.67
2	16.11
3	16.85
Ave	16.54
SD	0.39

8.2.1.4 Formulation 4

In the following tables 8.2.1.4 A – G, flowability data and results are given regarding MicroceLac®-containing dry powder formulation 4.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	2.80	6.95	21.94
2	2.80	6.70	22.68
3	2.90	6.85	22.95
		Ave	22.52
		SD	0.523

B: COD

	COD (mm)
	Orifice
1	3.00
2	3.00
3	3.00
Ave	3.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	2.90	9.80
2	3.00	8.50
3	3.00	8.60
Ave	2.97	8.97
SD	0.058	0.723

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	182.00	148.00
2	181.00	147.00
3	180.00	147.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.55	0.68
2	0.55	0.68
3	0.56	0.68
Ave	0.55	0.68
SD	0.003	0.003

F: Hausner ratio's

	Hausner ratio
1	1.23
2	1.23
3	1.22
Ave	1.23
SD	0.004

G: Carr's indices

	Carr's index (%)
1	18.68
2	18.78
3	18.33
Ave	18.60
SD	0.236

8.2.2 MICROCELAC[®]-CONTAINING GRANULE FORMULATIONS

8.2.2.1 Formulation 1

In the following tables 8.2.2.1 A – G, flowability data and results are given regarding MicroceLac[®]-containing granule formulation 1.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	3.60	7.50	24.23
2	4.20	7.50	29.25
3	4.50	7.50	30.96
	Ave		28.15
	SD		3.498

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.80	12.30
2	3.90	11.20
3	3.90	12.20
Ave	3.87	11.90
SD	0.058	0.608

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	290.00	239.00
2	285.00	233.00
3	283.00	229.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.34	0.42
2	0.35	0.43
3	0.35	0.44
Ave	0.35	0.43
SD	0.004	0.009

F: Hausner ratio's

	Hausner ratio
1	1.21
2	1.22
3	1.24
Ave	1.22
SD	0.011

G: Carr's indices

	Carr's index (%)
1	17.59
2	18.25
3	19.08
Ave	18.30
SD	0.749

8.2.2.2 Formulation 2

In the following tables 8.2.2.2 A – G, flowability data and results are given regarding MicroceLac®-containing granule formulation 2.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.50	7.80	29.98
2	4.50	7.50	30.96
3	4.30	7.65	29.34
		Ave	30.09
		SD	0.816

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.10	10.30
2	3.10	10.30
3	3.10	10.30
Ave	3.10	10.30
SD	0	0

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	335.00	275.00
2	330.00	265.00
3	330.00	270.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.30	0.36
2	0.30	0.38
3	0.30	0.37
Ave	0.30	0.37
SD	0.003	0.007

F: Hausner ratio's

	Hausner ratio
1	1.22
2	1.25
3	1.22
Ave	1.23
SD	0.015

G: Carr's indices

	Carr's index (%)
1	17.91
2	19.70
3	18.18
Ave	18.60
SD	0.963

8.2.2.3 Formulation 3

In the following tables 8.2.2.3 A – G, flowability data and results are given regarding MicroceLac®-containing granule formulation 3.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.30	7.70	29.18
2	4.70	7.85	30.91
3	4.70	7.70	31.40
		Ave	30.50
		SD	1.166

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10mm	15mm
1	0.00	9.30
2	0.00	9.90
3	0.00	9.90
Ave	0.00	9.70
SD	0	0.346

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	338.00	280.00
2	330.00	275.00
3	335.00	280.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.30	0.36
2	0.30	0.36
3	0.30	0.36
Ave	0.30	0.36
SD	0.003	0.003

F: Hausner ratio's

	Hausner ratio
1	1.21
2	1.20
3	1.20
Ave	1.20
SD	0.005

G: Carr's indices

	Carr's index (%)
1	17.16
2	16.67
3	16.42
Ave	16.75
SD	0.378

8.2.2.4 Formulation 4

In the following tables 8.2.2.4 A – G, flowability data and results are given regarding MicroceLac®-containing granule formulation 4.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	4.20	7.65	28.77
2	4.30	7.50	29.83
3	4.10	7.55	28.50
		Ave	29.03
		SD	0.703

B: COD

	COD (mm)
	Orifice
1	12.00
2	12.00
3	12.00
Ave	12.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	3.40	11.10
2	3.40	11.10
3	3.40	11.10
Ave	3.40	11.10
SD	0	0

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	325.00	268.00
2	320.00	265.00
3	330.00	275.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.31	0.37
2	0.31	0.38
3	0.30	0.36
Ave	0.31	0.37
SD	0.005	0.007

F: Hausner ratio's

	Hausner ratio
1	1.21
2	1.21
3	1.20
Ave	1.21
SD	0.006

G: Carr's indices

	Carr's index (%)
1	17.54
2	17.19
3	16.67
Ave	17.13
SD	0.439

8.2.3 MICROCELAC[®]-CONTAINING BEAD FORMULATIONS

8.2.3.1 Formulation 1

In the following tables 8.2.3.1 A – G, flowability data and results are given regarding MicroceLac[®] – containing bead formulation 1.

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	1.80	6.75	14.93
2	1.70	6.50	14.66
3	1.80	6.70	15.04
		Ave	14.88
		SD	0.196

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	137.00	127.00
2	135.00	124.00
3	139.00	126.00

B: COD

	COD (mm)
	Orifice
1	8.00
2	8.00
3	8.00
Ave	8.00
SD	0

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.73	0.79
2	0.74	0.81
3	0.72	0.79
Ave	0.73	0.80
SD	0.011	0.010

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	11.00	33.30
2	11.00	33.30
3	11.00	33.30
Ave	11.00	33.30
SD	0	0

F: Hausner ratio's

	Hausner ratio
1	1.08
2	1.09
3	1.10
Ave	1.09
SD	0.012

G: Carr's indices

	Carr's index (%)
1	7.30
2	8.15
3	9.35
Ave	8.27
SD	1.032

8.2.3.2 Formulation 2

In the following tables 8.2.3.2 A – G, flowability data and results are given regarding MicroceLac®-containing bead formulation 2

A: Angle of repose

	Angle of repose		
	Height (cm)	Radius (cm)	Degrees
1	1.70	6.65	14.34
2	1.70	6.25	15.22
3	1.60	6.55	13.73
		Ave	14.43
		SD	0.749

B: COD

	COD (mm)
	Gap size
1	8.00
2	8.00
3	8.00
Ave	8.00
SD	0

C: Flow rates

	Flow rate (g/s)	
	Diameter size	
	10 mm	15 mm
1	10.60	32.30
2	10.60	32.30
3	10.60	32.30
Ave	10.60	32.30
SD	0	0

D: Bulk and tapped volume

	Volume	
	V _o (cm ³)	V _{tap} (cm ³)
1	140.00	128.00
2	137.00	124.00
3	135.00	122.00

E: Bulk and tapped densities

	Densities	
	Bulk ρ	Tapped ρ
1	0.71	0.78
2	0.73	0.81
3	0.74	0.82
Ave	0.73	0.80
SD	0.013	0.020

F: Hausner ratio's

	Hausner ratio
1	1.09
2	1.10
3	1.11
Ave	1.10
SD	0.007

G: Carr's indices

	Carr's index (%)
1	8.57
2	9.49
3	9.63
Ave	9.23
SD	0.575

9 ANNEXURE C: TABLET EVALUATION DATA

9.1 CRUSHING STRENGTH

9.1.1 AVICEL[®]-CONTAINING TABLET FORMULATIONS

9.1.1.1 *Dry powder-containing tablets*

In Tables 9.1.1.1 A and B, the crushing strength values for all formulations of the flat faced and concave Avicel[®]-containing dry powder tablets are given.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	92	98	89	98
2	92	96	92	96
3	95	96	93	96
4	95	95	89	95
5	95	97	92	94
6	93	95	89	95
7	94	93	91	96
8	92	95	90	99
9	98	94	86	93
10	96	96	86	93
Ave	94.20	95.50	89.70	95.50
SD	1.989	1.434	2.406	1.958

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2	F3	F4
1	87	111	98	102
2	88	113	100	95
3	87	111	94	96
4	89	109	94	94
5	89	107	98	98
6	86	106	96	96
7	84	105	97	97
8	89	109	96	92
9	84	100	100	97
10	87	105	94	92
Ave	87.00	107.60	96.70	95.90
SD	1.886	3.806	2.312	2.961

9.1.1.2 *Granule – containing tablets*

In the Tables 9.1.1.2 A and B, the crushing strength values for all formulations of the flat faced and concave Avicel[®]-containing granule tablets are given.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	77	76	92	79
2	83	81	103	105
3	72	72	98	115
4	82	66	104	87
5	80	78	106	117
6	71	78	90	78
7	78	58	96	102
8	74	86	98	114
9	82	69	136	100
10	86	76	118	99
Ave	78.50	74.00	104.10	99.60
SD	4.994	8.042	13.747	14.269

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2	F3	F4
1	76	70	77	59
2	80	54	68	64
3	59	68	65	68
4	63	65	70	61
5	69	65	67	49
6	70	60	71	65
7	61	61	78	60
8	97	64	62	55
9	67	65	72	53
10	66	72	75	48
Ave	70.80	64.40	70.50	58.20
SD	11.233	5.190	5.191	6.779

9.1.1.3 Bead-containing tablets

In Tables 9.1.1.3 A and B, the crushing strength values for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets can be found.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2
1	93	95
2	108	99
3	108	110
4	103	78
5	95	103
6	103	103
7	95	85
8	87	93
9	105	100
10	111	84
Ave	100.80	95.00
SD	7.843	10.044

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2
1	122	82
2	103	93
3	94	100
4	108	89
5	103	81
6	112	88
7	121	83
8	107	90
9	105	90
10	99	92
Ave	107.40	88.80
SD	8.909	5.750

9.1.2 MICROCELAC®-CONTAINING TABLET FORMULATIONS

9.1.2.1 Dry powder-containing tablets

In Tables 9.1.2.1 A and B, the crushing strength values for all formulations of the flat faced and concave Microcelac® – containing dry powder formulated tablets are given.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	109	104	111	103
2	94	106	107	103
3	108	107	120	109
4	109	109	107	105
5	105	108	128	103
6	97	101	109	104
7	104	108	109	104
8	106	108	115	116
9	95	108	109	107
10	96	108	109	108
Ave	102.30	106.70	112.40	106.20
SD	6.111	2.452	6.786	4.077

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2	F3	F4
1	132	107	106	111
2	137	81	104	108
3	129	101	108	105
4	128	98	107	103
5	131	96	104	109
6	133	101	104	109
7	127	104	104	115
8	129	93	104	106
9	131	106	103	107
10	128	100	101	107
Ave	130.50	98.70	104.50	108.00
SD	2.991	7.573	2.014	3.333

9.1.2.2 Granule-containing tablets

In Tables 9.1.2.2 A and B, the crushing strength values for all formulations of the flat faced and concave MicroceLac® – containing granule formulated tablets can be found.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	149	132	146	108
2	148	142	166	104
3	160	140	155	106
4	142	127	125	100
5	140	141	158	112
6	145	125	76	109
7	120	125	68	128
8	150	152	120	104
9	85	142	129	112
10	153	195	179	112
Ave	139.20	142.10	132.20	109.50
SD	21.760	20.594	36.817	7.649

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2	F3	F4
1	118	92	127	139
2	108	112	104	145
3	126	85	124	120
4	119	76	125	113
5	122	86	115	109
6	120	100	115	123
7	103	100	146	123
8	103	75	121	127
9	120	53	103	102
10	134	84	137	117
Ave	117.30	86.30	121.70	121.80
SD	9.945	16.391	13.425	13.011

9.1.2.3 Bead-containing tablets

In Tables 9.1.2.3 A and B, the crushing strength values for all formulations of the flat faced and concave MicroceLac®–containing bead formulated tablets can be found.

Table A: The crushing strength values (N) of the flat faced tablets

Tablet nr.	F1	F2
1	102	92
2	85	96
3	111	98
4	105	98
5	66	80
6	81	94
7	110	107
8	93	112
9	89	104
10	95	92
Ave	93.70	97.30
SD	14.103	8.970

Table B: The crushing strength values (N) of the concave tablets

Tablet nr.	F1	F2
1	108	92
2	112	95
3	101	85
4	97	107
5	118	111
6	107	94
7	116	115
8	88	98
9	88	93
10	109	101
Ave	104.40	99.10
SD	10.658	9.374

9.2 TABLET THICKNESS

9.2.1 AVICEL[®]–CONTAINING TABLET FORMULATIONS

9.2.1.1 Dry powder–containing tablets

In Tables 9.2.1.1 A and B, the tablet thickness values for all formulations of the flat faced and concave Avicel[®]–containing dry powder formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	3.29	3.35	3.43	3.37
2	3.30	3.34	3.44	3.37
3	3.29	3.34	3.44	3.36
4	3.30	3.35	3.44	3.35
5	3.31	3.34	3.44	3.35
6	3.31	3.35	3.44	3.36
7	3.30	3.35	3.43	3.37
8	3.30	3.35	3.41	3.36
9	3.30	3.34	3.43	3.35
10	3.30	3.32	3.41	3.34
Ave	3.30	3.34	3.43	3.36
SD	0.007	0.009	0.012	0.010

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	4.16	4.06	4.13	4.13
2	4.17	4.04	4.12	4.15
3	4.17	4.06	4.13	4.12
4	4.15	4.03	4.11	4.12
5	4.17	4.02	4.14	4.12
6	4.17	4.05	4.15	4.12
7	4.17	4.03	4.11	4.16
8	4.16	4.06	4.13	4.16
9	4.14	4.03	4.12	4.13
10	4.14	4.03	4.13	4.12
Ave	4.16	4.04	4.13	4.13
SD	0.012	0.015	0.013	0.017

9.2.1.2 Granule–containing tablets

In Tables 9.2.1.2 A and B, the tablet thickness values for all formulations of the flat faced and concave Avicel[®] – containing granule formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	3.77	3.77	3.60	3.63
2	3.77	3.76	3.59	3.65
3	3.78	3.79	3.60	3.62
4	3.78	3.80	3.63	3.64
5	3.78	3.78	3.62	3.64
6	3.77	3.79	3.62	3.63
7	3.78	3.80	3.62	3.63
8	3.78	3.76	3.60	3.62
9	3.76	3.79	3.62	3.64
10	3.77	3.78	3.62	3.62
Ave	3.77	3.78	3.61	3.63
SD	0.007	0.015	0.013	0.010

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	4.66	4.65	4.63	4.65
2	4.65	4.66	4.64	4.66
3	4.65	4.66	4.61	4.66
4	4.67	4.65	4.65	4.66
5	4.66	4.65	4.64	4.65
6	4.66	4.65	4.64	4.66
7	4.66	4.65	4.64	4.65
8	4.65	4.64	4.55	4.63
9	4.63	4.62	4.62	4.65
10	4.63	4.65	4.63	4.61
Ave	4.65	4.65	4.63	4.65
SD	0.013	0.011	0.029	0.016

9.2.1.3 Bead-containing

In Tables 9.2.1.3 A and B, the tablet thickness values for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2
1	3.20	3.33
2	3.18	3.34
3	3.19	3.35
4	3.20	3.33
5	3.18	3.34
6	3.20	3.36
7	3.18	3.33
8	3.18	3.34
9	3.18	3.34
10	3.17	3.32
Ave	3.19	3.34
SD	0.011	0.011

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr	F1	F2
1	4.05	4.09
2	3.99	4.11
3	4.00	4.11
4	4.10	4.12
5	4.02	4.11
6	3.99	4.11
7	4.08	4.12
8	3.99	4.11
9	4.00	4.09
10	3.99	4.10
Ave	4.02	4.11
SD	0.041	0.011

9.2.2 MICROCELAC®-CONTAINING TABLET FORMULATIONS

9.2.2.1 Dry powder-containing tablets

In Tables 9.2.2.1 A and B, the tablet thickness values for all formulations of the flat faced and concave MicroceLac®-containing dry powder formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	3.10	3.18	3.23	3.25
2	3.07	3.17	3.25	3.25
3	3.10	3.17	3.26	3.25
4	3.11	3.18	3.26	3.27
5	3.10	3.17	3.29	3.27
6	3.09	3.18	3.25	3.26
7	3.12	3.18	3.26	3.25
8	3.09	3.18	3.27	3.28
9	3.05	3.16	3.23	3.26
10	3.06	3.17	3.21	3.24
Ave	3.09	3.17	3.25	3.26
SD	0.022	0.007	0.023	0.012

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	3.85	3.99	3.98	3.99
2	3.87	3.98	3.98	4.00
3	3.85	3.98	3.99	3.98
4	3.85	3.97	3.99	3.99
5	3.86	3.98	3.99	4.00
6	3.86	3.97	3.99	4.00
7	3.87	3.99	3.99	4.01
8	3.86	3.99	3.99	3.98
9	3.84	3.98	3.98	3.98
10	3.83	3.97	3.96	3.97
Ave	3.85	3.98	3.98	3.99
SD	0.013	0.008	0.010	0.012

9.2.2.2 Granule-containing tablets

In Tables 9.2.2.2 A and B, the tablet thickness values for all formulations of the flat faced and concave MicroceLac®-containing granule formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	3.12	3.04	3.31	3.32
2	3.14	3.06	3.33	3.33
3	3.11	3.04	3.32	3.32
4	3.13	3.04	3.31	3.32
5	3.11	3.06	3.36	3.36
6	3.10	3.04	3.52	3.33
7	3.10	3.04	3.52	3.37
8	3.11	3.05	3.28	3.33
9	3.01	3.04	3.29	3.32
10	3.13	3.16	3.34	3.32
Ave	3.11	3.06	3.36	3.33
SD	0.036	0.037	0.088	0.018

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	4.15	4.09	4.18	4.15
2	4.14	4.22	4.17	4.16
3	4.12	4.08	4.21	4.17
4	4.16	4.08	4.15	4.17
5	4.16	4.10	4.11	4.19
6	4.12	4.16	4.16	4.19
7	4.15	4.16	4.20	4.22
8	4.11	4.11	4.18	4.14
9	4.14	4.02	4.16	4.16
10	4.14	4.13	4.14	4.20
Ave	4.14	4.12	4.17	4.18
SD	0.017	0.055	0.029	0.025

9.2.2.3 Bead – containing tablets

In Tables 9.2.2.3 A and B, the tablet thickness values for all formulations of the flat faced and concave MicroceLac®-containing bead formulated tablets are given.

Table A: The tablet thickness (mm) for the flat faced tablets

Tablet nr.	F1	F2
1	3.31	3.20
2	3.29	3.19
3	3.33	3.21
4	3.33	3.24
5	3.24	3.19
6	3.29	3.20
7	3.30	3.26
8	3.27	3.22
9	3.28	3.19
10	3.27	3.25
Ave	3.29	3.22
SD	0.028	0.026

Table B: The tablet thickness (mm) for the concave tablets

Tablet nr.	F1	F2
1	4.03	3.98
2	4.03	4.00
3	3.97	3.96
4	3.98	4.03
5	3.99	4.01
6	4.03	4.01
7	4.00	4.04
8	3.95	4.00
9	3.95	3.99
10	4.01	3.98
Ave	3.99	4.00
SD	0.031	0.024

9.3 TABLET DIAMETER

9.3.1 AVICEL[®]–CONTAINING FORMULATIONS

9.3.1.1 Dry powder–containing tablets

In Tables 9.3.1.1 A and B, the tablet diameter values for all formulations of the flat faced and concave Avicel[®]–containing dry powder formulated tablets are given.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	8.98	8.98	8.98	8.98
2	8.98	8.98	8.98	8.98
3	8.98	8.98	8.98	8.98
4	8.98	8.98	8.98	8.99
5	8.98	8.99	8.98	8.98
6	8.98	8.98	8.99	8.98
7	8.99	8.98	9.98	8.98
8	8.98	8.98	8.99	8.98
9	8.99	8.98	8.98	8.98
10	8.98	8.98	8.99	8.98
Ave	8.98	8.98	9.08	8.98
SD	0.004	0.003	0.315	0.003

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	8.98	8.98	8.98	8.98
2	8.99	8.98	9.00	8.99
3	9.00	8.98	9.01	8.98
4	8.99	8.98	8.98	8.98
5	9.02	8.98	8.99	8.98
6	8.99	8.98	8.98	8.98
7	9.00	8.98	8.98	8.98
8	9.01	8.99	8.99	8.98
9	8.99	8.99	8.98	8.98
10	8.99	8.98	8.98	8.98
Ave	9.00	8.98	8.99	8.98
SD	0.012	0.004	0.011	0.003

9.3.1.2 Granule–containing tablets

In Tables 9.3.1.2 A and B, the tablet diameter values for all formulations of the flat faced and concave Avicel[®]–containing granule formulated tablets are given.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	8.99	8.99	8.98	8.96
2	9.00	8.99	8.98	8.98
3	8.98	9.00	8.98	8.95
4	8.99	9.00	8.98	8.96
5	8.99	9.00	9.00	8.98
6	8.98	8.99	9.00	8.99
7	8.99	9.00	9.00	8.98
8	8.99	8.99	9.00	8.97
9	8.99	8.99	8.99	8.99
10	8.98	8.99	8.99	8.98
Ave	8.99	8.99	8.99	8.97
SD	0.006	0.005	0.009	0.013

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	8.99	8.99	9.00	9.00
2	9.01	9.03	9.01	9.00
3	9.00	9.01	9.00	9.04
4	9.00	8.99	9.04	9.01
5	9.01	9.03	9.00	9.00
6	9.04	8.99	9.02	9.02
7	9.01	8.99	9.01	9.00
8	9.00	9.00	9.00	9.00
9	9.00	8.99	8.99	9.00
10	8.99	8.98	9.00	9.04
Ave	9.01	9.00	9.01	9.01
SD	0.014	0.018	0.014	0.017

9.3.1.3 Bead-containing tablets

In Tables 9.3.1.3 A and B, the tablet diameter values for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets are given.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2
1	8.98	8.98
2	8.97	8.99
3	8.99	8.99
4	8.96	8.98
5	8.99	8.99
6	8.96	8.99
7	8.97	8.98
8	8.97	8.99
9	8.99	8.99
10	8.99	8.99
Ave	8.98	8.99
SD	0.013	0.005

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2
1	9.00	9.00
2	9.00	9.02
3	9.00	8.99
4	9.02	9.06
5	9.04	9.03
6	9.00	8.99
7	9.03	9.02
8	9.00	9.02
9	8.99	8.99
10	8.99	9.00
Ave	9.01	9.01
SD	0.017	0.023

9.3.2 MICROCELAC®-CONTAINING FORMULATIONS

9.3.2.1 Dry powder-containing tablets

In Tables 9.3.2.1 A and B, the tablet diameter values for all formulations of the flat faced and concave MicroceLac®-containing dry powder formulated tablets are given.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	8.99	8.99	8.97	8.99
2	8.98	8.99	8.99	8.99
3	8.99	8.99	8.99	8.99
4	8.98	9.00	8.97	9.00
5	8.99	8.99	8.99	8.99
6	8.98	9.00	8.99	8.97
7	8.98	8.99	8.99	8.99
8	8.99	8.99	8.99	9.00
9	8.98	8.99	8.98	8.99
10	8.99	8.99	8.99	8.99
Ave	8.99	8.99	8.99	8.99
SD	0.005	0.004	0.008	0.008

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	8.99	9.00	8.98	8.99
2	8.99	9.02	9.00	8.99
3	8.99	9.00	8.99	8.99
4	8.99	8.98	8.99	8.99
5	8.99	9.01	9.02	9.01
6	8.99	9.00	8.97	8.98
7	8.99	8.99	8.99	8.98
8	8.99	9.02	9.00	8.99
9	8.98	9.01	8.99	8.98
10	9.01	8.99	9.00	8.99
Ave	8.99	9.00	8.99	8.99
SD	0.007	0.013	0.013	0.009

9.3.2.2 Granule-containing tablets

In Tables 9.3.2.2 A and B, the tablet diameter values for all formulations of the flat faced and concave MicroceLac[®]-containing granule formulated tablets are given.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	8.98	8.99	8.97	8.98
2	8.98	9.00	8.97	8.98
3	8.98	8.99	8.98	8.98
4	9.01	9.00	8.98	8.97
5	8.98	8.99	8.98	8.97
6	8.98	9.00	9.00	7.97
7	8.98	8.99	9.00	8.98
8	8.98	8.99	8.98	8.96
9	8.99	8.99	8.98	8.96
10	8.98	8.99	8.96	8.98
Ave	8.98	8.99	8.98	8.87
SD	0.010	0.005	0.012	0.317

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	9.00	8.99	8.99	8.98
2	8.99	8.99	9.00	9.00
3	8.98	8.99	8.99	9.00
4	9.00	9.00	9.00	8.99
5	9.00	9.01	9.00	9.00
6	8.98	8.99	9.00	9.00
7	8.99	9.01	8.99	9.00
8	8.99	9.04	9.01	8.98
9	9.01	9.00	8.98	9.00
10	9.00	8.99	8.98	8.97
Ave	8.99	9.00	8.99	8.99
SD	0.010	0.016	0.010	0.011

9.3.2.3 Bead-containing tablets

In Tables 9.3.2.3 A and B, the tablet diameter values for all formulations of the flat faced and concave MicroceLac[®]-containing bead formulated tablets can be found.

Table A: The tablet diameters (mm) for the flat faced tablets

Tablet nr.	F1	F2
1	8.98	9.00
2	9.00	9.00
3	9.00	8.99
4	8.98	9.05
5	9.00	9.00
6	9.01	9.01
7	8.99	8.99
8	9.00	9.00
9	9.00	8.98
10	8.99	9.00
Ave	9.00	9.00
SD	0.010	0.019

Table B: The tablet diameters (mm) for the concave tablets

Tablet nr.	F1	F2
1	9.00	9.00
2	9.00	9.04
3	9.01	9.01
4	9.00	9.02
5	9.00	9.01
6	8.99	9.03
7	9.03	9.01
8	9.00	9.04
9	9.00	9.01
10	9.00	9.01
Ave	9.00	9.02
SD	0.011	0.014

9.4 TABLET DISINTEGRATION TIME

9.4.1 AVICEL[®]–CONTAINING FORMULATIONS

9.4.1.1 Dry powder–containing tablets

In Tables 9.4.1.1 A and B, the tablet disintegration times for all formulations of the flat faced and concave Avicel[®]–containing dry powder formulated tablets are given.

Table A: The disintegration times (sec)
for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	16	20	25	32
2	22	20	25	32
3	22	25	25	32
4	22	20	25	32
5	22	13	25	32
6	22	25	25	32
Ave	21.00	20.50	25.00	32.00
SD	2.449	4.416	0.000	0.000

Table B: The disintegration times (sec)
for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	22	39	34	34
2	22	39	34	30
3	22	39	34	30
4	22	39	34	30
5	22	34	34	34
6	22	34	34	34
Ave	22.00	37.33	34.00	32.00
SD	0.000	2.582	0.000	2.191

9.4.1.2 Granule–containing tablets

In Tables 9.4.1.2 A and B, the tablet disintegration times for all formulations of the flat faced and concave Avicel[®]–containing granule formulated tablets are given.

Table A: The disintegration times (sec)
for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	20	20	104	75
2	20	20	104	112
3	20	15	97	124
4	20	22	104	44
5	20	15	115	44
6	20	22	152	101
Ave	20.00	19.00	112.67	83.33
SD	0	3.225	20.116	34.500

Table B: The disintegration times (sec)
for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	13	11	15	18
2	13	11	15	19
3	13	14	17	11
4	13	14	17	11
5	13	14	19	19
6	13	14	19	19
Ave	13.00	13.00	17.00	16.17
SD	0	1.549	1.789	4.021

9.4.1.3 Bead-containing tablets

In Tables 9.4.1.3 A and B, the tablet disintegration times for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets are given.

Table A: The disintegration times (sec) for the flat faced tablets

Tablet nr.	F1	F2
1	28	18
2	13	18
3	13	10
4	28	10
5	28	18
6	28	10
Ave	23.00	14.00
SD	7.746	4.382

Table B: The disintegration times (sec) for the concave tablets

Tablet nr.	F1	F2
1	58	15
2	33	15
3	69	15
4	33	30
5	47	30
6	47	30
Ave	47.83	22.50
SD	14.091	8.216

9.4.2 MICROCELAC®-CONTAINING FORMULATIONS

9.4.2.1 Dry powder-containing tablets

In Tables 9.4.2.1 A and B, the tablet disintegration times for all formulations of the flat faced and concave Microcelac®-containing dry powder formulated tablets can be found.

Table A: The disintegration times (sec) for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	187	170	347	230
2	153	164	312	216
3	153	150	300	196
4	162	148	360	220
5	282	148	300	220
6	268	170	288	208
Ave	200.83	158.33	317.83	215.00
SD	58.949	10.838	28.944	11.713

Table B: The disintegration times (sec) for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	407	148	277	180
2	422	150	300	184
3	420	130	300	203
4	379	115	289	158
5	420	130	270	180
6	420	142	300	201
Ave	411.33	135.83	289.33	184.33
SD	16.753	13.333	13.171	16.476

9.4.2.2 Granule-containing tablets

In Tables 9.4.2.2 A and B, the tablet disintegration times for all formulations of the flat faced and concave MicroceLac®-containing granule formulated tablets are given.

Table A: The disintegration times (sec)
for the flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	480	600	660	382
2	469	417	820	698
3	173	505	588	457
4	285	436	660	556
5	500	448	656	462
6	285	382	760	651
Ave	365.33	464.67	690.67	534.33
SD	135.594	77.650	83.854	122.707

Table B: The disintegration times (sec)
for the concave tablets

Tablet nr.	F1	F2	F3	F4
1	540	353	720	613
2	540	300	780	469
3	393	410	570	613
4	454	470	753	442
5	540	470	700	633
6	360	345	510	632
Ave	471.17	391.33	672.17	567.00
SD	81.212	70.261	107.667	87.226

9.4.2.3 Bead-containing tablets

In Tables 9.4.2.3 A and B, the tablet disintegration times for all formulations of the flat faced and concave MicroceLac®-containing bead formulated tablets are given.

Table A: The disintegration times
(sec) for the flat faced tablets

Tablet nr.	F1	F2
1	660	602
2	600	476
3	535	438
4	662	434
5	758	688
6	457	632
Ave	612	545
SD	106.036	109.360

Table B: The disintegration times
(sec) for the concave tablets

Tablet nr.	F1	F2
1	851	597
2	798	556
3	892	543
4	885	474
5	660	528
6	746	496
Ave	805.33	532.33
SD	90.155	43.812

9.5 TABLET FRIABILITY (%)

9.5.1 AVICEL®-CONTAINING FORMULATIONS

9.5.1.1 Dry powder-containing tablets

In Tables 9.5.1.1 A and B, the % friability for all formulations of the flat faced and concave Avicel®-containing dry powder formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.47	2.509	2.515	2.495
2 (10 tablets)	2.47	2.507	2.513	2.494
% Friability	0.00	0.08	0.08	0.04
SD	0.000	0.001	0.001	0.001

Table B: The % friability of the concave tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.492	2.507	2.500	2.504
2 (10 tablets)	2.492	2.506	2.500	2.504
% Friability	0.00	0.04	0.00	0.00
SD	0.000	0.001	0.000	0.000

9.5.1.2 Granule-containing tablets

In Tables 9.5.1.2 A and B, the % friability for all formulations of the flat faced and concave Avicel®-containing granule formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.561	2.561	2.524	2.53
2 (10 tablets)	2.56	2.56	2.522	2.53
% Friability	0.04	0.04	0.08	0.00
SD	0.001	0.001	0.001	0.000

Table B: The % friability of the concave tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.563	2.512	2.52	2.527
2 (10 tablets)	2.561	2.506	2.519	2.517
% Friability	0.08	0.24	0.04	0.40
SD	0.001	0.004	0.001	0.007

9.5.1.3 Bead-containing tablets

In Tables 9.5.1.3 A and B, the % friability for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2
1 (10 tablets)	2.547	2.565
2 (10 tablets)	2.545	2.564
% Friability	0.08	0.04
SD	0.001	0.001

Table B: The % friability of the concave tablets

Mass nr.	F1	F2
1 (10 tablets)	2.566	2.551
2 (10 tablets)	2.566	2.551
% Friability	0.00	0.00
SD	0.000	0.000

9.5.2 MICROCELAC[®]–CONTAINING FORMULATIONS

9.5.2.1 Dry powder–containing tablets

In Tables 9.5.2.1 A and B, the % friability for all formulations of the flat faced and concave MicroceLac[®]–containing dry powder formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.405	2.506	2.520	2.546
2 (10 tablets)	2.404	2.504	2.520	2.546
% Friability	0.04	0.08	0.00	0.00
SD	0.001	0.001	0.000	0.000

Table B: The % friability of the concave tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.509	2.515	2.492	2.506
2 (10 tablets)	2.506	2.511	2.49	2.502
% Friability	0.12	0.16	0.08	0.16
SD	0.002	0.003	0.001	0.003

9.5.2.2 Granule–containing tablets

In Tables 9.5.2.2 A and B, the % friability for all formulations of the flat faced and concave MicroceLac[®]–containing granule formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.498	2.432	2.567	2.496
2 (10 tablets)	2.496	2.428	2.567	2.496
% Friability	0.08	0.16	0.00	0.00
SD	0.001	0.003	0.000	0.000

Table B: The % friability of the concave tablets

Mass nr.	F1	F2	F3	F4
1 (10 tablets)	2.498	2.497	2.57	2.535
2 (10 tablets)	2.496	2.492	2.567	2.535
% Friability	0.08	0.20	0.12	0.00
SD	0.001	0.004	0.002	0.000

9.5.2.3 Bead–containing tablets

In Tables 9.5.2.3 A and B, the % friability for all formulations of the flat faced and concave MicroceLac[®]–containing bead formulated tablets are given.

Table A: The % friability of the flat faced tablets

Mass nr.	F1	F2
1 (10 tablets)	2.564	2.565
2 (10 tablets)	2.562	2.565
% Friability	0.08	0.00
SD	0.001	0.000

Table B: The % friability of the concave tablets

Mass nr.	F1	F2
1 (10 tablets)	2.572	2.553
2 (10 tablets)	2.572	2.552
% Friability	0.00	0.04
SD	0.000	0.001

9.6 TABLET MASS VARIATION

9.6.1 AVICEL[®]-CONTAINING FORMULATIONS

9.6.1.1 *Dry powder-containing tablets*

In Tables 9.6.1.1 A and B, the tablet mass values for all formulations of the flat faced and concave Avicel[®]-containing dry powder formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	0.247	0.250	0.252	0.251
2	0.247	0.250	0.252	0.248
3	0.248	0.250	0.251	0.251
4	0.248	0.249	0.252	0.249
5	0.248	0.249	0.251	0.254
6	0.248	0.251	0.252	0.247
7	0.250	0.251	0.252	0.252
8	0.248	0.250	0.251	0.252
9	0.249	0.250	0.252	0.249
10	0.247	0.250	0.254	0.250
11	0.246	0.252	0.253	0.249
12	0.246	0.250	0.249	0.250
13	0.247	0.252	0.252	0.250
14	0.246	0.250	0.251	0.250
15	0.249	0.252	0.252	0.249
16	0.248	0.252	0.251	0.250
17	0.246	0.249	0.251	0.249
18	0.247	0.250	0.253	0.248
19	0.247	0.251	0.252	0.252
20	0.248	0.251	0.251	0.248
Ave mass	0.248	0.250	0.252	0.250
SD	0.001	0.001	0.001	0.002
%RSD	0.445	0.399	0.410	0.686

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2	F3	F4
1	0.249	0.252	0.250	0.250
2	0.251	0.251	0.250	0.251
3	0.248	0.250	0.249	0.251
4	0.252	0.254	0.250	0.251
5	0.249	0.253	0.250	0.252
6	0.252	0.250	0.249	0.252
7	0.249	0.250	0.251	0.251
8	0.250	0.252	0.250	0.250
9	0.250	0.251	0.251	0.251
10	0.251	0.253	0.251	0.251
11	0.251	0.251	0.249	0.251
12	0.251	0.251	0.249	0.252
13	0.248	0.250	0.249	0.249
14	0.249	0.252	0.251	0.249
15	0.248	0.251	0.251	0.252
16	0.249	0.252	0.251	0.250
17	0.250	0.250	0.250	0.250
18	0.248	0.250	0.250	0.249
19	0.250	0.249	0.250	0.251
20	0.248	0.251	0.250	0.251
Ave	0.250	0.251	0.250	0.251
SD	0.001	0.001	0.001	0.001
%RSD	0.540	0.505	0.304	0.390

9.6.1.2 Granule-containing tablets

In Tables 9.6.1.2 A and B, the tablet mass values for all formulations of the flat faced and concave Avicel®-containing granule formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	0.254	0.254	0.242	0.259
2	0.256	0.256	0.262	0.253
3	0.254	0.255	0.256	0.258
4	0.255	0.259	0.261	0.256
5	0.254	0.252	0.257	0.258
6	0.256	0.252	0.260	0.253
7	0.258	0.251	0.253	0.254
8	0.256	0.258	0.260	0.249
9	0.255	0.255	0.253	0.249
10	0.251	0.256	0.243	0.260
11	0.256	0.256	0.260	0.255
12	0.259	0.256	0.261	0.255
13	0.256	0.257	0.245	0.257
14	0.257	0.252	0.251	0.255
15	0.258	0.259	0.251	0.250
16	0.254	0.254	0.257	0.257
17	0.258	0.258	0.254	0.254
18	0.258	0.255	0.245	0.253
19	0.252	0.255	0.256	0.249
20	0.250	0.259	0.244	0.245
Ave mass	0.255	0.255	0.254	0.254
SD	0.002	0.002	0.007	0.004
%RSD	0.953	0.963	2.621	1.546

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2	F3	F4
1	0.250	0.255	0.251	0.257
2	0.256	0.255	0.256	0.257
3	0.256	0.247	0.249	0.255
4	0.256	0.255	0.253	0.249
5	0.264	0.256	0.246	0.248
6	0.257	0.243	0.247	0.259
7	0.258	0.255	0.253	0.249
8	0.255	0.256	0.251	0.246
9	0.251	0.254	0.251	0.258
10	0.258	0.248	0.256	0.249
11	0.254	0.247	0.247	0.254
12	0.255	0.254	0.251	0.259
13	0.253	0.241	0.260	0.248
14	0.251	0.260	0.254	0.258
15	0.258	0.257	0.253	0.248
16	0.253	0.256	0.252	0.248
17	0.255	0.256	0.252	0.250
18	0.252	0.255	0.251	0.251
19	0.252	0.257	0.247	0.248
20	0.252	0.255	0.257	0.257
Ave mass	0.255	0.253	0.252	0.252
SD	0.003	0.005	0.004	0.005
%RSD	1.296	1.994	1.448	1.824

9.6.1.3 Bead-containing tablets

In Tables 9.6.1.3 A and B, the tablet mass values for all formulations of the flat faced and concave Avicel®-containing bead formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2
1	0.257	0.258
2	0.257	0.258
3	0.254	0.258
4	0.26	0.256
5	0.254	0.261
6	0.252	0.257
7	0.254	0.257
8	0.255	0.257
9	0.26	0.259
10	0.258	0.26
11	0.258	0.261
12	0.246	0.26
13	0.252	0.254
14	0.259	0.258
15	0.261	0.25
16	0.255	0.251
17	0.25	0.254
18	0.253	0.26
19	0.259	0.256
20	0.254	0.261
Ave mass	0.255	0.257
SD	0.004	0.003
%RSD	1.484	1.217

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2
1	0.252	0.253
2	0.256	0.254
3	0.257	0.255
4	0.258	0.256
5	0.257	0.255
6	0.252	0.253
7	0.254	0.259
8	0.256	0.261
9	0.256	0.261
10	0.258	0.257
11	0.252	0.251
12	0.254	0.253
13	0.256	0.258
14	0.258	0.257
15	0.256	0.261
16	0.253	0.254
17	0.254	0.255
18	0.256	0.258
19	0.259	0.26
20	0.253	0.259
Ave mass	0.255	0.257
SD	0.002	0.003
%RSD	0.864	1.190

9.6.2 MICROCELAC®-CONTAINING FORMULATIONS

9.6.2.1 Dry powder-containing tablets

In Tables 9.6.2.1 A and B, the tablet mass values for all formulations of the flat faced and concave MicroceLac®-containing dry powder formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	0.248	0.251	0.252	0.254
2	0.247	0.250	0.250	0.256
3	0.249	0.251	0.250	0.253
4	0.249	0.251	0.255	0.255
5	0.246	0.250	0.253	0.255
6	0.250	0.251	0.252	0.254
7	0.244	0.250	0.252	0.254
8	0.249	0.251	0.258	0.254
9	0.250	0.249	0.257	0.254
10	0.248	0.249	0.252	0.254
11	0.246	0.252	0.252	0.255
12	0.245	0.250	0.252	0.255
13	0.245	0.249	0.252	0.256
14	0.249	0.250	0.256	0.254
15	0.248	0.253	0.252	0.253
16	0.249	0.252	0.254	0.253
17	0.245	0.250	0.252	0.253
18	0.248	0.250	0.250	0.253
19	0.244	0.252	0.251	0.254
20	0.250	0.251	0.252	0.255
Ave mass	0.247	0.251	0.253	0.254
SD	0.002	0.001	0.002	0.001
%RSD	0.824	0.437	0.881	0.374

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2	F3	F4
1	0.249	0.252	0.248	0.251
2	0.251	0.250	0.252	0.250
3	0.250	0.251	0.249	0.250
4	0.250	0.250	0.251	0.251
5	0.250	0.251	0.251	0.251
6	0.250	0.252	0.250	0.249
7	0.252	0.252	0.249	0.251
8	0.252	0.254	0.249	0.251
9	0.250	0.249	0.249	0.249
10	0.251	0.249	0.251	0.251
11	0.249	0.251	0.249	0.254
12	0.251	0.252	0.250	0.253
13	0.253	0.252	0.250	0.252
14	0.249	0.250	0.247	0.252
15	0.252	0.251	0.250	0.250
16	0.250	0.250	0.249	0.250
17	0.251	0.251	0.249	0.249
18	0.250	0.251	0.248	0.251
19	0.256	0.252	0.249	0.250
20	0.251	0.252	0.252	0.251
Ave mass	0.251	0.251	0.250	0.251
SD	0.002	0.001	0.001	0.001
%RSD	0.650	0.482	0.526	0.511

9.6.2.2 Granule-containing tablets

In Tables 9.6.2.2 A and B, the tablet mass values for all formulations of the flat faced and concave MicroceLac[®]-containing granule formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2	F3	F4
1	0.236	0.247	0.254	0.249
2	0.256	0.242	0.253	0.245
3	0.242	0.246	0.258	0.254
4	0.240	0.244	0.259	0.250
5	0.248	0.258	0.255	0.242
6	0.244	0.255	0.253	0.249
7	0.238	0.256	0.246	0.243
8	0.237	0.245	0.256	0.258
9	0.252	0.246	0.255	0.251
10	0.255	0.241	0.258	0.242
11	0.242	0.242	0.246	0.255
12	0.248	0.244	0.256	0.257
13	0.252	0.261	0.254	0.254
14	0.255	0.252	0.259	0.251
15	0.249	0.244	0.259	0.240
16	0.256	0.254	0.259	0.243
17	0.250	0.269	0.252	0.244
18	0.246	0.248	0.260	0.245
19	0.254	0.246	0.252	0.250
20	0.260	0.250	0.254	0.243
Ave mass	0.248	0.250	0.255	0.248
SD	0.007	0.007	0.004	0.005
%RSD	2.872	2.944	1.558	2.214

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2	F3	F4
1	0.240	0.251	0.260	0.250
2	0.250	0.255	0.263	0.264
3	0.253	0.244	0.251	0.250
4	0.253	0.258	0.253	0.260
5	0.248	0.257	0.254	0.255
6	0.258	0.240	0.253	0.253
7	0.250	0.248	0.261	0.254
8	0.253	0.248	0.255	0.254
9	0.260	0.255	0.254	0.260
10	0.260	0.255	0.258	0.256
11	0.250	0.253	0.265	0.256
12	0.258	0.251	0.252	0.261
13	0.258	0.247	0.260	0.252
14	0.251	0.254	0.256	0.253
15	0.254	0.248	0.253	0.259
16	0.256	0.248	0.251	0.259
17	0.254	0.254	0.256	0.259
18	0.255	0.251	0.256	0.259
19	0.258	0.234	0.260	0.257
20	0.254	0.251	0.254	0.250
Ave mass	0.254	0.250	0.256	0.256
SD	0.005	0.006	0.004	0.004
%RSD	1.877	2.338	1.581	1.575

9.6.2.3 Bead-containing tablets

In Tables 9.6.2.3 A and B, the tablet mass values for all formulations of the flat faced and concave MicroceLac®-containing bead formulated tablets are given.

Table A: The mass values (g) for flat faced tablets

Tablet nr.	F1	F2
1	0.250	0.253
2	0.249	0.256
3	0.252	0.257
4	0.259	0.258
5	0.258	0.251
6	0.260	0.254
7	0.252	0.251
8	0.255	0.260
9	0.261	0.253
10	0.248	0.253
11	0.250	0.261
12	0.259	0.257
13	0.251	0.258
14	0.261	0.253
15	0.251	0.253
16	0.257	0.257
17	0.261	0.252
18	0.252	0.256
19	0.259	0.257
20	0.257	0.257
Ave mass	0.255	0.255
SD	0.005	0.003
%RSD	1.780	1.138

Table B: The mass values (g) for concave tablets

Tablet nr.	F1	F2
1	0.258	0.257
2	0.250	0.251
3	0.248	0.257
4	0.260	0.255
5	0.252	0.256
6	0.256	0.253
7	0.262	0.255
8	0.253	0.255
9	0.255	0.255
10	0.258	0.257
11	0.256	0.254
12	0.260	0.255
13	0.250	0.251
14	0.250	0.254
15	0.261	0.255
16	0.255	0.250
17	0.248	0.257
18	0.254	0.253
19	0.262	0.249
20	0.256	0.253
Ave mass	0.255	0.254
SD	0.005	0.002
%RSD	1.778	0.937

10 ANNEXURE D: DISSOLUTION DATA

10.1 DISSOLUTION DATA

10.1.1 AVICEL[®]-CONTAINING FORMULATIONS

10.1.1.1 Dry powder-containing tablets

In Tables 10.1.1.1 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave Avicel[®]-containing dry powder formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	81.55	72.13	66.75	80.52
5	92.85	93.56	92.09	88.86
10	92.68	96.02	95.05	90.66
15	91.10	93.79	92.87	88.60
30	93.02	94.85	93.52	89.25
60	92.34	94.65	91.95	91.10
90	93.41	94.58	93.85	89.33
120	93.10	95.49	93.19	90.74
180	98.22	100.86	98.86	97.86
240	97.12	95.20	96.72	94.40

Ave MDT	6.85	0	5.88	5.79
Ave IDR	4.21	4.72	4.81	4.09

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	65.53	63.90	71.56	63.68
5	85.76	82.21	90.65	90.46
10	88.85	89.83	91.70	91.61
15	91.13	92.15	89.51	91.88
30	90.63	88.37	90.98	91.21
60	92.16	91.81	92.08	91.58
90	93.80	92.73	91.69	91.03
120	94.23	94.15	90.88	91.33
180	97.51	94.30	97.74	97.35
240	97.37	98.33	97.31	96.10

Ave MDT	9.07	13.76	10.35	8.29
Ave IDR	4.66	4.82	4.41	4.78

10.1.1.2 Granule-containing tablets

In Tables 10.1.1.2 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave Avicel[®]-granule formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	64.44	81.15	14.59	18.61
5	83.08	89.51	69.19	49.94
10	86.24	91.63	86.37	79.73
15	86.86	92.36	85.88	89.80
30	87.24	92.57	88.24	92.00
60	87.27	91.65	89.03	93.64
90	89.54	93.69	86.89	89.77
120	89.47	93.97	91.18	91.99
180	95.05	95.90	99.62	96.61
240	98.26	93.71	98.61	97.33

Ave MDT	18.7	1.03	17.79	14.31
Ave IDR	4.41	4.3	5.95	6.08

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	71.65	76.60	87.01	59.55
5	92.81	93.18	92.79	86.22
10	93.68	93.43	92.19	88.84
15	92.72	93.02	92.80	89.77
30	92.73	92.09	92.24	91.54
60	92.16	93.14	91.71	91.62
90	93.27	94.26	93.50	92.80
120	91.91	94.74	94.20	92.77
180	100.58	98.12	92.45	94.34
240	100.34	101.92	96.14	101.57

Ave MDT	12.91	15.34	7.85	20.26
Ave IDR	4.62	4.48	4.14	4.75

10.1.1.3 Bead-containing tablets

In Tables 10.1.1.3 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave Avicel[®]-bead formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2
0	0.00	0.00
2	66.53	79.86
5	90.39	90.28
10	90.63	90.98
15	90.69	91.65
30	89.78	86.82
60	91.71	89.51
90	91.30	92.18
120	91.67	90.45
180	100.43	95.27
240	97.89	98.25

Ave MDT	10.13	15.35
Ave IDR	4.6	4.28

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2
0	0.00	0.00
2	71.01	70.42
5	88.32	88.45
10	87.93	89.67
15	85.33	88.77
30	87.72	89.99
60	88.61	89.90
90	88.84	90.73
120	88.45	90.51
180	98.39	97.54
240	96.91	99.85

Ave MDT	13.79	17.27
Ave IDR	4.12	4.37

10.1.2 MICROCELAC[®]-CONTAINING FORMULATIONS

10.1.2.1 Dry powder – containing tablets

In Tables 10.1.2.1 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave MicroceLac[®]-dry powder formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	12.01	14.34	8.17	9.47
5	28.51	41.70	20.15	27.49
10	50.74	83.07	32.06	44.98
15	66.00	93.40	43.10	57.02
30	90.07	94.34	56.96	90.27
60	86.13	96.46	90.33	94.90
90	89.05	96.58	91.27	94.38
120	89.57	97.53	90.41	93.09
180	98.63	97.75	97.97	97.13
240	100.84	95.12	98.43	97.92

Ave MDT	23.07	3.65	31.76	17.53
Ave IDR	4.41	6.57	2.83	3.83

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	11.27	17.08	10.44	14.33
5	19.36	45.23	22.74	29.01
10	30.13	85.63	32.41	40.83
15	42.25	90.04	40.66	49.74
30	73.31	90.44	60.12	87.71
60	90.66	90.53	92.02	93.35
90	92.89	92.92	91.89	92.26
120	93.51	92.87	94.64	93.77
180	99.58	98.54	94.75	92.84
240	97.26	100.05	97.45	97.45

Ave MDT	25.16	17.95	22.35	14.96
Ave IDR	2.65	6.33	2.6	3.16

10.1.2.2 Granule-containing tablets

In Tables 10.1.2.2 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave MicroceLac® – granule formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	10.42	7.63	7.58	5.23
5	20.37	19.89	13.57	12.72
10	47.48	29.25	23.80	21.77
15	61.06	39.96	30.52	31.28
30	87.42	67.90	58.03	55.65
60	102.10	95.73	85.21	86.16
90	92.88	96.09	92.82	89.54
120	94.35	95.73	93.49	94.72
180	97.05	96.46	95.91	97.44
240	94.66	100.08	95.94	101.42

Ave MDT	3.66	26.33	23.15	38.03
Ave IDR	4.17	2.6	1.98	2.05

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
2	8.31	10.28	8.75	5.58
5	20.45	19.71	12.93	12.90
10	31.30	40.26	21.37	22.02
15	50.27	51.44	29.32	28.31
30	74.53	82.46	58.46	48.46
60	92.33	91.79	82.46	82.43
90	95.63	93.38	89.72	90.92
120	98.49	91.77	93.36	93.99
180	98.74	95.61	97.51	98.40
240	101.07	98.23	102.32	99.12

Ave MDT	20.67	18.91	36.77	37.84
Ave IDR	3.22	3.45	1.83	1.88

10.1.2.3 Bead-containing tablets

In Tables 10.1.2.3 A and B, the % dissolution values recorded at different withdrawal times for all formulations of the flat faced and concave MicroceLac® – bead formulated tablets are given, together with the mean dissolution time (MDT) and initial dissolution rate (I_{dr}) values for the specific formulations.

Table A: The % dissolution, MDT and I_{dr} values for the flat faced tablets

Withdrawal times (min)	F1	F2
0	0.00	0.00
2	11.48	8.46
5	16.71	16.40
10	31.92	27.87
15	57.50	56.72
30	89.46	92.39
60	92.00	93.89
90	92.60	92.22
120	95.57	94.07
180	95.59	94.32
240	96.23	100.53

Ave MDT	18.63	27.09
Ave IDR	3.59	3.54

Table B: The % dissolution, MDT and I_{dr} values for the concave tablets

Withdrawal times (min)	F1	F2
0	0.00	0.00
2	5.80	8.29
5	16.92	16.45
10	23.16	38.19
15	36.32	65.67
30	82.48	88.94
60	89.59	88.63
90	92.28	92.00
120	91.31	90.55
180	96.97	97.27
240	98.56	100.99

Ave MDT	29.15	28.93
Ave IDR	2.32	4.31

10.1.3 CONCLUSIVE TABLE

In Table 10.1.3, the average MDT and I_{dr} data is given for all formulation as well as the average disintegration times and crushing strength values.

Table 10.1.3: Table depicting the average MDT and I_{dr} values for all tablet formulations formulated in this study, as well as the average disintegration time and crushing strength values.

	MDT (min)	± SD	I_{dr} (%.min ⁻¹)	SD	Disinte- gration time (s)	± SD	Crushing strength (N)	± SD
ADP FF1	7.93	9.404	4.21	0.540	21.00	2.449	94.20	1.989
ADP FF2	2.37	4.113	4.72	0.139	20.50	4.416	95.50	1.434
ADP FF3	5.88	1.488	4.81	0.217	25.00	0.000	89.70	2.406
ADP FF4	5.79	5.920	4.09	0.180	32.00	0.000	95.50	1.958
ADP CF1	5.79	10.749	4.66	0.247	22.00	0.000	87.00	1.886
ADP CF2	13.76	16.143	4.82	0.569	37.33	2.582	107.60	3.806
ADP CF3	12.09	10.560	4.41	0.183	34.00	0.000	96.70	2.312
ADP CF4	8.86	7.787	4.78	0.431	32.00	2.191	95.90	2.961
AG FF1	18.70	6.427	4.41	0.090	20.00	0.000	78.50	4.994
AG FF2	3.09	4.229	4.30	0.090	19.00	3.225	74.00	8.042
AG FF3	17.79	10.878	5.95	0.168	112.67	20.116	104.10	13.747
AG FF4	14.31	7.410	6.08	0.622	83.33	34.500	99.60	14.269
AG CF1	12.91	9.315	4.62	0.253	13.00	34.500	70.80	11.233
AG CF2	15.34	14.121	4.48	0.176	13.00	1.549	64.40	5.190
AG CF3	8.91	15.429	4.14	0.250	17.00	1.789	70.50	5.191
AG CF4	20.26	10.677	4.75	0.681	16.17	4.021	58.20	6.779
AB FF1	10.13	8.763	4.60	0.262	23.00	7.746	100.80	7.843
AB FF2	17.27	12.803	4.28	0.296	14.00	4.382	95.00	10.044
AB CF1	13.79	6.822	4.12	0.055	47.83	14.091	107.40	8.909
AB CF2	17.27	12.803	4.37	0.294	22.50	8.216	88.80	5.750
MDP FF1	23.07	6.248	4.41	1.152	200.83	58.949	102.30	6.111
MDP FF2	3.65	3.769	6.57	0.226	158.33	10.838	106.70	2.452
MDP FF3	31.76	2.925	2.83	0.432	317.83	28.944	112.40	6.786
MDP FF4	17.53	3.136	3.83	0.190	215.00	11.713	106.20	4.077
MDP CF1	25.16	7.096	2.65	0.312	411.33	16.753	130.50	2.991
MDP CF2	17.95	0.645	6.33	0.328	135.83	13.333	98.70	7.573
MDP CF3	22.35	7.669	2.60	0.268	289.33	13.171	104.50	2.014
MDP CF4	14.96	8.747	3.16	0.367	184.33	16.476	108.00	3.333
MG FF1	5.34	5.490	4.17	1.730	365.33	135.594	139.20	21.760
MG FF2	26.33	3.165	2.60	0.195	464.67	77.650	142.10	20.594
MG FF3	23.15	8.344	1.98	0.180	690.67	83.854	132.20	36.817
MG FF4	38.03	8.143	2.05	0.679	534.33	122.707	109.50	7.649
MG CF1	20.67	6.525	3.22	0.860	471.17	81.212	117.30	9.945
MG CF2	18.91	6.508	3.45	0.764	391.33	70.261	86.30	16.391
MG CF3	36.77	8.005	1.83	0.408	672.17	107.667	121.70	13.425
MG CF4	37.84	2.992	1.88	0.180	567.00	87.226	121.80	13.011
MB FF1	18.63	14.349	3.59	0.966	612.00	106.036	93.70	14.103
MB FF2	27.09	21.908	3.54	0.854	545.00	109.360	97.30	8.970
MB CF1	29.15	11.243	2.32	0.545	805.33	90.155	104.40	10.658
MB CF2	28.93	8.623	4.31	1.982	532.33	43.812	99.10	9.374