Evaluation of tricalcium citrate as a direct compressible diluent using the SeDeM Expert Diagram System

JC Kruger

orcid.org/0000-0002-5224-5347

Dissertation accepted in fulfilment of the requirements for the degree Master of Science in Pharmaceutics at the North-West University

Supervisor:	Prof J Steenekamp
Co-Supervisor:	Prof S Hamman
Co-Supervisor:	Dr H Hamman

Graduation:	June 2023
Student number:	26988852

ACKNOWLEDGEMENTS

For the ability to be able to study and do a Master's degree in Pharmaceutics, as well as giving me the strength and determination to continue even through tough times, I would like to thank the Lord our saviour.

Furthermore, I would like to thank Theuns Kruger, my father, and Elna Kruger, my mother for the continued support both emotionally and financially through all my studies. Without you all this would not have been possible. I would also thank the rest of my family for all the support that they provided through the years.

Prof. Jan Steenekamp, thank you for being an excellent supervisor. Thank you for always making time and effort to help me to the best of your ability. Without you I would have had no idea of how to tackle the enormous task of a postgraduate study. I could not have asked for a better supervisor.

Prof. Sias Hamman, thank you for all the advice and help with the unconventional situations that arose during my study. I really appreciate all the help and support. I would also like to thank Dr. Hannlie Hamman for the excellent tools that you made available as well as your time and effort to proofread all my work. Thank you both for being my co-supervisors.

To Neil Barnard, thank you for all the technical help in the labs, it was greatly appreciated.

To all my friends and colleagues, thank you for all the support provided, I really appreciate it.

To the North-West University (NWU) (Potchefstroom Campus), thank you for providing me with the opportunity to study at the university as well as providing the funding and materials used to complete my Master's degree.

ABSTRACT

Oral administration of medicine is one of the most common delivery routes still in use today. Various dosage forms are administered via the oral route including tablets, capsules, syrups, solutions and emulsions. Tablets constitute a large part of orally available dosage forms due to ease of administration amongst other advantages. Tablets comprise a large part of the oral dosage form market due to a less complicated manufacturing method when compared to other dosage forms such as parenteral dosage forms. There are several tablet manufacturing methods of which direct compression is one of the most common methods. Direct compression also has an advantage over methods such as dry- and wet granulation for ingredients that are thermolabile and moisture sensitive can be included in the formulation.

To manufacture tablets, excipients are usually included in tablet formulations. An important excipient is the filler, which constitutes the bulk of the volume of the tablet. Besides the excipients, it is essential that tablet formulations contain an active pharmaceutical ingredient (API), which provides the pharmacological effect associated with the specific medicine. Traditionally tricalcium citrate (TCC) was used as a calcium supplement and was recently investigated and used as a filler in tablet formulations, especially during direct compression.

The SeDeM Expert Diagram System (SeDeM EDS) is a scientific approach that strives to characterise substances or mixtures based on their respective individual or collective suitability for direct compression. This characterisation is accomplished by evaluating twelve parameters based on powder flow and compression characteristics. Data obtained from a SeDeM EDS analysis, can be used during tablet pre-formulation to determine the theoretical amount of an excipient to add to the formulation to achieve optimal powder flow and compression properties. This excipient added to correct the powder properties is called the corrective excipient.

Fillers also have a property called the dilution potential. Dilution potential refers to the extent of a diluent's ability to contain an API, while still being able to produce quality tablets. This property is specific to a specific filler-API combination.

The aim of this study was to characterise TCC according to the SeDeM EDS as well as compare TCC to other commonly used fillers, including Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, and Tablettose® according to their SeDeM EDS profiles. A ranking order was established using these results. The theoretical dilution potential for the abovementioned fillers was also determined for different APIs (furosemide, paracetamol and pyridoxine) using the SeDeM EDS. Afterwards, the true or real dilution

potential was also determined experimentally and compared to the theoretical dilution potential.

The results obtained indicated that TCC is suitable to be used during tablet manufacturing using the direct compression manufacturing method. While other fillers other also obtained SeDeM EDS values indicating suitability for direct compression, TCC and MicroceLac® were the only fillers to pass all the SeDeM EDS requirements to be a filler suitable for direct compression. TCC was also able to form acceptable tablets containing furosemide, paracetamol, and pyridoxine as APIs.

Keywords:

Tricalcium citrate (TCC), SeDeM Expert Diagram System (SeDeM EDS), Direct compression diluents, Dilution potential, Tablet manufacturing, Tablet quality tests

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

%H	Hygroscopicity
%HR	Loss on drying
%PF	Percentage of particles smaller than 50 µm
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
D_a	Bulk density
D_c	Tapped density
IC	Carr's index
Icd	Cohesion index
Ie	Inter-particle porosity
IGC	Index of good compressibility
IH	Hausner ratio
IP	Index parameter
IPP	Index of profile parameter
Iθ	Homogeneity index
SeDeM EDS	SeDeM Expert Diagram System
t"	Powder flow time

TCC	Tricalcium citrate
USP	United States Pharmacopoeia
α	Angle of repose

CHAPTER 1:
INTRODUCTION, PROBLEM STATEMENT, AIM AND OBJECTIVES

1.1 Introduction

During the 19th century, the most common dosage forms were pills, powders, tinctures and spirits. Before this period, linctuses, lochochs, electuaries, and confections were still commonly used (Helfand & Cowen, 1983:3). Today, the oral drug administration route is the most frequently used route for administration of medicines. This route of drug administration includes both solid and liquid formulations. Solid oral pharmaceutical formulations exist as different dosage forms such as tablets, capsules, chewing gums, and powders. Tablets are the most commonly used dosage form for medicine administration (Hagelstein *et al.*, 2018:1631).

The majority of drug formulations that are delivered via the oral route are swallowed and move through the oesophagus into the gastrointestinal tract. The active pharmaceutical ingredients (APIs) in these formulations must dissolve in the gastrointestinal fluids in order to be absorbed from the gastrointestinal tract across the epithelium into the blood circulation (Bhutani *et al.*, 2021:1).

1.2 Direct Compression

During tablet manufacturing, there are mainly two methods used, namely granulation (including wet and dry granulation) and direct compression (Alderborn & Frenning, 2018:524). Direct compression could be seen as the simpler of the two above mentioned methods, for it only involves the mixing of powders and then compressing this powder mixture into tablets (Alderborn & Frenning, 2018:525). Some advantages of direct compression over the granulation method of tablet manufacturing include reduced costs, depending on the excipients used, as well as improved chemical stability of certain APIs, since this method does not require water or heat to be applied to the powders (Alderborn & Frenning, 2018:525).

For the direct compression of powder mixtures into tablets to succeed, the powder mixtures should possess certain characteristics. Such characteristics include good compression characteristics as well as adequate powder flow characteristics (Alderborn & Frenning, 2018:525; Hagelstein *et al.*, 2018:1631). These powder properties are important as the resulting tablet's strength is dependent on these characteristics (Jivraj *et al.*, 2000:58). If the

compressibility of the powder mixture is insufficient, the resulting tablets will deform, break or not be formed at all during the compaction process (Jivraj, *et al.,* 2000: 58). The powder characteristics that are needed to produce acceptable tablets during direct compression can be evaluated using the SeDeM Expert Diagram System (SeDeM EDS) (Perez *et al.*, 2006:351), which will be described in more detail below.

1.3 SeDeM Expert Diagram System

The SeDeM Expert Diagram System (SeDeM EDS) is a method applied to powders (APIs, excipients, and powder mixtures), to evaluate the specific excipient or mixture's potential for direct compression (Suñé-Negre *et al.*, 2011:464). This system can also be used to validate the tablet production process as the powder characteristics should consistently comply to minimum standards (Pérez, *et al.*, 2006:351).

During a SeDeM EDS analysis, twelve parameters related to powder flow properties are evaluated. These include bulk density (D_a), tapped density (D_c), inter-particle porosity (Ie), Carr's index (IC), Hausner index (IH), angle of repose (α), powder flow (t"), loss on drying (%HR), hygroscopicity (%H), particle size (%Pf) and homogeneity index (Iθ) (Suñé-Negre *et al.*, 2011). The results obtained for these parameters can be converted to radial values (between 1 and 10) and visually expressed as a polygon (Fig. 1). The twelve parameters are then further grouped into five categories or otherwise known as incidence factors namely dimension incidence, compressibility incidence, flowability incidence, lubricity/stability incidence and lubricity/dosage incidence (Dai, *et al.,* 2019:518-519). Data obtained from the SeDeM EDS method can then be used to calculate three additional indices. These indices are the index parameter (IP), index of profile parameter (IPP) and the index of good compressibility (IGC). These three indices provide data to manufacturers or researchers about a powder's potential for compression (Dai, *et al.,* 2019:521).

During the pre-formulation phase, each ingredient, including the API should be analysed in terms of the SeDeM EDS parameters. The characteristics of each excipient should be complimentary to ensure a compressible powder mixture. At this stage, the theoretical compressibility of the powder mixture could be calculated and optimised and the powder mixture's potential for direct compression determined (Suñé-Negre *et al.*, 2011:464). If the powder's potential for compression is deemed unsuitable, the data obtained from the SeDeM EDS method could be used to identify an excipient with the correct properties to be added to the formulation. The SeDeM EDS method can also be used to determine the theoretical minimum amount of that particular corrective excipient to be added to the formulation to obtain the best result (Dai *et al.*, 2019:523).

1.4 Direct compressible excipients

Tablets consist of one or more API(s) and several other substances called excipients. The type of excipients varies greatly between tablet formulations and there is no fixed recipe for selecting excipients to use. It should, however, be stated that certain excipients provide greater benefits when paired with specific APIs, manufacturing methods and dosage forms (Jivraj, *et al.*, 2000:58). One important excipient in tablet formulation is a filler, also known as a diluent. The inclusion of a filler is considered to be essential and mandatory for the manufacturing of direct compressible tablet formulations (Jivraj, *et al.* 2000: 59). Microcrystalline cellulose and tricalcium citrate (TCC) are examples of filler materials that can be used in the formulation of direct compressible tablets.

1.4.1 Tricalcium citrate (TCC)

TCC is an excipient that was recently proposed for use as a filler material/diluent during tablet formulation but was previously used as a source of calcium and a food additive. Two types of TCC exist, namely tricalcium citrate tetrahydrate (TCCth) and tricalcium citrate anhydrate (TCCah). Both types of TCC exhibit low water solubility of about 1 g/L (Hagelstein *et al.*, 2018:1632). SEM (scanning electron microscopy) analysis of TCC powder particles was performed by Hagelstein and colleagues (2018). This study revealed that TCC particles are roughly spherical in shape but forms large agglomerates that may also be visible on the surface of tablets manufactured with TCC (Hagelstein *et al.*, 2018:1633-1634). Compacted TCC also presents strong inter-particle Van der Waals forces that result in tablets with lower friability as well as higher tensile strength at a lower compression force (Hagelstein *et al.*, 2018: 1634). It also appears as if the disintegration time of tablets manufactured with TCC is dependent on the tensile strength and thus on the compression force. Tablets manufactured with TCC also showed relatively quick disintegration times even when no extra disintegration enhancers were added (Hagelstein *et al.*, 2018:1634 & 1638). Because tensile strength of TCC based tablets is directly dependent on compression force, and disintegration time is dependent on tensile strength, the disintegration time can therefore be increased by increasing the compression force. TCC also expressed good powder flowability as well as brittle fragmentation instead of plastic deformation during tabletting. This means that lubricants have a minimal effect on tensile strength of tablets manufactured from TCC and tabletting speed does not affect tabletting effectivity (Hagelstein *et al.*, 2018:1638-1639).

1.4.2 Dilution potential and high dosage formulations

During medicine manufacturing, it is sometimes necessary to formulate tablets containing high doses of one or more APIs. These tablets tend to be bigger in size than their lower dosage counterparts due to the simple fact that these tablets contain more powder per tablet. This is also applicable for APIs that have a low compressibility and requires more excipients (either fillers or binders) to obtain an acceptable tablet. These bigger tablets prove to be a challenge due to a lower patient compliancy as well as increased production costs (Kabeya *et al.*, 2021:863-865).

A solution to avoid formulation of relatively big tablets is to use a filler with a high dilution potential. The higher the dilution potential, the less filler is needed to obtain an acceptable tablet, thus resulting in smaller, more cost-effective tablets (Habib *et al.*, 1996:206). Dilution potential studies are therefore important for the pharmaceutical industry. It should, however, be noted that each filler's dilution potential differs. The same filler's dilution potential also differs between different APIs (Haruna, *et al.,* 2020:8). Consequently, dilution potential studies can be time consuming, especially if the dilution potential for a specific API needs to be precisely determined. Fillers which express high dilution potential for APIs that are known for compressibility issues tend to also express high dilution potential for other active ingredients (Haruna, *et al.,* 2020:8). If dilution potential values are readily available, the time needed to select potential suitable fillers during the pre-formulation phase of medicine development are considerably shorter (Haruna, *et al.,* 2020:5).

1.5 Research problem

Fairly recently, tricalcium citrate (TCC) was initiated as an excipient during direct compression tabletting (Hagelstein *et al.*, 2018:1631). The problem is that limited information is available on TCC's characteristics as a direct compression excipient in tablet manufacturing. While studies have shown that TCC yields strong tablets and is minimally affected by tabletting speed without additional lubrication (Hagelstein *et al.*, 2018:1631-1632), SeDeM EDS characterisation and comparison of TCC to other direct compressible fillers is not available. This information will contribute to the knowledge and application of TCC as direct compressible filler.

1.6 Aims and objectives

This study aims to analyse the powder properties of TCC using the SeDeM EDS as well as comparing these characteristics of TCC to other widely used direct compressible fillers as well as to determine TCC's dilution potential as applied to direct compression of tablets.

To complete this study, the following objectives were set:

- Characterise TCC powder in terms of SeDeM EDS parameters including bulk density, tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner index, angle of response, powder flow, loss on drying, hygroscopicity, particle size and homogeneity index.

- Compare the powder properties of TCC to that of other known excipients (diluents) such as Emcompress® (dicalcium phosphate), Avicel® PH200 (microcrystalline cellulose), Tablettose® (α-lactose-monohydrate), FlowLac® (mixture of lactose and O-β-D-galactopyranosyl-(1,4)-α-D-glucopyranose monohydrate), CombiLac® (mixture of alpha-lactose monohydrate, microcrystalline cellulose, and corn starch) and MicroceLac® (mixture of lactose and microcrystalline cellulose).

- Determine TCC's dilution potential for paracetamol, furosemide, and pyridoxine as active pharmaceutical ingredients (API's) as applied to direct compression tablets.

- Manufacture tablets by means of direct compression with the above-mentioned selected APIs and TCC to evaluate these tablets with respect to mass variation, friability, crushing strength, tensile strength and disintegration behaviour.

1.7 Layout of dissertation

Chapter 1 aims to deliver a brief overview of the research problem as well as the aims, objectives, and motivations regarding the research. Chapter 2 focusses on the literature regarding pharmaceutical excipients especially fillers combined with SeDeM EDS characterisations and dilution potentials of said fillers. Chapter 3 outlines the experimental methods used to characterise a substance according to the SeDeM EDS as well as determining its dilution potential. Chapter 4 provides the results obtained from the experimental methods as well as a discussion of the results. Chapter 5 contains a short summary of the research and results as well as a few recommendations for future studies.

CHAPTER 2:
LITERATURE STUDY

2.1 Formulation of tablets as solid dosage forms

Medicines may be administered via various routes of administration to patients depending on the properties of the drug, also referred to as an API, therapeutic considerations and biopharmaceutical considerations. The most popular method of drug administration today, is the oral route (Bhutani *et al.*, 2021:23). The popularity of the oral route can be attributed to a number of advantages, including ease of use, a competitive manufacturing and selling cost, high dosage reliability, a less intensive manufacturing process, as well as a lower risk of disease transmission compared to alternative routes such as parental drug administration (Bhutani *et al.*, 2021:23-24).

While the oral drug administration route has many advantages, it also has some disadvantages. One disadvantage of the oral delivery route is the harsh environment of the gastrointestinal (GI) tract that formulations will encounter while traversing the gastro intestinal (GI) tract (Homayun *et al.*, 2019:2). The GI tract consists of several regions with the buccal cavity, stomach and duodenum being the most important areas to consider during solid oral dosage form formulation. The different pH values, enzymes and biological barriers present in the GI tract can severely limit a drug's ultimate bioavailability (Bhutani *et al.*, 2021:23,25; Homayun *et al.*, 2019:2). A drug's bioavailability refers to the fraction of intact drug that reaches the systemic circulation and therefore elicit a therapeutic response (Bhutani *et al.*, 2021:24). To overcome the limited bioavailability of certain orally administered drugs such as antihyperlipidemic agents (simvastatin), and antibiotics such as cefpodoxime, researchers have developed various approaches including structural and chemical modifications to be applied to drugs or formulation approaches (Desai *et al.*, 2012:87,88; Gomez-Orellana, 2005:420). Specific examples of modifications to overcome the GI tract's influence on drugs are the formulation of hydrogels, prodrugs, and the coating of tablets or capsules (Bhutani *et al.*, 2021:29-30; Gomez-Orellana, 2005:420-424; Helfand & Cowen, 1983:3).

Another physico-chemical drug factor to take into consideration when developing solid oral dosage forms is the water solubility of the drug. For a drug to be absorbed, it should be in solution, therefore solubility affects bioavailability. To increase the solubility, especially for poorly soluble drugs, techniques such as complexation, nano-particles, lipid based vesicles and micelle formulations can be applied (Bhutani *et al.*, 2021:23,25). The oral drug delivery route is suited for the administration of several dosage forms including tablets, capsules,

powders, emulsions, and suspensions. By the 19th century, most pharmaceutical formulations were available as pills, powders, solutions, tinctures or spirits (Helfand & Cowen, 1983:3). These formulations resemble more refined dosage forms that are still available today (Helfand & Cowen, 1983:3). Oral dosage forms can be divided further into several subcategories. One of these subcategories is solid oral dosage forms, which as the name suggests, comprises only solid dosage forms that can be taken orally such as tablets, capsules and powders (Bhutani *et al.*, 2021:23). The advantages of using solid oral dosage forms include the ease of self-administration for the patient, as well as accurate predefined doses per administration (Bhutani *et al.*, 2021:23).

2.2 Tablet manufacturing process

During the past century, the basic approach to tablet manufacturing stayed relatively constant except that the technology improved drastically (Bhowmik *et al.*, 2014:24368). This improvement of technology resulted improvement especially in terms of tabletting speed and tablet uniformity. These improvements in turn resulted in tablet costs that stayed relatively low compared to other dosage forms. Today tablets are probably the most used solid oral dosage form (Bhowmik *et al.*, 2014:24368). Tablets exists in different shapes and sizes from spherical and elliptic to triangular and cylindrical (Bhowmik *et al.*, 2014:24368). Just like tablets have different shapes, they also have different sizes and weights depending on the excipients used as well as the site of administration (e.g. gastro-intestinal tract, sublingual and buccal mucosa) and characteristics of the drug. The advantages of tablets are that they can be produced, packaged and shipped at a relatively low cost, while still maintaining high stability (Bhowmik *et al.*, 2014:24368-24369). All manufactured pharmaceutical products, including tablets, must pass certain specified quality tests and obtain regulatory body approval (Gavi & Reynolds, 2014:130).

Tablets can be divided into two general categories namely compressed tablets and moulded tablets (Bhowmik *et al.*, 2014:24368). Moulded tablets are manufactured by pouring the liquid material into a mould, usually cylindrically shaped and left to dry (Bhowmik *et al.*, 2014:24368). A requirement for moulded tablets is that the final tablet as well as all the excipients should be readily soluble. Compressed tablets on the other hand are manufactured through the compression of powder mixtures consisting of a combination of excipients usually including a binder, disintegrant, lubricant, diluent and sometimes a colourant (Abrantes *et al.*, 2016:2019; Bhowmik *et al.*, 2014). Compression is also the most commonly used tablet manufacturing method containing several sub methods with the most common being direct compression, wet granulation and dry granulation (Šantl *et al.*, 2011:131). By applying different manufacturing techniques and compositions to compressed tablets, different tablet types can be obtained

such as coated tablets for enteric protection, sustained release tablets, buccal and sublingual tablets as well as effervescent tablets and many more (Bhowmik *et al.*, 2014:23468; Bi *et al.*, 1999:571-572; Helfand & Cowen, 1983:12-16).

The biggest challenges faced when manufacturing compressed tablets are resistance to compression and poor powder flowability (Bhowmik *et al.*, 2014:24369; Rojas *et al.*, 2013:17). Independent of whether direct compression, wet or dry granulation is used for the manufacturing process, there are some common steps that are always present. The first compulsory step is the accurate weighing of the correct pharmaceutical ingredients (Bhowmik *et al.*, 2014:24370; Gavi & Reynolds, 2014:133). The second step is the mixing of the weighed ingredients according to the chosen manufacturing process's specifications. It should, however, be noted that perfect homogeneity can never be achieved. There will always be some separation or inhomogeneity because of particle size differences, density differences and particle shape differences (Bhowmik *et al.*, 2014:24370). The last compulsory step in the manufacturing of compressed tablets is the compression of the powder mixture into tablets. This process of tablet compression on a tablet press is illustrated in figure 2.1. During stage 1, the powder flows into the die hole onto the bottom punch. Excess powder is removed during stage 2 and the upper punch presses down onto the powder during stage 3. In stage 4, the bottom punch pushes the tablet out of the die and after it is removed the die can be filled again with powder (stage 5) (Bhowmik *et al.*, 2014:24371).

The mixture to be compressed, may refer to either granules or powders depending on the manufacturing process used. During this step, the mixture is compressed inside the press's die, between the upper and lower punch (Bhowmik *et al.*, 2014:24370; Gavi & Reynolds, 2014:133). During tablet compression, there are two main methods with which the powder particles agglomerate or compact to form a tablet. These two processes are called fragmentation and deformation. Deformation can be split into plastic and elastic deformation, which are irreversible and reversible processes, respectively (Šantl *et al.*, 2011:131). During and after a batch of tablets are compressed, random samples are chosen, and quality tests are performed one these chosen tablets. It should also be noted that a higher compression potential does not always lead to better compactibility, especially for more complex powder mixtures (Šantl *et al.*, 2011:139).

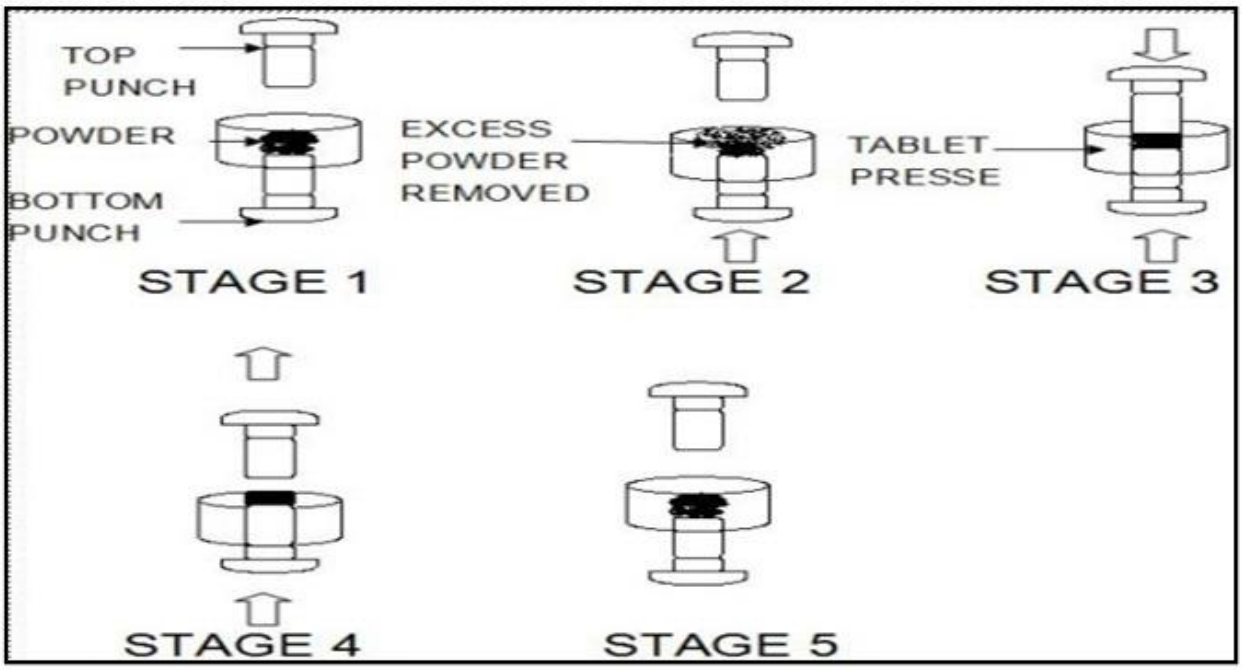

Figure 2.1: Illustration of the tablet compression steps on a tablet press (Bhowmik *et al.*, 2014:24371).

2.2.2 Direct compression

During the direct compression tablet manufacturing process, a powder mixture is compressed directly into a tablet after mixing the active pharmaceutical ingredient (API) and the excipients (Bhowmik *et al.*, 2014:24369; Gavi & Reynolds, 2014:133). The advantages of using direct compression over wet or dry granulation are lower production costs, less intensive manufacturing methods which leads to shorter production time (Bhowmik *et al.*, 2014:24369-24371; Šantl *et al.*, 2011:137-139). Direct compression also removes the need for storage of intermediate products (Van Snick *et al.*, 2017:391) as well as allowing moisture labile APIs to be compressed for there are no wetting of the excipients involved (Šantl *et al.*, 2011:132). The effects of heat on thermolabile drugs are also reduced during direct compression, for the processes present in dry granulation such as roller compaction or slugging is absent. Furthermore, there is no heating step as is the case with wet granulation (Šantl *et al.*, 2011:132-133). The most notable challenge with direct compression, however, is that the powder mixture should possess good powder flow as well as good compression properties as these properties are essential for successful tablet compression (Bhowmik *et al.*, 2014:24367-24370). The tabletting speed is also dependent on the powder mixture's flow characteristics, compressibility and compactibility (Van Snick *et al.*, 2017:391). A powder's compressibility refers to the powder's ability to reduce in volume when pressure is applied to the powder, while compactibility refers to the relation between the final tablet's tensile strength and the

powder's porosity (Patel *et al.*, 2006:7). The term tabletability aims to combine these terms and can be described as the relation between a tablet's tensile strength and the compaction force used to produce the tablet (Patel *et al.*, 2006:7). Direct powder compression can be a continuous process. The hardest step to implement continually is the weighing and mixing of the powders (Van Snick *et al.*, 2017:391). This problem can, however, be overcome with feeding machines, continuous mixers and in line analysers. The problem with using continuous mixers is drug uniformity (Van Snick *et al.*, 2017:391). Moisture content of the pharmaceutical excipients added to the formulation also contributes to the success of the formulation. There is unfortunately no definitive rule that defines whether moisture increases or decreases tablet strength. Both an increase and decrease in tablet strength may be observed, depending on the ingredients used (Khan & Pilpel, 1986:145).

2.2.3 Wet granulation

The wet granulation tablet manufacturing method is still the most widely used process today with almost 80% of all tablets being manufactured using this method (Rojas *et al.*, 2013:17). Granulation is the process where small powder particles are enlarged by agglomeration (Forrest *et al.*, 2003:91). The primary reason for enlarging particles is to improve powder flow. Wet granulation includes three extra steps during the manufacturing process namely granulation, drying and screening. During granulation, the powder mixture without the lubricant, is wetted using a suitable liquid binder solution (Bhowmik *et al.*, 2014:24369; Forrest *et al.*, 2003:91). Granules form when particles collide and stick together (Forrest *et al.*, 2003:91). The wet granules are then dried in an oven at a predetermined temperature depending on the specific excipients and active ingredient used in the formulation. After the granules are dried, they are screened/milled to ensure uniform granule size.

The flow properties of wet granulated mixtures are generally superior to that of both plain powders and dry granulated granules (Šantl *et al.*, 2011:139). Tablets compressed from wet granulated granules are also more inclined to have an improved friability as it tends to express a lower mass loss but a longer disintegration time compared to directly compressed and dry granulated tablets at the same hardness (Šantl *et al.*, 2011:139). A disadvantage of using the wet granulation process is an increase in production time and effort, therefore increased production cost (Bhowmik *et al.*, 2014:24369). Moisture and temperature sensitive drugs are usually excluded from the wet granulation method because of stability issues (Rojas *et al.*, 2013:17).

2.2.4 Dry granulation

During the dry granulation tablet manufacturing process, granules are also formed as with wet granulation. The main difference between wet and dry granulation is that dry granulation does not use a liquid binder solvent to agglomerate particles (Bhowmik *et al.*, 2014:24369). Herein lies the advantage of using dry granulation over wet granulation, namely dry granulation can be used for moisture as well as heat sensitive products since there are no liquid or drying steps involved in the process (Bhowmik *et al.*, 2014:24369). A disadvantage of dry granulation is the production of dust as a by-product. This dust causes the granules to lose some of their compression potential (Šantl *et al.*, 2011:131). Dry granulation consists of two extra steps in the tabletting process. These steps are roller compaction or slugging, and screen milling (Gavi & Reynolds, 2014:132; Šantl *et al.*, 2011:132). Roller compaction is where the powder is compacted into a solid sheet between two counter rotating rollers (Gavi & Reynolds, 2014:132) whereas slugging is when the powder mixture is compressed into slugs (Šantl *et al.*, 2011:132) whereafter it is milled within a sieve. The sieve allows for the correct size granules to pass through while the larger agglomerates are broken into smaller granules (Gavi & Reynolds, 2014:132). After the desired sized granules are obtained, the granules are pressed into tablets. During the granulation process, the particles are fully fragmented. This leaves only plastic or elastic deformation, depending on the particles, available during the final tablet compression process (Šantl *et al.*, 2011:136). This phenomenon may lead to tablet manufacturers with dry granulation having tablets with a lower tensile strength and therefore a higher friability than tablets produced with either direct compression or wet granulation (Šantl *et al.*, 2011:135).

2.2.5 Quality tests

Quality is a broad term, which in terms of pharmaceutical dosage forms, may include suitability for use, efficacy, safety and the assessment of label claims (Chavan *et al.*, 2018:60). During and after tablet manufacturing, random samples of each batch of tablets are chosen and quality tests are performed on these tablets. These tests and their acceptable results are defined in the latest version of various pharmacopoeias, most notably the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP). These tablet quality tests include friability, disintegration, uniformity of mass, and crushing strength tests (Gavi & Reynolds, 2014:132-133). These quality control tests must be performed at regular intervals during the manufacturing process of the tablets (Chavan *et al.*, 2018:60). When one or more of these quality tests fail to meet the prescribed requirements, the manufacturing of the batch must be stopped and adjustments to the compression machine settings, or the formulation, must be made (Chavan *et al.*, 2018:60-61). The abovementioned quality tests are called in-

process quality control tests (Chavan *et al.*, 2018:61). Once the manufacturing of a batch has been completed, random tablets from the batch are chosen and additional quality tests, such as assay, and dissolution are performed on these tablets. No batch may be released or distributed if any of the quality tests fails to meet the acceptance criteria.

2.2.5.1 Uniformity of mass

The purpose of the uniformity of mass test is to ensure that each tablet does not deviate more than a certain amount from the required mass. The test is performed on 20 randomly selected tablets whose individual weight is each measured, an average calculated and each tablet's deviation from the average determined (Chavan *et al.*, 2018:61-62). The tablet batch fails this test when more than two tablets deviate from the prescribed deviation percentage or one tablet deviates more than double from the deviation percentage (BP, 2021; Chavan *et al.*, 2018:62). The prescribed deviations according to the BP and USP is given in table 2.1.

Table 2.1: Prescribed deviation for the uniformity of mass test for tablets according to the BP and USP (Chavan *et al.*, 2018:62)

Average tablet weight (mg)		**% Deviation**
BP	**USP**	
≤ 80 mg	≤ 130 mg	± 10%
> 80 mg, < 250 mg	> 130 mg, < 324 mg	± 7.5%
≥ 250 mg	≥ 324 mg	± 5%

2.2.5.2 Friability

The friability test measures an aspect that indicates if the manufactured tablets would break during normal handling or transport. To perform this test, ten random tablets are chosen, dusted, and weighed. They are placed into a friabilator which are operated at 25 rpm for 4 min, for a total of 100 revolutions whereafter they are again dusted and weighed (Chavan *et al.*, 2018:62). The tablets pass this test when they do not lose more than 1% weight where percentage weight loss expresses friability (Chavan *et al.*, 2018:62).

2.2.5.3 Disintegration

Disintegration refers to a tablet's ability to break apart when in contact with a water-based fluid. To simulate a human body, the disintegration fluid is heated to 37°C (Chavan *et al.*, 2018:62). To perform this test, six tablets are chosen randomly and placed into the disintegration apparatus which dips it repeatedly into the disintegration fluid. The passing requirements for the disintegration test are that all six tablets should be completely disintegrated as measured by breaking up into small enough particles that can fit through a sieve with specified openings within 15 min. If one tablet does not disintegrate within the specified time, the test is repeated an additional two times. The tablets fail the test when more than 16 of the 18 tablets fails to disintegrate completely (Chavan *et al.*, 2018:62-63). It should, however, be noted that different tablet types have different required disintegration times as can be seen in table 2.2.

Table 2.2: Required disintegration times according to the BP and USP for different tablet types (Chavan *et al.*, 2018:63)

Tablet type	Disintegration time (min)	
	BP	**USP**
Uncoated tablets	15 min	5 – 30 min
Coated tablets	60 min	60 – 120 min
Enteric-coated tablets	-	60 min or as specified in monograph
Film-coated tablets	-	30 min or as specified in monograph
Effervescent tablets	5 min	< 3 min or as specified in monograph
Soluble tablets	3 min	-
Dispersible tablets	3 min	< 3min or as specified in monograph
Gastro-resistant tablets	60 min	-
Oral lyophilizates	3 min	-

2.2.5.4 Crushing and tensile strength

Crushing strength, also called hardness of tablets, refers to the force needed to break the tablet (Chavan *et al.*, 2018:62). The BP specifies the crushing strength test as an unofficial test. This means that the tablet batch will not officially fail if the result of the test is not within the 80 to 120 Newton (N) range, which is only used as a guide. The test is used as an indicator for tablet strength. The range of 80 to 120 N is set as a guideline where most tablets would not break too easily but would comply with the specifications related to disintegration. The

crushing strength is determined by taking ten randomly chosen tablets and using a crushing strength apparatus to determine each tablet's hardness (Haruna *et al.*, 2020:3).

Tensile strength is calculated from the results of a crushing strength test as well as the diameter and thickness of the tablets. The equation used to calculate the tensile strength of the tablets depends on the tablet's shape (Haruna *et al.*, 2020:3).

2.2.5.5 Quality test result correlations

Each of the quality tests provides different information about the manufactured tablets. Though it appears that there is no correlation between the results of the tests that is untrue. It is generally observed that tensile strength and disintegration time is directly proportional to each other (Gavi & Reynolds, 2014:139), while the percentage friability is inversely proportional to the tensile strength (Osorio-Fierros *et al.*, 2017:285).

2.2.5.6 Other quality control tests

Besides the main quality control tests performed on tablets, there are additional tests that may be performed. These additional tests include size and shape, colour and odour descriptions, unique markings, moisture content, diameter and thickness of the tablets (Chavan *et al.*, 2018:61-62). These tests are developed to identify and describe the tablets as well as to check for impurities (Chavan *et al.*, 2018:61).

2.3 SeDeM Expert Diagram System

The selection of the correct excipients is of critical importance during tablet formulation (Aguilar-Díaz *et al.*, 2009:417). In the past, the success of a tablet formulation was primarily dependent on previous experience and the formulation scientist's knowledge. This led to formulation being a time consuming, resource intensive and very costly process as the whole process was based on experimentation (Dai *et al.*, 2019:518). As an alternative process for tablet formulation, the International Conference on Harmonisation of Technical Requirements for registration of pharmaceuticals for human use, otherwise known as the ICH, proposed the Quality by Design (QbD) pre-formulation process (Dai *et al.*, 2019:518). The QbD formulation process is a systematic approach based on quality risk management and science (Dai *et al.*, 2019:518). The QbD formulation approach contains minimal trial and error but focusses rather on scientific design processes (Dai *et al.*, 2019:518). The SeDeM Expert Diagram System (SeDeM EDS) was developed from the QbD as a scientific approach to analyse powders in terms of their potential for direct compression (Dai *et al.*, 2019:518). The results obtained from

the SeDeM EDS analysis proved to be sufficiently reliable and reproducible (Aguilar-Díaz *et al.*, 2009:417).

2.3.1 Applications of the SeDeM EDS

The SeDeM EDS primarily has two applications namely analysing a powder's suitability for direct compression and determining the theoretical amount of a specific excipient, named a corrective excipient, to add to the mixture to ensure theoretical optimal compression potential (Aguilar-Díaz *et al.*, 2009:417; Dai *et al.*, 2019:523). The SeDeM EDS analyses pharmaceutical powders through their physical properties (Dai *et al.*, 2019:518). The most influential properties are expressed as twelve parameters as explained later in this chapter under SeDeM EDS parameters.

A secondary use of the SeDeM EDS is to categorise pharmaceutically active ingredients (APIs) into one of four groups based on the manufacturing classification system (MCS) as proposed by the Academy for Pharmaceutical Sciences (APS) in 2014 (Dai *et al.*, 2019:525). These four groups include direct compression, dry granulation, wet granulation and the use of other methods (Dai *et al.*, 2019:525). The classification of a powder in one of these groups is based on the powder's physical properties. For direct compression, the powder's angle of response should be < 41° and the bulk and true densities should be > 0.5 g/ml and 1 – 2.5 g/ml respectively (Leane *et al.*, 2015:13). For dry granulation, the powder's flowability should be assessed by using the Carr's index. A value of < 35% is acceptable for dry granulation (Leane *et al.*, 2015:13). Wet granulation should be considered for powders with poor flow and wettability. Wet granulation may, however, cause instabilities due to moisture and heat added in the process, so the powder should not be moisture sensitive and have an ideal melting point of higher than 90°C (Leane *et al.*, 2015:14). The last category is for powders that does not fit in any of the other categories such as an API that is prone to degradation. In this example, the formulation of coated tablets may be considered (Leane *et al.*, 2015:14).

Another major breakthrough in the pharmaceutical space pertaining to the SeDeM EDS was when granules, formulated by wet-granulation, were successfully analysed and tablets could be successfully compressed (Dai *et al.*, 2019:518). This breakthrough showed that not only can SeDeM EDS be used to analyse powders for direct compression, but it can potentially also be used for other applications.

2.3.2 SeDeM EDS parameters

During a SeDeM EDS analysis, the physical properties most important for direct compression is analysed (Aguilar-Díaz *et al.*, 2009:417). These important physical properties may differ

based on the type of tablet being manufactured. For example orally dispersible tablets (ODT) have a higher importance for disintegration than normal tablets (Aguilar-Díaz *et al.*, 2009:414). There are twelve basic parameters build into SeDeM EDS. These parameters are bulk density (D_a), tapped density (D_c), inter-particle porosity (Ie), Carr's index (IC), cohesion index (Icd), Hausner ratio (IH), angle of response (α), powder flow (t"), loss on drying (%RH), hygroscopicity (%H), percentage of particles smaller than 50 µm (%Pf) and the homogeneity index (Iθ) (Aguilar-Díaz *et al.*, 2009:417). After the results for each parameter is determined experimentally, the values are converted into a value scale from 0 to 10 (Dai *et al.*, 2019:517-520). These converted values are plotted on a polygon as shown in figure 2.2. The twelve parameters are also grouped into five categories called indices. These indices consist of the dimension index, compressibility index, flowability index, lubricity/stability index and the lubricity/dosage index (Suñé-Negre *et al.*, 2011:465). A summary of these parameters and their respective equations and acceptable ranges are given in table 2.3.

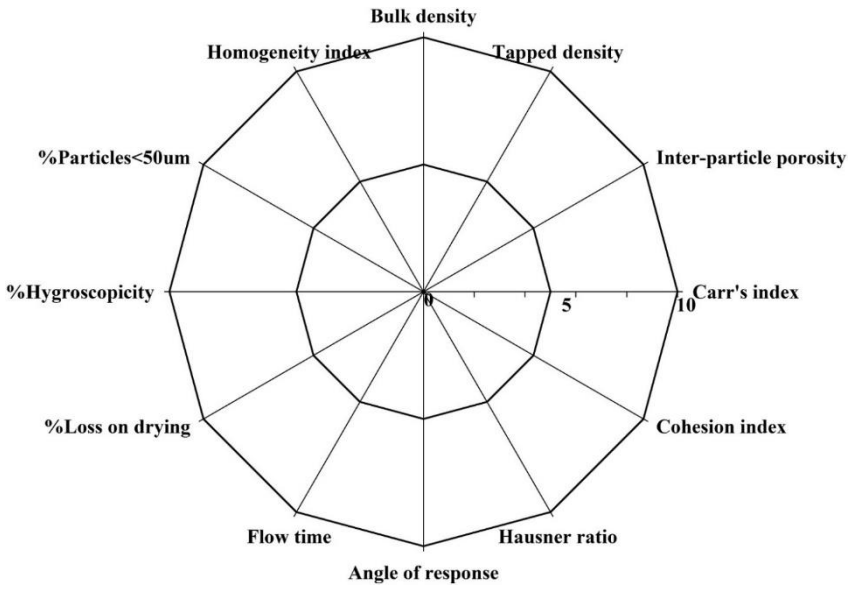

Figure 2.2: Polygon representation of the twelve basic SeDeM EDS parameters (Dai et al., 2019:521).

An additional three indices can be calculated to determine the suitability for direct compression. These are the index of profile parameter (IPP), index parameter (IP) and the index of good compressibility (IGC) (Perez *et al.*, 2006:353-355). A powder mixture can be deemed suitable for direct compression when the IPP and IGC have a value ≥ 5 and the IP a value ≥ 0.5 (Dai *et al.*, 2019:518). Studies also revealed that some parameter's acceptable ranges can be adjusted from the original proposed values while still maintaining the reliability of the method (Suñé-Negre *et al.*, 2011:464-465). Some optimisations include the Hausner ratio. The original range was 3 to 0, but when the powder's tapped density is less than its bulk

density, the powder would express poor flow as well as adherence to the container's walls (Suñé-Negre *et al.*, 2011:466). The Hausner ratio is calculated using Equation 2.1, and therefore the result in such a case, would be less than 1 (Suñé-Negre *et al.*, 2011:466). Because powders with poor powder flow express poor compressibility as well as ultimately poor flow into the tablet press die, the accepted Hausner ratio range can be adjusted from the range of 3–0 to 3–1 (Suñé-Negre *et al.*, 2011:466).

$$IH = \frac{Dc}{Da}$$

Equation 2.1 (Suñé-Negre *et al.*, 2011:466)

The relative humidity can also be optimised to a new acceptable range of 1 – 3%. This optimisation can be made on the assumption that powders with a moisture content of less than 1% will not compress and powders with a moisture content greater than 3% leads to agglomeration and these powders tend to stick to the die during tablet compression (Dai *et al.*, 2019:522; Suñé-Negre *et al.*, 2011:466).

A summary of the SeDeM EDS parameters and their respective equations as well as acceptable ranges are shown in table 2.3

Table 2.3: Twelve basic parameters of the SeDeM EDS analysis with their respective equations and acceptable range values (Dai *et al.*, 2019:520).

Incidence	Parameter	Symbol	Unit	Equation	Acceptable ranges
Dimension	Bulk density	Da	g/ml	Da = m/Va	0–1
	Tapped density	Dc	g/ml	Dc = m/Vc	0–1
Compressibility	Inter-particle porosity	Ie	-	Ie = Dc-Da/Dc*Da	0–1,2
	Carr's index	IC	%	IC = (Dc-Da)/Dc * 100	0–50
	Cohesion index	Icd	N	Experimental	0–200
Flowability	Hausner ratio	IH	-	IH = Dc/Da	3–1
	Angle of response	α		Experimental	50–0
	Powder flow	t"	s	Experimental	20–0
Lubricity/ Stability	Loss on drying	%HR	%	Experimental	10–0
	Hygroscopicity	%H	%	Experimental	20–0
Lubricity/ Dosage	Percentage of particles < 50 µm	%Pf	%	Experimental	50–0
	Homogeneity index	Iθ	-	Iθ = Fm(100 + ΔFmn)	0–0.02

2.4 Pharmaceutical excipients

Tablets, especially formulations comprising of medium to high potency APIs, usually contains just up to 30% API (Jivraj *et al.*, 2000:58). The rest of the tablet's mass is made up of pharmaceutical excipients. Pharmaceutical excipients can be defined as substances or groups of substances that fills a volume of a mixture in which an API is incorporated (Abrantes *et al.*, 2016:2019). One of the properties of pharmaceutical excipients is to ensure the correct weight, consistency and dose of the administered API in each dosing unit, e.g. a tablet (Pifferi & Restani, 2003:541). The primary sources of pharmaceutical excipients are animals (e.g. lactose), plants (e.g. starch), minerals (e.g. calcium phosphate) and chemical synthesis (e.g. polyethylene glycol (PEG)) (Pifferi & Restani, 2003:542). Compounds contained in these natural resources are often times of a substandard quality, and should be heavily refined before usage is possible (Pifferi & Restani, 2003:542). In 2003, the estimate of the number of pharmaceutical excipients being used worldwide exceeded a thousand, today it increased notably as new excipients were discovered and synthesised (Pifferi & Restani, 2003:542). Each excipient has its own functionality, such as disintegrants, binders, fillers, colourants and lubricants (Jivraj *et al.*, 2000:59-62).

Pharmaceutical excipients have three general requirements to fulfil before usage in pharmaceutical products can be considered. These requirements align with the basic requirement of APIs which is quality, efficacy, and safety. The only difference from these requirements are that efficacy is replaced with functionality (Pifferi & Restani, 2003:543). Excipients used during direct compression formulations must possess certain specific physical properties such as reproducible quality, a high bulk density, a particle size distribution that does not encourage segregation as well as being inert (Jivraj *et al.*, 2000:59). Segregation is an issue encountered with many pharmaceutical formulations. Segregation is defined as the process when particles or components of an otherwise mostly uniform mixture separate leading to non-uniform distribution of ingredients in pharmaceutical products. Segregation can happen during storage or with general handling of the product, but is more likely to happen when the mixture's particles' size differs greatly (Rojas *et al.*, 2012:1160).

Some excipients can fulfil multiple roles, which means a single excipient can replace more than one type of excipient. An example of a multi-functional excipient is microcrystalline cellulose, which can act as a disintegrant as well as a diluent (Jivraj *et al.*, 2000:59). An important excipient, especially with direct compression, is the filler that is also called a diluent. The purpose of a diluent is to provide a binding force for the API(s), which is in many cases are poorly compressible. The amount of API that can be added to the specific diluent determines the filler's dilution potential (Habib *et al.*, 1996:206). Choosing the correct

combination of excipients during tablet formulation is of utmost importance. There are several methods which can assist researchers to choose the correct excipients for a tablet formulation. One such method is the SeDeM Expert Diagram System (SeDeM EDS), which was discussed earlier in this chapter (Suñé-Negre *et al.*, 2011).

Pharmaceutical excipients can also be categorised into three general categories. The first category consists of excipients previously used in the food industry and is generally considered as safe for consumption. The second category is excipients synthesised by making structural modifications to compounds from category one, and the last category consists of newly developed or discovered compounds (Pifferi & Restani, 2003:542). Pharmaceutical excipients were first seen as nothing more than inert substances that were used to achieve consistency in the formulation (Abrantes *et al.*, 2016:2019). Contrary to popular believe, even inert compounds may have adverse or even toxic effects, proving the old saying that all substances, given in the correct dose, can be a poison (Pifferi & Restani, 2003:543-544). This proves to be especially true when the excipients are not manufactured, tested or administered properly or correctly (Pifferi & Restani, 2003:543). Certain conditions may also lead to adverse reactions because of excipients used during product formulation, such as lactose in a lactose intolerant population (Pifferi & Restani, 2003:548). Excipients may also affect the effectivity of the pharmaceutical product because of a physical reaction, such as magnesium stearate which may lower the dissolution rate of the product, and therefore decreasing the APIs bioavailability, or a chemical reaction between two excipients or an excipient and the API, that may lead to the formation of a potential toxic substance (Abrantes *et al.*, 2016:2022; Pifferi & Restani, 2003:543-544). Some of these issues, may, however, be overcome by appropriate changes during the formulation process. For example the abovementioned issue caused by magnesium stearate can be overcome by decreasing the blending time with the lubricant present to less than five minutes (Rojas *et al.*, 2012:1160). Today, excipients may even be used to achieve an increase in bioavailability and drug efficacy (Abrantes *et al.*, 2016:2022).

2.4.1 Dilution potential

Dilution potential, otherwise known as dilution capacity, can be defined as the portion of a poorly compressible powder that can be mixed with the filler to produce a powder mixture with acceptable compression properties as well as tablets with friability of less than one percent (Habib *et al.*, 1996:206; Rojas *et al.*, 2013:18). Dilution potential for each combination of powders is determined independently. The experimental method for determining dilution potential consists of a systematic approach where increasing ratios of the two powders are compressed into tablets that are subjected to evaluation. For example, different ratios of API to diluent are compressed into tablets on which tests are performed such as quality tests,

especially friability (Habib *et al.*, 1996:206; Rojas *et al.*, 2013:19). An important note, however, is that compression force affects the results of this method and should be kept constant as far as possible (Habib *et al.*, 1996:206). Another approach is to compare each mixture's tensile strength at different compression forces by quadratic regression as proposed by Minchom and Armstrong during the British Pharmaceutical Conference in 1987 (Habib *et al.*, 1996:206). This method, however, does not produce reliable results for powders exhibiting brittle fracture (Habib *et al.*, 1996:212).

2.4.2 Diluents (Fillers)

Pharmaceutical excipients, especially diluents can be classified as either having plastic or elastic deformation as well as brittle fragmentation mechanisms (Hagelstein *et al.*, 2018:1631). Plastic behaviour occurs when the particles of the powder mixture deform permanently under pressure. This deformation usually decreases the distance between the particles, which increases the intermolecular forces, especially Van der Waals forces (Hagelstein *et al.*, 2018:1631). Microcrystalline cellulose is an example of a diluent which undergoes plastic deformation. Microcrystalline cellulose also happens to be the diluent most used during direct compression (Hagelstein *et al.*, 2018:1631). Brittle fragmentation, however, occurs when materials, like dicalcium phosphate's particles cannot deform. In this scenario, brittle fragmentation occurs. Brittle fragmentation can be defined as the fragmentation of bigger particles into smaller particles. These fragmented particles can then fill the empty spaces between the particles, also leading to increased intermolecular Van der Waal forces and therefore keeping its new shape (Hagelstein *et al.*, 2018:1631-1632). Plastic deforming excipients usually requires less energy to compress than brittle excipients. Excipients consisting of smaller particles should also theoretically require less energy for they do not need to fracture but only rearrange (Hagelstein *et al.*, 2018:1632). The reason for choosing brittle fragmenting excipients over plastic deforming excipients is that brittle materials tend to compress independently of tabletting speed and lubrication. The disadvantage of using brittle materials, however, is a decrease in hardness and therefore lower tensile strength (Hagelstein *et al.*, 2018:1362).

Diluents can also be divided into two groups namely single component and co-processed excipients (Haruna *et al.*, 2020:1). Co-processed diluents were developed to enhance powder flow, compressibility, dilution potential, stability as well as several other physical and chemical properties (Haruna *et al.*, 2020:1). Co-processed diluents are manufactured by changing the excipient's physical properties like particle size and not the chemical composition or properties (Haruna *et al.*, 2020:1). One such example of a co-processed diluent is MicroceLac® (Haware *et al.*, 2015:3619).

2.4.2.1 Avicel 200® (Microcrystalline cellulose)

Microcrystalline cellulose is primarily used as a binder or a diluent but can also serve several other different functions in a formulation (Quinn & Sun, 2017:194). The functions of microcrystalline cellulose are dependent on the concentration in the formulation. The functions include an anti-adherent at 5 – 20%, a disintegrant at 5 – 15% and a binder/diluent at 20 – 90% (Quinn & Sun, 2017:194). Microcrystalline cellulose is suitable for use during wet granulation, dry granulation as well as direct compression (Quinn & Sun, 2017:194). Special formulations for delayed release action were also manufactured using microcrystalline cellulose together with nano-particles and hydrogels (Quinn & Sun, 2017:194). Microcrystalline cellulose's physical description is a white, odourless, tasteless, and porous powder (Quinn & Sun, 2017:194). Microcrystalline cellulose has a flowability, which was found to be sufficient at high tabletting speeds (Quinn & Sun, 2017:195). The larger particle-size grades of microcrystalline cellulose (Avicel® PH200) usually provides better powder flow than the smaller particle size grades (Quinn & Sun, 2017:197). Avicel PH200® has a mean particle size of about 180 µm and a moisture content of ≤1.5% (Quinn & Sun, 2017:197). Other physical properties of microcrystalline cellulose includes an angle of response of 34.4°, a bulk and tapped density of about 0.337 and 0.478 g/cm^3 respectively, a powder flow rate of 1.41 g/s and a specific surface area of 0.78 – 1.18 m^2/g (Quinn & Sun, 2017:195). The values for these physical properties may change depending on the grade and brand of powder used.

Microcrystalline cellulose is a hygroscopic powder and should therefore be stored in a dry environment whenever possible (Quinn & Sun, 2017:196). Microcrystalline cellulose is generally considered as safe for human consumption and handling but may cause irritation when in contact with the eyes and a laxative effect when consumed in large quantities (Quinn & Sun, 2017:196). Microcrystalline cellulose's bonding mechanism is considered plastic deformation and compressibility depends on moisture content, particle size and porosity (Quinn & Sun, 2017:197).

2.4.2.2 CombiLac® (70 % alpha-lactose monohydrate, 20 % microcrystalline cellulose and 10 % corn starch)

CombiLac®, being a co-processed excipient contains three components namely lactose, cellulose and starch which is inseparable by physical means (MEGGLE, 2020:2). The primary component of CombiLac® is lactose monohydrate. CombiLac® shows improved compression and flow properties when compared to pure lactose, making it suitable for direct compression (MEGGLE, 2020:2). Tablets formulated with CombiLac® shows disintegration times that are unaffected by the tablet hardness (MEGGLE, 2020:2). CombiLac® was designed to be used

for direct compression, but can also be used during dry granulation (MEGGLE, 2020:3). When compared to MicroceLac®, CombiLac®'s flowability is about equal, tablets formulated are a bit softer while disintegration times are generally longer (MEGGLE, 2020:4). When analysing CombiLac®'s relative humidity, it was found that the starch component increases the moisture absorption (MEGGLE, 2020:5). Starch, that can also be employed as a disintegrant, is also partly responsible for CombiLac®'s fast disintegration times even at harder tablet hardness values (MEGGLE, 2020:7). The physical appearance of CombiLac® is a white, odourless, free flowing and partly water soluble powder (MEGGLE, 2020:5). The physical properties of CombiLac® consists of an angle of repose of about 30°, a bulk and tapped density of 0.45 and 0.54 g/cm^3 respectively, a Hausner ratio of 1.19, a Carr's index of 16 and a BET-surface of 0.49 m^2/g (MEGGLE, 2020).

2.4.2.3 Emcompress® (Dibasic calcium phosphate dihydrate)

Emcompress® is chemically known as dibasic calcium phosphate dihydrate, which is also used in pharmaceutical preparations as a source of calcium and phosphate (Moreton, 2017:149). The bonding mechanism of Emcompress® during tabletting is brittle fracture. Emcompress® is known for good flow and compression properties, but almost always require a lubricant during tabletting because of its abrasive nature (Moreton, 2017:149). There exists two main types of Emcompress® namely milled and course grade powder which is mainly used during wet granulation and direct compression respectively (Moreton, 2017:149). The physical appearance of Emcompress® is a white, odourless, tasteless powder (Moreton, 2017:149). The physical properties for Emcompress® includes an average angle of repose of 28.3°, a bulk and tapped density of 0.915 and 1.17 g/cm^3, a powder flow rate of 27.3 g/s and an average surface area of 0.44 – 0.46 m^2/g (Moreton, 2017:149). Emcompress® is only soluble in diluted acids, but neither in water nor ethanol (Moreton, 2017:149). Emcompress® is non-hygroscopic under normal room temperature conditions but moisture may evaporate from the powder at higher temperatures (Moreton, 2017:149). During the packaging development process as well as storage of products containing Emcompress®, this phenomenon of moisture collection should be taken into consideration and techniques applied to minimise potential damage to the product (Moreton, 2017:149). When developing a formulation with Emcompress® as an ingredient, it should be noted that Emcompress® is incompatible with APIs such as tetracyclines, erythromycin, aspirin, indomethacin as well as other APIs that is sensitive to a slight alkaline nature (Moreton, 2017:150).

2.4.2.4 FlowLac® (Spray-dried lactose)

FlowLac® is a mixture consisting of amorphous and crystalline lactose monohydrate, also known as O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate, and is used as a diluent during direct compression (Penz & Zeleznik, 2015a:527). Spray-dried lactose can also be used as a binder and a powder flow improver (Penz & Zeleznik, 2015a:527). The physical appearance of FlowLac® is an almost white, odourless, sweet powder (Penz & Zeleznik, 2015a:527). Other physical properties of FlowLac® include an angle of repose of 29°, a bulk and tapped density of 0.57 and 0.67 g/cm^3 respectively and a mean particle size of less than 200 µm (Penz & Zeleznik, 2015a:527-529). The bonding mechanism of spray-dried lactose is both brittle fracture as well as plastic deformation pertaining to crystalline α-lactose monohydrate (80 – 90%) and amorphous lactose (10 – 20%) content respectively (Penz & Zeleznik, 2015a:527).

2.4.2.5 MicroceLac® (Co-processed lactose monohydrate & microcrystalline cellulose)

MicroceLac® is a co-processed pharmaceutical excipient containing lactose monohydrate (73 – 77%) and microcrystalline cellulose (23 – 27%) (Penz & Zeleznik, 2015b:521). MicroceLac® usually expresses good flowability due to its relatively spherical particle shape as well as its relatively constant particle size (Penz & Zeleznik, 2015b:521). The physical appearance of MicroceLac® is a white to almost white and odourless powder, with physical properties that includes an average angle of repose of 34°, a bulk and tapped density of 0.5 and 0.64 g/cm^3, a Hausner ratio of 1.16 and a mean loss of less than 1.5% mass on drying (Penz & Zeleznik, 2015b:521). MicroceLac® is used in pharmaceutical product manufacturing during direct compression as well as roller compaction as a diluent with additional binder properties (Penz & Zeleznik, 2015b:521). MicroceLac® was developed to be used during tabletting of APIs that exhibit poor powder flow or compressibility (Penz & Zeleznik, 2015b:522).

2.4.2.6 Tablettose® (Lactose monohydrate)

Tablettose® consists of only lactose monohydrate with a chemical composition of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate. Tablettose® is specifically used during tablet formulations and dry powder inhalations (Penz & Zeleznik, 2017a:513). Tablets manufactured using direct compression usually contains a smaller dose of API and is usually formulated using agglomerated/granulated lactose monohydrate which may contain traces of anhydrous lactose which is specifically used during direct compression (Penz & Zeleznik, 2017a:513; 2017b:507). The physical appearance of lactose monohydrate is a white, sweet-

tasting and odourless powder with physical properties that can be found in table 2.4 (Penz & Zeleznik, 2017a:513). Tablettose® powder as well as the products manufactured with Tablettose® should be stored in a cool, dry and odourless container (Penz & Zeleznik, 2017a:514). The reason for these storage conditions is that lactose tends to absorb odours from its surroundings, form mould growth and change in colouration when conditions are warm and humid (Penz & Zeleznik, 2017a:514). The use of products containing lactose, may cause symptoms like diarrhoea in people who are lactose intolerant. Products containing more than three grams of lactose is especially likely to cause these adverse effects (Penz & Zeleznik, 2017a:515,517).

Table 2.4: Physical properties of the different Tablettose® formulations as well as lactose monohydrate in general (Penz & Zeleznik, 2017a:513-515).

	Bulk density (g/cm^3)	**Tapped density (g/cm^3)**	**Moisture content (%)**
Tablettose 70®	0.55	0.67	-
Tablettose 80®	0.61	0.74	-
Tablettose 100®	0.57	0.69	-
Lactose monohydrate in general	-	-	4.5 – 5.5

2.4.2.7 Tricalcium citrate (TCC)

Tricalcium citrate was previously used as a calcium source in the pharmaceutical industry (Hagelstein *et al.*, 2018:1631). During the search for a diluent - which exhibit good compression characteristics while binding with brittle fragmentation as an alternative to microcrystalline cellulose - lead to the study of TCC (Hagelstein *et al.*, 2018:1632). Two types of TCC are available, namely TCCth (tricalcium citrate tetrahydrate) and TCCah (tricalcium citrate anhydrate) (Hagelstein *et al.*, 2018:1632). TCC's physical appearance can be described as a white powder which is poorly soluble in water (Hagelstein *et al.*, 2018:1362). A chemical analysis has shown that TCC is slightly acidic with a pH of around 5.7 (Hagelstein *et al.*, 2018:1632). An analysis of TCC done by Hagelstein *et al.* (2018) and the notable results are shown in table 2.5. TCC was found to express a linear tensile strength increase as compression force increased (Hagelstein *et al.*, 2018:1634). The data of tensile strength's relation to compression force can be found in figure 2.3. An interesting characteristic of TCC is that it expresses no notable difference in tensile strength while using an internal lubricant compared to an external lubricant (Hagelstein *et al.*, 2018:1634).

Table 2.5: Properties of TCC as presented by Hagelstein *et al.* (2018:1633-1634)

TCC Property	Value
Particle size	± 135 µm
Bulk density	± 0.63 g.cm^{-3}
Tapped density	± 0.70 g.cm^{-3}
Hausner ratio	± 1.11
Carr's index	± 10.0
True density	1.9550 ± 0.0081 g.cm^{-3}

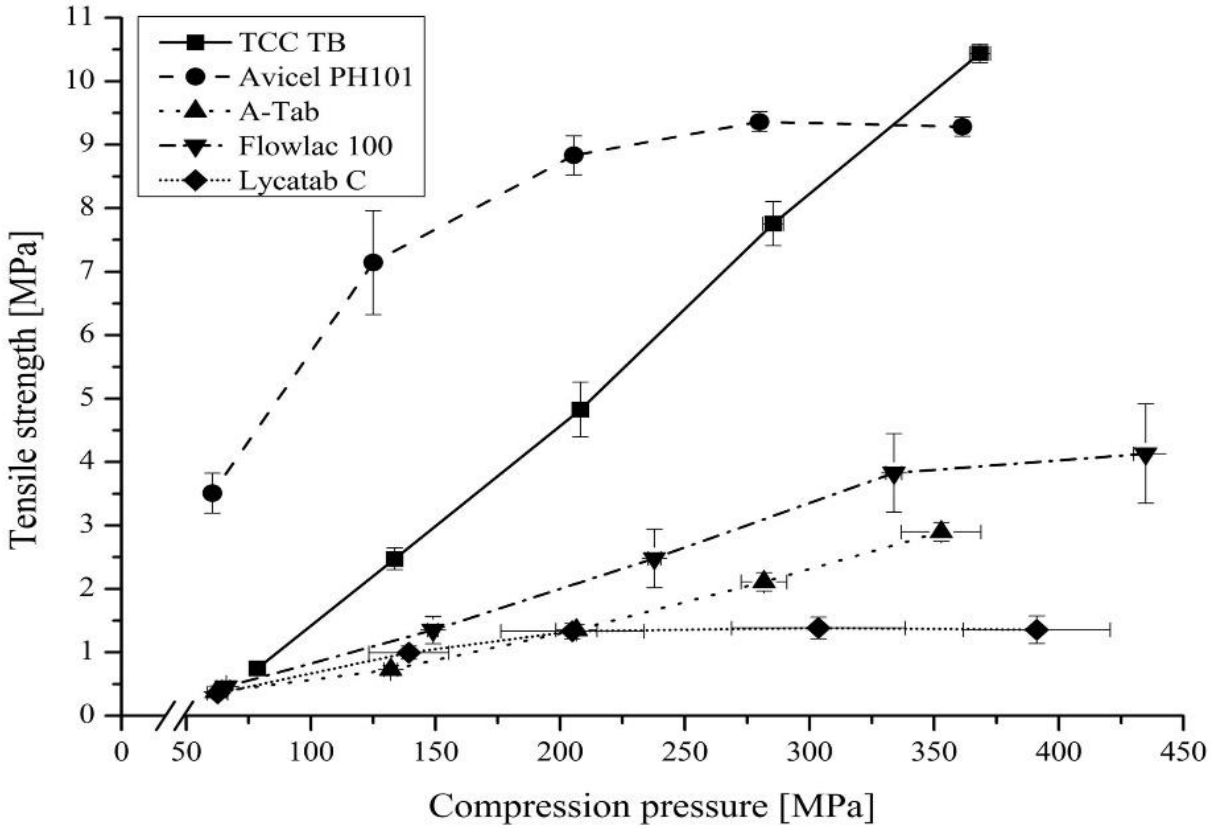

Figure 2.3: Relationship between compression force and tensile strength of tricalcium citrate (TCC) vs various other diluents (Hagelstein *et al.*, 2018:1635).

2.4.3 Active Pharmaceutical Ingredients (APIs)

The API may be argued to be the most important ingredient within the pharmaceutical tablet formulation, because without an API, the manufactured tablet would not provide any therapeutic effect. Being an ingredient added to the powder mixture, the API influence the mixture's physical properties such as compressibility and powder flow (Suñé-Negre *et al.*, 2011). It is therefore important to research the specific API's properties as well as the effect of those properties on the tabletting process (Singh & Kumar, 2012:87).

APIs such as paracetamol, furosemide and pyridoxine, have flowability and compressibility characteristics that is unsuitable for direct compression without the addition of a corrective excipient (Scholtz *et al.*, 2017:227-228; Singh & Kumar, 2012:91). These APIs are in general use for commonly occurring medical conditions. The reason why these APIs were specifically chosen were that they are readily available while also being known as problem APIs with regard to their ability to be formulated into directly compressed tablets.

2.4.3.1 Paracetamol

Paracetamol is an API used for the treatment of pain. Paracetamol is commonly available in the form of oral tablets. The physical properties of paracetamol, especially the poor powder flow and compressibility, makes paracetamol a challenging API with regard to tablet formulation. This is proven by SeDeM EDS studies that resulted in IP, IPP and IGC results of 0.50, 4.22 and 0.69 respectively (Singh & Kumar, 2012:91). These results as well as the SeDeM diagram given in figure 2.4, clearly indicate that paracetamol is a poor flowing powder with poor compression characteristics (Singh & Kumar, 2012:90-92). To compensate for these poor powder properties, other suitable excipients should be added to the formulation especially when using direct compression where the die filling is dependent on gravitational powder feeding (Singh & Kumar, 2012:92).

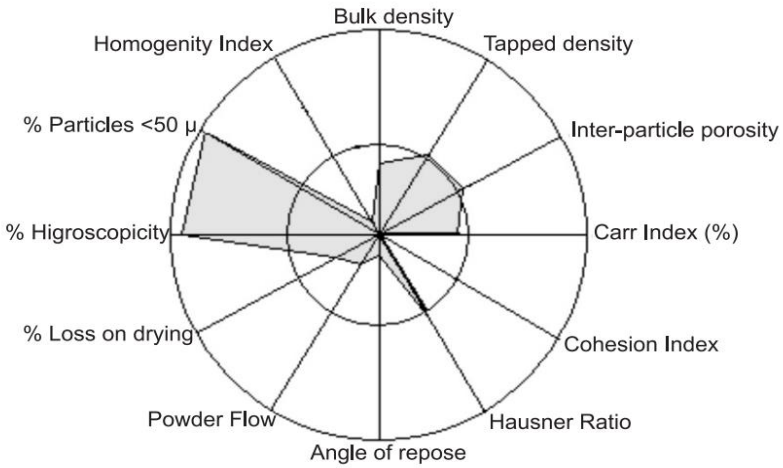

Figure 2.4: SeDeM EDS diagram for paracetamol (Singh & Kumar, 2012:89)

2.4.3.2 Furosemide

Furosemide is a portent diuretic used for treating conditions like oedema and hypertension (Rossiter *et al.*, 2016:148-149). Furosemide is usually formulated into tablets for oral administration. Studies done by Scholtz *et al.* (2017), showed that furosemide, like

paracetamol possesses poor powder flow properties as can be seen in figure 2.5. With IP, IPP and IGC values of 0.50, 5.25 and 5.00 respectively, furosemide's compression potential should be suitable for direct compression (Scholtz *et al.*, 2017:227). However, furosemide exhibits very poor flow characteristics and these characteristics result in poor die filling during tablet manufacturing (Scholtz *et al.*, 2017:227-228).

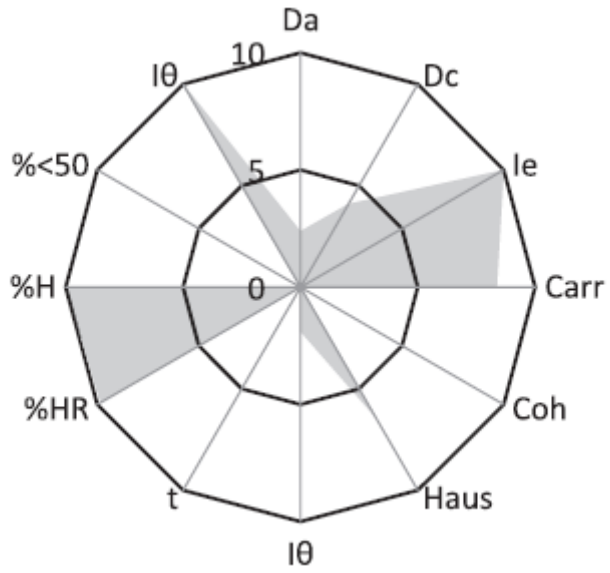

Figure 2.5: SeDeM EDS diagram for furosemide (Scholtz *et al.*, 2017:228)

2.4.3.3 Pyridoxine

Studies performed on pyridoxine show that the API also has very poor powder flow as well as a very high amount of particles smaller than 50 µm as can be seen in figure 2.6 (Scholtz *et al.*, 2017:227). Pyridoxine also has a cohesion index of 1.6 which is lower than the accepted value for SeDeM (Scholtz et al., 2017:228). The IP, IPP and IGC values of pyridoxine is 0.67, 5.34 and 5.08 respectively which would render the API suitable for direct compression by SeDeM EDS standards (Scholtz et al., 2017:228).

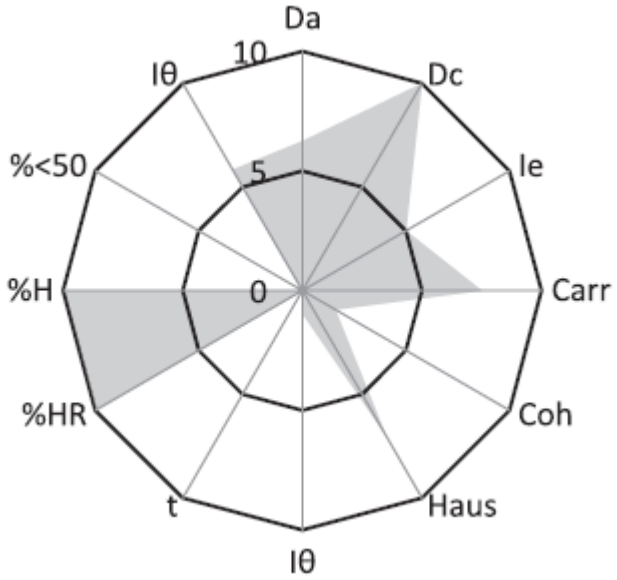

Figure 2.6: SeDeM EDS diagram for pyridoxine (Scholtz *et al.*, 2017:228)

2.5 Summary

While there are many different methods of delivering pharmaceutical products into the systemic circulation, the oral route of drug administration is still the most popular today. This route includes several dosage forms of which tablets are most commonly used (Bhutani *et al.*, 2021:23). During the tablet manufacturing process, pharmaceutical companies have a choice of several different manufacturing methods including but not limited to direct compression and granulation, each with its own advantages as well as disadvantages (Šantl *et al.*, 2011:131). One aspect that all these methods have in common is that there has to be a pharmaceutical powder mixture available to be compressed into tablets. These pharmaceutical powder mixtures usually consist of different excipients and an API mixed together, to form a nearly homogenous blend (Abrantes *et al.*, 2016:2019). Henceforth stems the problem of potential unsatisfactory physical properties of these powders to produce acceptable tablets, such as poor flowability. The bulk of solid oral pharmaceutical formulations usually consists of a filler such as Emcompress® or tricalcium citrate together with API and other excipients. Some manufacturing methods attempts to correct powder flow. For example, granulation of powders improves their flowability, but not all problems can be solved this way (Bhowmik *et al.*, 2014:24369). To solve problems associated with the direct compression method of tablet manufacture, additional excipients with corrective properties can be added to the powder mixture. Traditionally, the amount of each excipient to be added were determined by trial and error, therefore scientific approaches have been developed to improve this process. For example, the quality by design approach called SeDeM EDS was developed.

The SeDeM EDS provides information about a powder's ability to be compressed into tablets by means of direct compression (Suñé-Negre *et al.*, 2011:464). It is also able to make predictions about the amount of corrective excipient that needs to be added to transform problematic API powders, such as furosemide and paracetamol, into powder mixtures capable of being compressed into tablets (Dai *et al.*, 2019:521). To perform the SeDeM EDS analysis, certain properties of a powder, such as the bulk and tapped densities as well as particle size analysis, must be known or should be determined experimentally (Suñé-Negre *et al.*, 2011:465).

Excipients such as fillers have a dilution potential, which refers to the maximum amount of API that can be incorporated into a tablet, while still complying with the official quality tests, as described in an official pharmacopoeia such as the BP (Chavan *et al.*, 2018:60-63; Habib *et al.*, 1996:206). The dilution potential is determined experimentally by mixing the powders in different ratios and then evaluate tablets compressed from these powders. The dilution potential of fillers differs for each API.

CHAPTER 3:
MATERIALS AND METHODS

3.1 Introduction

As previously discussed, tablets are one of the most popular pharmaceutical dosage forms for drug administration. There are various methods that can be employed to formulate and manufacture tablets. These methods include direct compression as well as dry- and wet granulation (Šantl *et al.*, 2011:131). Each method of tablet manufacturing has its own advantages as well as disadvantages. Some of the advantages of direct compression over wet granulation is that APIs that are moisture and heat labile can be manufactured into tablets using this method (Šantl *et al.*, 2011:131). Direct compression also has the advantage of being an inherently continuous method (Van Snick *et al.*, 2017:391). The advantage of direct compression being a continuous method is that it is possible to avoid certain problems, which may occur during the upscaling process (Leuenberger, 2003:225-226; Van Snick *et al.*, 2017:391-392). When tabletting via the direct compression method, the individual excipients' properties tend to have a more pronounced influence on the properties of the resulting powder mixture when compared to other manufacturing methods such as wet granulation (Dai *et al.*, 2019:518). Traditionally, pharmaceutical powder mixtures intended for tabletting were designed and refined via trial-and-error as well as conducting experiments by changing one variable at a time.

The SeDeM EDS was developed as a way of accelerating this process with less material waste, by identifying excipients that may potentially be problematic during the tabletting phase (Dai *et al.*, 2019:518; Sune-Negre *et al.*, 2008:1029). The SeDeM EDS also aims to provide a way to correct the problematic nature of said excipients by means of adding a corrective excipient (Dai *et al.*, 2019:521; Sune-Negre *et al.*, 2008:1029; Suñé-Negre *et al.*, 2011:464-466). To use the SeDeM EDS, there must, however, be powder flow data about the specific excipient available or the required data must be collected. In this study, tricalcium citrate (TCC), which is relatively new to the pharmaceutical excipient world, has been characterised via SeDeM EDS and compared to the characteristics of other commercially available filler materials including Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate. This chapter provides the methods of characterising tricalcium citrate according to the SeDeM EDS as well as other commonly used directly compressible fillers such as Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, and Tablettose®. This chapter also provides the methods used to categorise

tricalcium citrate's dilution potential as a filler using furosemide, paracetamol, and pyridoxine as APIs, which was compared to that of the other filler materials.

3.2 Materials

The materials used in this study are listed in table 3.1.

Table 3.1: List of materials

Material	Manufacturer	Batch Number
Avicel® PH200	FMC International, Cork, Ireland	M939 C
CombiLac®	MEGGLE Group, Wasserburg, Germany	L100060516A535
Emcompress®	Penwest, West Midlands, UK	D04A
FlowLac® 100	MEGGLE Group, Wasserburg, Germany	L 1408
Furosemide	Suleshvari Pharma, Gujarat, India	18/FRS/001
MicroceLac® 100	MEGGLE Group, Wasserburg, Germany	L 1411
Paracetamol	SRI Krishna Pharmaceuticals Limited, Hyderabad, India	0815/07
Pyridoxine hydrochloride	Huazhong Pharma, Cape Town, South Africa	Y032021103046
Tablettose® 80	MEGGLE Group, Wasserburg, Germany	L 1409
Tricalcium citrate	Jungbunlauer, Ladenburg, Germany	3051454/07.24

3.3 Experimental layout

This study was completed in 3 phases consisting of SeDeM EDS analysis, corrective excipient calculations and determination and comparison of dilution potential. The flow of these three phases is given in figure 3.1 to figure 3.3.

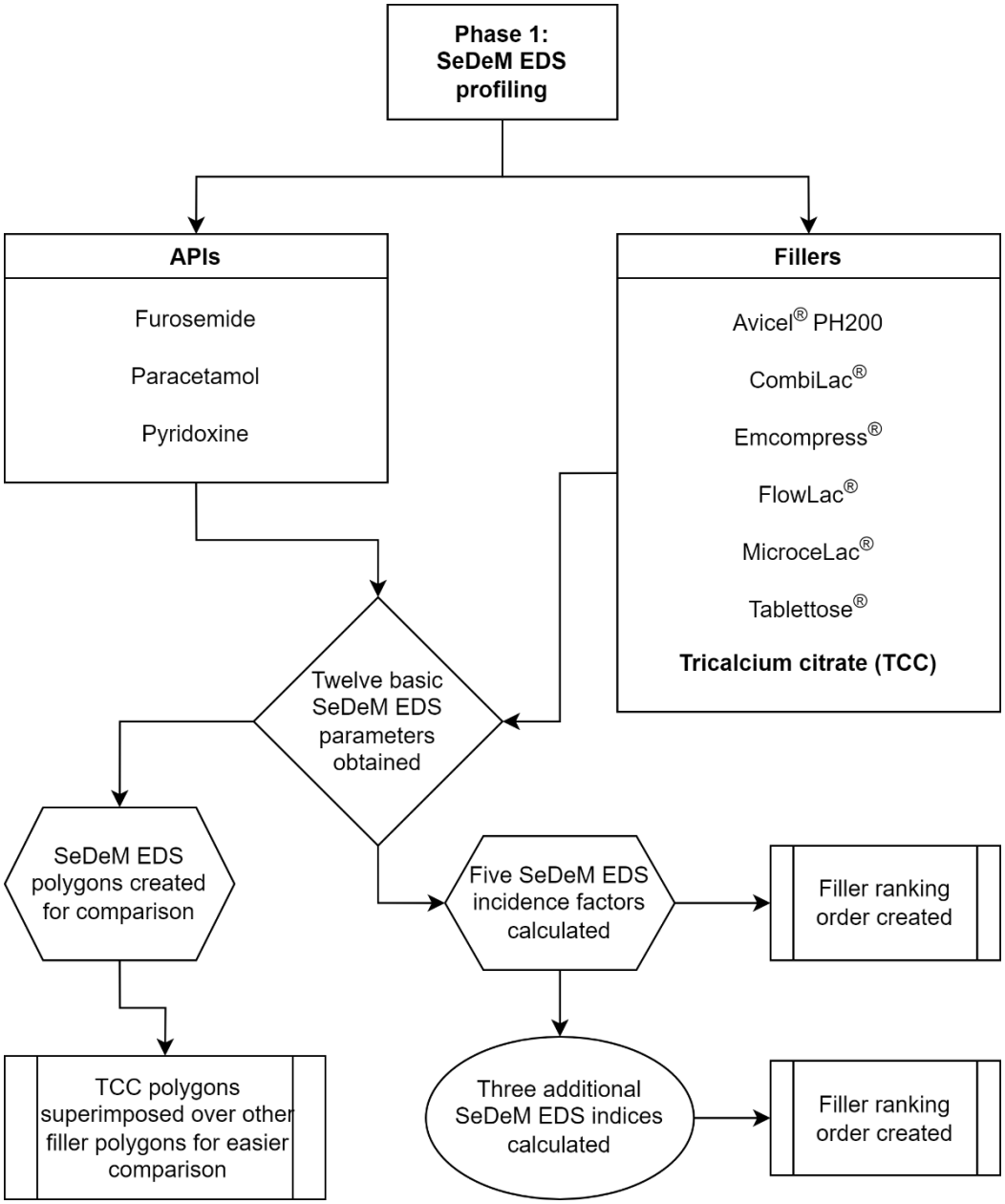

Figure 3.1: Experimental flow of phase 1 (SeDeM EDS comparison of directly compressible fillers)

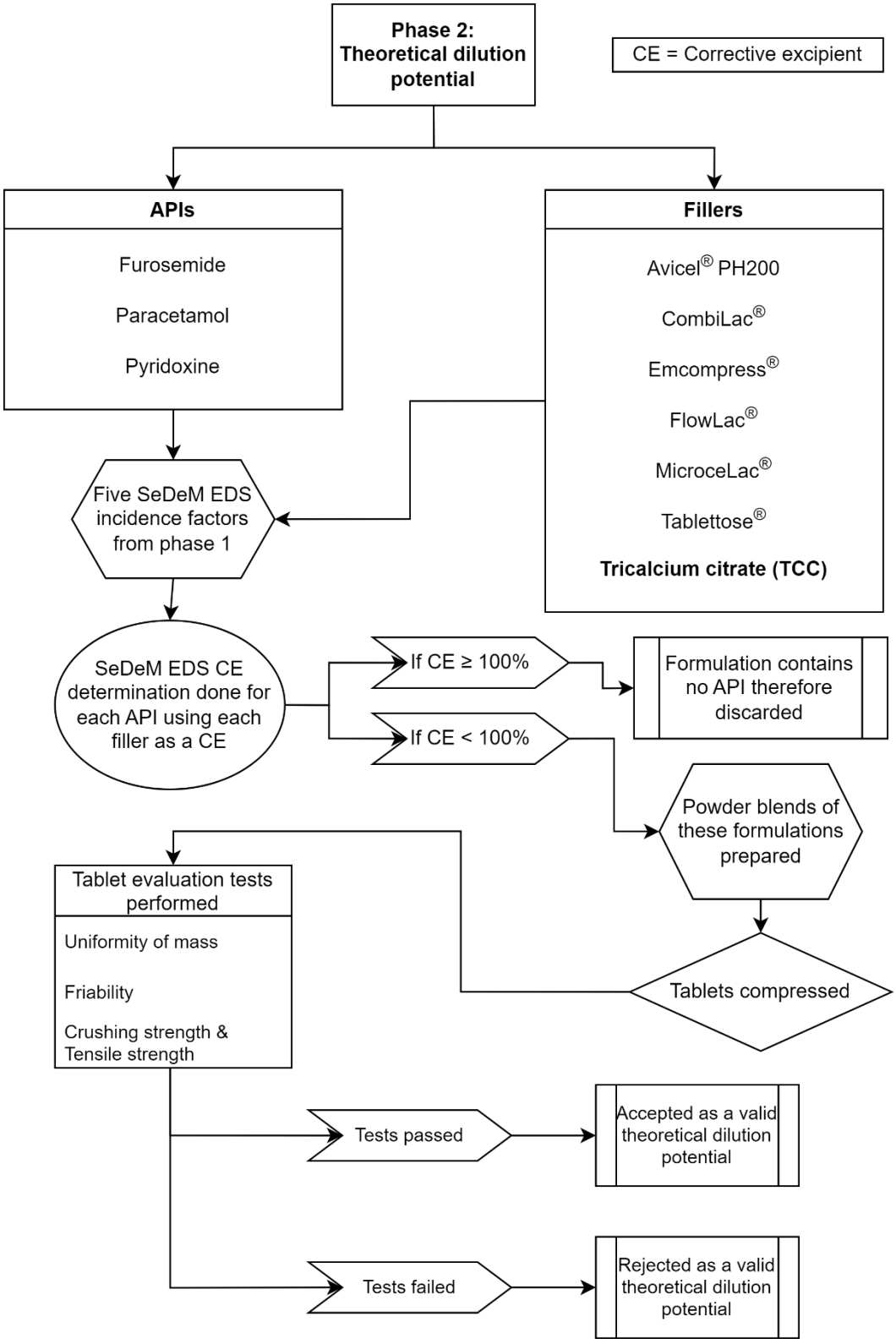

Figure 3.2: Experimental flow of phase 2 (Theoretical dilution potential according to SeDeM EDS corrective excipient predictions)

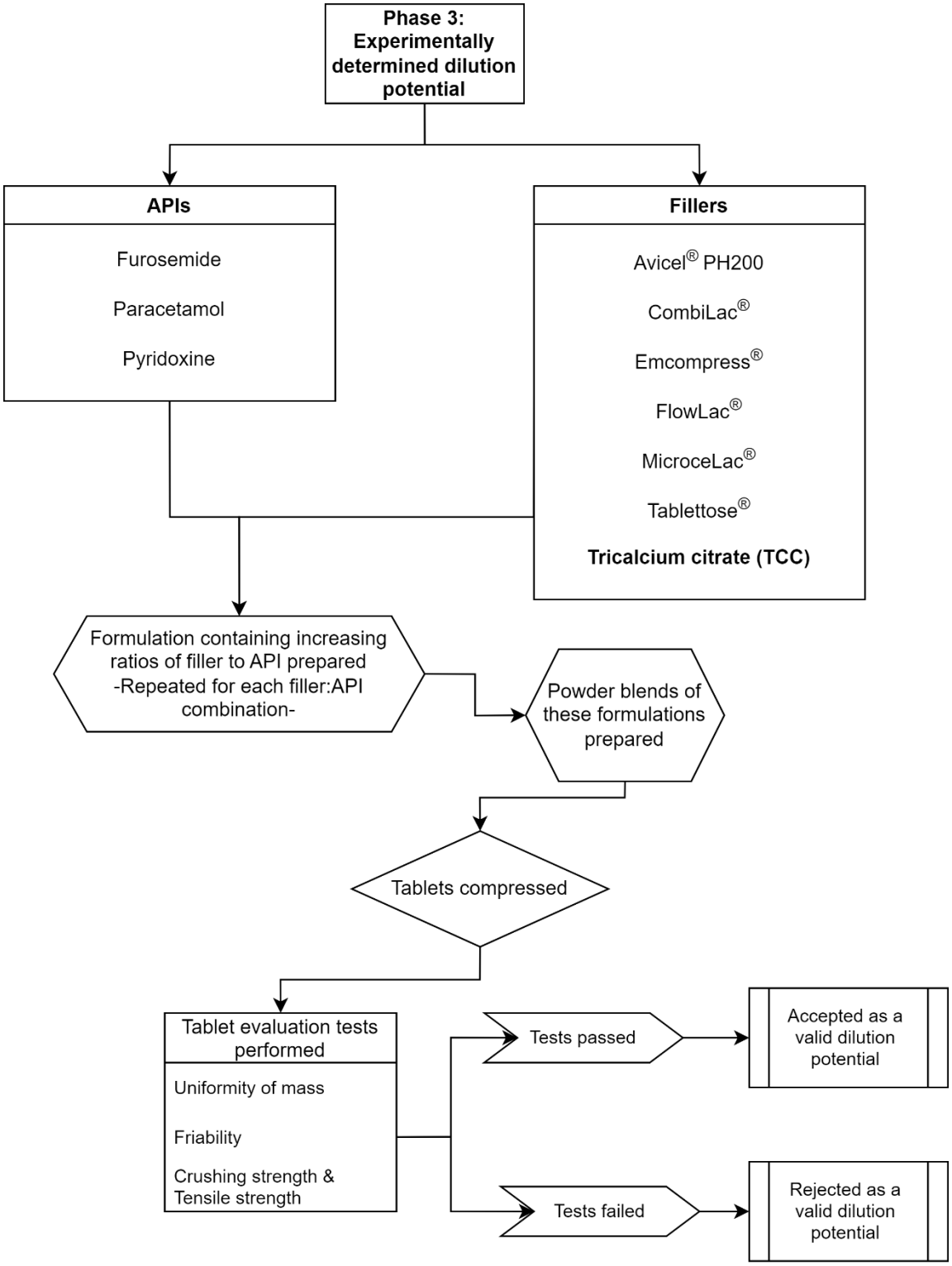

Figure 3.3: Experimental flow of phase 3 (Experimental determination of dilution potential)

The methods used to determine each aspect of experimental phases one to three as shown in figure 3.1 to 3.3, are detailed in the following sections of this chapter.

3.4 Phase 1: SeDeM Expert Diagram System

The SeDeM EDS system was developed to categorise powders and powder mixtures according to their suitability for direct compression. It takes several properties of these powders into consideration such as their flowability and compressibility (Perez *et al.*, 2006:351-352; Suñé-Negre *et al.*, 2011:464-465). The following subsections provide the methods used to characterise powders according to the SeDeM EDS.

3.4.1 Twelve basic SeDeM EDS parameters

The SeDeM EDS consists of twelve basic parameters, which was used to classify the fillers and APIs investigated in this study, according to their SeDeM EDS profiles. These twelve parameters include bulk density, tapped density, cohesion index, angle of repose, powder flow rate, loss on drying, hygroscopicity, homogeneity index, percentage of particles smaller than 50 µm, the inter-particle porosity, Carr's index and Hausner ratio (Sune-Negre *et al.*, 2008:1030). To characterise the different fillers and APIs in terms of the SeDeM EDS, 100 g samples of each individual filler and API was weighed using an analytical balance (Zeiss, Oberkochen, Germany) and weighing vessels, and then used to determine the twelve basic SeDeM EDS parameters. The methods that were used to determine these different parameters applicable to the SeDeM EDS, will be discussed in the following subsections.

3.4.1.1 Bulk density

The bulk density (D_a) of each individual filler and API was determined by weighing a fixed amount (100 g) of the specific powder and measuring the volume displaced by that predetermined amount of powder. The volume was measured by pouring the powder into a graduated measuring cylinder and noting the volume that the powder displaced (BP, 2021). The equation to calculate the bulk density of a powder is given in equation 3.1.

$$D_a = {}^{m}/_{V_0} \qquad \text{Eq. 3.1}$$

Where D_a represents bulk density, m the weight of the powder sample and V_0 the volume occupied by the untapped powder (BP, 2021).

3.4.1.2 Tapped density

The tapped density of each individual filler and API was then determined by fixing the graduated measuring cylinder, containing the individual powder, to an Erweka® SVM 223 tapped density tester (Erweka ® GmbH, Heusenstamm, Germany). After 1250 taps, the resulting volume of the powder was taken and if the difference between the previous

measurement and the new measurement was more than 2 ml, the powder was tapped for an additional 1250 taps. This was repeated until the difference in volume was less than 2 ml, whereafter the final measurement was taken, and the tapped density calculated (BP, 2021; Perez *et al.*, 2006:352). The equation used to calculate the tapped density is given in equation 3.2.

$$D_c = {}^{m}/_{V_f} \qquad \text{Eq. 3.2}$$

Where D_c represents the tapped density, m the weight of the powder sample and V_f the final volume of the tapped powder sample (BP, 2021).

3.4.1.3 Cohesion index

The cohesion index of each individual filler and API was determined by compressing tablets on a Korsch® XP1 single punch tablet press (Korsch®, Berlin, Germany). The tablets were compressed at the maximum force that still yielded acceptable tablets according to the BP's (2021) specification of friability and uniformity of mass. The crushing strength of these tablets were determined on a tablet hardness tester (Erweka® TBH 425, Heusenstamm, Germany). The average results of 10 tablets was taken as the cohesion index of the specific powder (Perez *et al.*, 2006:352).

3.4.1.4 Angle of repose

To determine the angle of repose of each individual filler and API, each powder (100 g) was placed into a smooth metal funnel on a pre-prepared base with a stand. The powders were then allowed to flow through the funnel with a diameter of 25 mm onto the base from a fixed height, whereafter the diameter and the height of the resulting powder cone were measured (BP, 2021). The angle of repose was then calculated for each powder using equation 3.3.

$$\alpha = \tan^{-1}\frac{h}{r} \qquad \text{Eq. 3.3}$$

Where α represents the angle of repose in degrees, h the height of the powder cone in mm and r the radius of the powder cone in mm (BP, 2021).

3.4.1.5 Powder flow rate

The flowability of each individual filler and API was determined by taking a fixed amount of each powder (100 g) and allowing it to flow through a fixed size funnel (15 mm diameter). The time it took for the powder to completely drain from the funnel was measured and used to calculate a flow rate. This value was presented in grams per second (g/s). An Erweka® powder

and granulate flow tester (Erweka®, Heusenstamm, Germany) was used to determine the flow rate of each powder (Perez *et al.*, 2006:353). This value, however, was not used in the SeDeM EDS calculations and was converted to the time it took the powder to completely drain from the funnel. This conversion was done using equation 3.4.

$$t = {}^{m}/_{t''} \qquad \text{Eq. 3.4}$$

Where t represents the time in seconds, m the powder mass in grams and t˝ the flow rate in grams per second.

3.4.1.6 Loss on drying

Loss on drying represents the amount of weight lost due to evaporation of moisture from a powder. To determine this amount of mass lost, a powder sample of known mass, from each individual filler and API, was placed into a glass container. The height of the powder in the container did not exceed 1 cm to ensure even heating of all the particles present in the powder sample. These containers were then placed into an Ecoterm® 972 (Labotec, South Africa) oven, at 105± 2°C for 24 h. After removing the samples from the oven, the weights were measured again and the mass loss expressed as the percentage mass lost on drying using equation 3.5 (Perez *et al.*, 2006:353).

$$\%HR = \frac{m_0 - m_f}{m_0} * 100 \qquad \text{Eq. 3.5}$$

Where %HR represents the percentage weight loss, m_0 the weight of the powder sample before drying and m_f the weight of the powder sample after drying (Dai *et al.,* 2019:520).

3.4.1.7 Hygroscopicity

Hygroscopicity represents the ability of a powder to absorb moisture from the surrounding atmosphere. To determine the amount of moisture absorbed, powder samples of each individual filler and API, with a known mass, were placed in a climate chamber (Model KBF 240, Binder® GmbH, Tuttlingen, Germany) with a temperature of 22 ± 2°C and a relative humidity of 76 ± 2%. The weight of each sample was measured after 24 h and the change in mass expressed as a percentage using equation 3.6 (Perez *et al.*, 2006:353). This represented the hygroscopicity of the powder.

$$\%H = \frac{m_f - m_0}{m_0} * 100$$ Eq. 3.6

Where %H represents the hygroscopicity of the powder, m_0 the weight of the powder sample before climatising and m_f the weight of the powder sample after climatising (Dai *et al.,* 2019:520).

3.4.1.8 Homogeneity index

To calculate the homogeneity index, each individual filler and API's particle size distribution was analysed using a Malvern® mastersizer 3000 (Malvern® Panalytical Ltd, Malvern, United Kingdom). The homogeneity index was then calculated using the particle size data and equation 3.7.

$$I\theta = \frac{F_m}{\begin{array}{c}100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m)F_{m+1} + \\ (d_m - d_{m-2})F_{m-2} + \cdots + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}\end{array}}$$ Eq. 3.7

Where Iθ represents the homogeneity index, F_m the percentage of particles in the majority range, F_{m-1} the percentage of particles in the range just below the majority range, F_{m+1} the percentage of particles in the range just above the majority range, d_m the diameter of the particles in the majority range, d_{m-1} the diameter of the particles in the range just below the majority range, d_{m+1} the diameter of the particles in the range just above the majority range, and n the modifier applied to specify the number of ranges removed from the majority range(Perez *et al.*, 2006:353).

3.4.1.9 Percentage of particles smaller than 50 µm

The percentage of particles smaller than 50 µm were extrapolated from the data obtained with the Malvern® mastersizer 3000 (Malvern® Panalytical Ltd, Malvern, United Kingdom) while performing the homogeneity index experiment. These determinations were done for each individual filler and API.

3.4.1.10 Inter-particle porosity

The inter-particle porosity represents the void spaces between the particles of a powder and was calculated using the tapped and bulk densities according to equation 3.8 for each individual filler and API tested in this study.

$$Ie = (D_C - D_a) / (D_c * D_a)$$ Eq. 3.8

Where Ie represents the inter-particle porosity, D_c the tapped density and D_a the bulk density (Dai *et al.*, 2019:520).

3.4.1.11 Carr's index

Carr's index, also known as the compressibility index, measures a powder's compressibility percentage and was calculated using equation 3.9 (Dai *et al.*, 2019:520; Khan *et al.*, 2022:3). This parameter was calculated for each filler and API individually.

$$IC = \left(\frac{D_c - D_a}{D_c}\right) * 100 \qquad \text{Eq. 3.9}$$

Where IC represents Carr's index, D_c the powder's tapped density, and D_a the powder's bulk density (Dai *et al.*, 2019:520).

3.4.1.12 Hausner ratio

The Hausner ratio provides an indication of the friction between powder particles (Khan *et al.*, 2022:3) and was calculated using equation 3.10 for each individual filler and API tested in this study.

$$IH = \frac{D_c}{D_a} \qquad \text{Eq. 3.10}$$

Where IH represents the Hausner ratio, D_c the tapped density and D_a the bulk density of the powder sample (Dai *et al.*, 2019:520).

3.4.2 Additional SeDeM EDS factors and incidences

The twelve basic parameters of the SeDeM EDS analyses were consequently used to calculate five incidence factors including a dimensional, compressibility, flowability, lubricity/stability, and lubricity/stability incidence factor, for each filler and API tested in this study, respectively (Sune-Negre *et al.*, 2008:1031). The data obtained from the SeDeM EDS analyses were also used to calculate three additional incidences namely the index of good compressibility (IGC), index of profile parameter (IPP), and the index parameter (IP) (Sune-Negre *et al.*, 2008:468-469).

3.4.2.1 Dimensional factor

To calculate the dimensional factor of the each individual filler and API, the bulk and tapped densities of the powders were taken and converted into radial values using the equations

found in table 3.2 (Sune-Negre *et al.*, 2008:1032). The mean of these radial values represented the dimensional factor.

3.4.2.2 Compressibility factor

To determine the compressibility factor for each filler and API tested in this study, the inter particle porosity, Carr's index and cohesion index was determined as stated in section 3.4.1. The compressibility factor was then calculated by converting Carr's index value, inter particle porosity value and the cohesion index value to their radial values with the conversion equations in table 3.2. The mean of these three converted values represented the compressibility factor for the corresponding powder (Sune-Negre *et al.*, 2008:1031).

3.4.2.3 Flowability factor

The flowability factor for each individual filler and API, was calculated by determining the mean of the radial values of the Hausner ratio, angle of repone and the powder flow time as determined in section 3.4.1 (Sune-Negre *et al.*, 2008:1031). The radius values were obtained through using the radius equations given in table 3.2. The mean radius value of these parameters represented the flowability factor.

3.4.2.4 Lubricity/Stability factor

The lubricity/stability factor was calculated using the loss on drying and hygroscopicity data of each individual filler and API tested in this study, respectively (Perez *et al.*, 2006:352). These two values were first converted into their radial values using the corresponding equation that can be found in table 3.2. The average of these radial values was calculated, and represented the lubricity/stability factor of the specific filler or API (Sune-Negre *et al.*, 2008:1031).

3.4.2.5 Lubricity/Dosage factor

To obtain the lubricity/dosage factor, each powder's homogeneity index and percentage of particles smaller than 50 µm were determined. Both these values were then converted into their radial values using the corresponding equation from table 3.2. The mean of these radial values was then calculated, and it represented the lubricity/dosage factor for each filler and APIs respectively.

Table 3.2: SeDeM EDS factors and their corresponding parameters and radial equations (Sune-Negre *et al.*, 2008:1031)

Factor	Parameters	Symbol	Radius equations
Dimension	Bulk density	D_a	10 x value
	Tapped density	D_c	10 x value
Compressibility	Inter-Particle porosity	Ie	(10 x value) / 1.2
	Carr's Index	IC	Value / 5
	Cohesion index	Icd	Value / 20
Flowability	Hausner ratio	IH	10 – (10 x value / 3)
	Angle of repose	α	10 – (value / 5)
	Powder flow	t	10 – (value / 2)
Lubricity/Stability	Loss on drying	%HR	10 – value
	Hygroscopicity	%H	10 – (value / 2)
Lubricity/Dosage	Particles < 50 µm	$\%P_f$	10 – (value / 5)
	Homogeneity index	Iθ	500 x value

3.4.2.6 Index of good compressibility, Index of profile parameter, Index parameter

The index parameter (IP) was calculated using equation 3.11, while the index of profile parameter (IPP) and the index of good compressibility (IGC) were calculated using equation 3.12 and equation 3.13 respectively. These indices were obtained for each individual filler and API. The results of these calculations were then analysed as follows. For the powder to be able to be directly compressed according to the SeDeM EDS, the IGC and IPP values should be greater than 5, while the IP should be greater than 0.5 (Perez *et al.*, 2006:354).

$$IP = {}^{N^0P \geq 5}/_{N^0Pt} \qquad \text{Eq. 3.11}$$

$$IPP = {}^{\sum radius\ values}/_{N^0Pt} \qquad \text{Eq. 3.12}$$

$$IGC = IPP * {}^{Polygon\ area}/_{Circle\ area} \qquad \text{Eq. 3.13}$$

Where $N^0P \geq 5$ represents the number of parameters which radius values exceeded 5 and N^0Pt represents the number of parameters tested (Dai, *et al.,* 2019: 521).

3.4.3 Comparison of fillers according to their SeDeM EDS profiles

Using the SeDeM EDS data obtained from the previous subsections, SeDeM EDS polygons, detailing the twelve basic parameters, were constructed for each filler and API for ease of comparison. Superimposed polygons of tricalcium citrate and each of the other fillers were also used to compare TCC with each of the other fillers.

The five SeDeM EDS incidence factors namely dimension, flowability, compressibility, lubricity/dosage, and lubricity/stability, as well as the three additional SeDeM EDS incidences (IP, IPP and IGC) were used to determine ranking orders for each individual filler tested in this study. These rankings were done based on the numerical value of each of the abovementioned factors.

3.5 Phase 2: Theoretical determination of dilution potential

The aim of dilution potential studies is to characterise powders, in this instance fillers, according to their ability to be diluted with an API, while still being able to produce tablets of acceptable pharmaceutical quality (Habib *et al.*, 1996:206; Salim *et al.*, 2022:182). The theoretical dilution potential of a filler can be linked to the corrective excipient calculated using the SeDeM EDS as described in the following subsections.

3.5.1 Calculating corrective excipients according to the SeDeM EDS

If a powder is deemed unsuitable for direct compression, a corrective excipient should be added to improve compressibility. If the SeDeM EDS parameter values for both the proposed corrective excipient and the unsuitable powder is known, the percentage corrective ingredient that should be added can be calculated using equation 3.14 (Suñé-Negre, *et al.,* 2008:1032). This percentage represents the total amount (% w/w) of the corrective excipient (filler) that needs to be added to the API in order to obtain a powder mixture with properties suitable for direct compression.

$$CP = 100 - \left(\frac{RE - R}{RE - RP} * 100\right) \qquad \text{Eq. 3.14}$$

Where CP represents the % corrective excipient to be added, RE the mean parameter radius value of the corrective excipient, R the mean parameter radius that should be obtained by the final powder mixture and RP the mean parameter radius value of the unsuitable powder (Suñé-Negre, *et al.,* 2008: 1032).

3.5.2 Using the SeDeM EDS corrective excipient to determine the theoretical dilution potential

For each one of the three APIs (furosemide, paracetamol, and pyridoxine), the percentage of each selected filler, needed to correct an unsuitable powder (in this study the different APIs) for direct compression was calculated using the method explained in section 3.5.1. In total, 21 of these calculations were performed for each API and filler combination corresponding to 21 powder formulations (mixtures). These calculated percentages of corrected excipient can be seen or considered as the theoretical dilution potential of each individual filler tested in this study.

To determine whether the calculated dilution potential represented a valid dilution potential, tablets were compressed for each of these formulations (21 formulations) according to the method as explained in section 3.7.1. If the theoretical dilution potential indicated that a concentration of filler ≥ 100% was needed to correct the unsuitable or deficient properties of the specific API, the formulation was deemed unsuitable for direct compression and was therefore not compressed. The reasoning behind this decision is based on the fact that a tablet containing ≥ 100% filler will in effect contain no API and will not be able to produce any therapeutical effect and would therefore not be practical to manufacture. After the tablets (which required less than 100% filler) were prepared, they were analysed according to the methods explained in section 3.7.2.

The results obtained from tablet analysis were then compared to the experimentally determined dilution potential, obtained according to the method explained in section 3.6, for each filler and API respectively. As previously stated, the percentage corrective excipient can be seen as a theoretical dilution potential for the respective filler and API. These theoretical dilution potential values were used to evaluate the accuracy of the dilution potential predicted by the SeDeM EDS when compared to the real experimentally determined dilution potential.

3.6 Phase 3: Experimental determination of true dilution potential

Determination of the true dilution potential was done by preparing powder mixtures of different concentrations of the APIs with each of the fillers tested in this study using the methodology described in subsection 3.6.1 (Haruna *et al.*, 2020:3). This true or real dilution potential was then compared to the theoretical dilution potential as predicted by the SeDeM EDS's corrective excipient calculation and the validity of the theoretically predicted dilution potential by the SeDeM EDS was thereby established.

3.6.1 Formulation of powder blends for determining dilution potential

For phase 3 of the study, several different powder blends were prepared, starting with a filler to API ratio of 100:0 and decreasing this ratio with increments of 10% (Haruna *et al.*, 2020:3). Upon mixing of these powder mixtures, tablets were compressed form these mixtures and these tablets were evaluated according to the methods and specifications described in section 3.7.2. The stepwise decreased increments of filler:API were prepared until powder mixtures rendered tablets that did not comply with the BP (2021) specifications. When the tablets failed to comply with the specifications of the evaluation tests, an increment of 5% was also tested in order to determine a more specific value for the dilution potential of the specific filler and API. All fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate) as well as the APIs (furosemide, paracetamol, and pyridoxine) that were evaluated in both phase 1 and phase 2 of the study were evaluated in phase 3 of the study. To experimentally determine the dilution potential of each individual filler, tablets were compressed using the method detailed in section 3.7.1.

3.6.2 Evaluation of tablet quality data to evaluate dilution potential results

To determine whether a specific formulation as described in section 3.5.2 (theoretical dilution potential) and 3.6.1 (true dilution potential) rendered an acceptable dilution potential, evaluation tests were performed on each tablet batch produced with the specific formulation according to the methods described in subsection 3.7.2. A dilution potential was deemed acceptable if tablets that were prepared from a particular powder mixture complied with the specifications of both the friability and uniformity of mass tests as specified by the BP (2021).

3.7 Manufacturing and evaluation of tablets used to determine dilution potential

To determine a filler's dilution potential, tablets were compressed using direct compression as explained in subsection 3.7.1. These tablets were evaluated using the methods as can be found in the BP (2021) and briefly explained in the subsection 3.7.2.

3.7.1 Direct compression of tablets from blended powder batches

As indicated in sections 3.5.2 and 3.6.1, powder mixtures were prepared consisting of a filler and an API. The ratio of filler to API was determined by the methods used to determine both the theoretical dilution potential (SeDeM EDS corrective excipient), as well as the experimental corrective excipient as was explained in section 3.5.2 and 3.6.1, respectively. These powder batches were prepared by weighing the specified ratio of each ingredient, making a total

powder mass of 100 g, on an analytical balance (Zeiss, Oberkochen, Germany), using weighing vessels. The ingredients of these batches were transferred to a glass jar, covered with parafilm, and secured by screwing the lid on the jar. The order in which these ingredients were added to the jar were as follows: first a half of the diluent, then the API, and lastly the second half of the diluent. The jar containing the unmixed powder was then secured in a Turbula T2C mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). Powder mixing was done for 5 min at a speed of 69 rpm. The goal during the mixing of powder batches was to ensure that the components of the final powder blend were distributed as homogenously as possible, throughout the mixture. It should, however, be noted that perfect homogeneity is practically impossible to obtain in powder mixtures (Bhowmik *et al.*, 2014:24370).

These powder blends were compressed into tablets, using a 12 mm punch and die set using a Korsch® XP1 single station tablet press (Korsch®, Berlin, Germany). The tablets were compressed at the maximum compression force possible. The tablets were then evaluated using the methods as described in the BP (2021) and briefly described in the following subsections.

3.7.2 Tablet evaluation

To determine the quality of the compressed tablets, a series of tests were performed on the tablets. These tests were conducted according to the methods and specifications of the BP after the compressed tablets were left to equilibrate for 24 h in order to allow their bonds to settle and therefore avoiding false test results (Salim *et al.*, 2022:177). These tests included uniformity of mass, friability, crushing strength and tensile strength (BP, 2021). While disintegration is also an official tablet evaluation method according to the BP (2021), it was not used to evaluate tablets during this study. Only the mechanical aspects of tablets, such as friability, uniformity of mass, and crushing strength evaluations were conducted.

3.7.2.1 Uniformity of mass

Uniformity of mass represents the deviation of a tablet's mass from the tablet batch's average mass. This variation was determined by selecting 20 random tablets and determining each individual tablet's weight on an analytical balance (Zeiss, Oberkochen, Germany). Before weighing the tablets, all excess dust was removed with a brush. The mean weight of the 20 tablets and the percentage deviation for each tablet from the mean tablet weight was calculated (BP, 2021). The accepted deviation percentage was then determined by using table 3.3. No tablet may deviate more than twice the accepted deviation percentage and only two

tablets may deviate from the accepted deviation percentage (BP, 2021; Chavan *et al.*, 2018:62)

Table 3.3: Accepted mass deviation for uncoated tablets (BP, 2021)

Average mass (mg)	Accepted deviation (%)
≤ 80	10
80 – 250	7.5
≥ 250	5

3.7.2.2 Friability

To determine the friability, the method as stipulated in the BP was followed. This method states that the amount of tablets to be used must be as close as possible to 6.5 g if an individual tablet weighs less than 650 mg (BP, 2021). Prior to weighing, the tablets were dusted. The mass of the tablets were determined and noted using an analytical balance (Zeiss, Oberkochen, Germany) and placed in a friabilator (Erweka®, Heusenstramm, Germany) which was operated at 25 rpm for 4 minutes for a total of 100 rotations (BP, 2021). After removing the tablets from the friabilator, the tablets were dusted again, and the weight determined and recorded. The percentage mass loss were calculated using equation 3.15 (Chavan *et al.*, 2018:62).

$$F = \frac{m_i - m_f}{m_i} \, x \, 100 \qquad \text{Eq. 3.15}$$

Where F represents the percentage mass loss, m_i represents the initial mass and m_f represents the final mass of the tablets (BP, 2021; Chavan *et al.*, 2018:62).

3.7.2.3 Crushing strength

The crushing strength test was performed to obtain the compressed tablets' resistance to being crushed, in other words the force needed to break the tablets (BP, 2021). To perform the test, 10 tablets were randomly selected and placed into a tablet hardness tester (Model TBH 425, Erweka®, Heusenstamm, Germany). The apparatus was set to determine the hardness, diameter, and thickness of the tablets. The results obtained were in Newton for the tablet hardness, and millimetres for tablet diameter as well as thickness. The mean hardness for 10 tablets were calculated.

3.7.2.4 Tensile strength

After the force needed to crush the tablets were determined, the tensile strength of the tablets was calculated. To determine the tensile strength of a tablet, the force needed to break the tablet, as well as the dimensions of the tablet were taken into consideration (Bereket & Admassu, 2021:11). The tensile strength of the tablets was calculated using equation 3.16. Equation 3.16 were used because the tablets were flat faced round tablets (Bereket & Admassu, 2021:13).

$$T = \frac{2\,F}{\pi\,d\,t} \qquad \text{Eq. 3.16}$$

Where T represents the tensile strength ($N.mm^{-2}$), t the thickness of the tablet (mm), d the diameter of the tablet (mm), and F the force needed to crush the tablet (N) (Bereket & Admassu, 2021:13).

3.8 Summary

Tablets are usually prepared from powder mixtures, which include pharmaceutical excipients as well as an API. The powders are mixed to produce a mixture as close as possible to a homogenous mixture (Bhowmik *et al.*, 2014:24370). To simplify the powder formulation procedure, the SeDeM EDS was developed. This system uses certain physical properties of the powders to predict their suitability to be directly compressed (Sune-Negre *et al.*, 2008:1029). The methods applicable to the SeDeM EDS were described to characterise the properties of different selected fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate), commonly used during direct compression of tablets as well as three different APIs (furosemide, paracetamol and pyridoxine) known for their poor flowability and tabletability.

Fillers and pharmaceutical mixtures intended to be combined with poorly compressible powders (for example APIs) for compression also have a property called dilution potential. Dilution potential refers to the maximum amount of a poorly compressible powder that can be incorporated into a mixture, while still maintaining the production of quality tablets (Salim *et al.*, 2022:174). This property is of notable importance to fillers since fillers make up the bulk of pharmaceutical powder mixtures intended for tabletting (Rojas *et al.*, 2013:17-18). The methods to determine and evaluate dilution potential were also discussed in this chapter. For each filler, the methods to determine the theoretical dilution potential, as predicted by the SeDeM EDS, and the true or real dilution potential were discussed.

CHAPTER 4:
RESULTS & DISCUSSION

4.1 Introduction

Delivery of therapeutic substances is commonly achieved through oral delivery. The most commonly used delivery system for this administration route is conventional tablets (Sun, 2011:483). This leads to tablets being one of the most produced dosage forms. Tablets as dosage form also have several advantages over other dosage forms such as an easily quantifiable dosage, per unit taken. This, however, only applies when the produced tablets are of high quality and complies with official criteria including uniformity of content, uniformity of tablet mass as well as adequate mechanical tablet strength (BP, 2021; Sun, 2011:483). There are currently three different production methods used to manufacture tablets from powders or powder mixtures. These methods include wet and dry granulation as well as direct compression (Leuenberger, 2003:225-226; Sun, 2011:483; Van Snick *et al.*, 2017:319). Continuous operation is also important for pharmaceutical manufacturing companies for it enables the benefits of smaller scale ups, reduced costs and faster product development (Van Snick *et al.*, 2017:319). Direct compression is ideal for this continuous process for it is an inherently continuous process with no need for granulation or spheronisation (Van Snick *et al.*, 2017:319). It is, however, important that the process is not interrupted by factors related to poor formulation of the powder mixture. This highlights the value of a scientific approach to formulation that is inherent to the SeDeM EDS. The SeDeM EDS provides information about a powder or a powder mixture's suitability to be directly compressed (Sune-Negre *et al.*, 2008:1029).

In this chapter the results obtained from the SeDeM EDS characterisation of the selected fillers (i.e., Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate (TCC)) as well as selected APIs (i.e., furosemide, paracetamol, and pyridoxine) will be provided and discussed. Based on the results presented it will be possible to compare TCC as filler to the other fillers regarding its potential as a direct compressible filler. The theoretical as well as the real dilution potential of each of the abovementioned fillers, will also be provided and discussed.

4.2 Phase 1: SeDeM analysis of powders and powder mixtures

As previously stated, SeDeM EDS analysis aims to give an indication of the likelihood of the success of a pharmaceutical powder, whether it be an excipient or API to be directly

compressed (Sune-Negre *et al.*, 2008:1029; Suñé-Negre *et al.*, 2011:464). The SeDeM EDS is also capable of providing information about the theoretical amount of a specific excipient (a corrective excipient), which should be added to a powder mixture with deficient properties in terms of powder flow or compressibility, to render the powder or powder mixture directly compressible (Sune-Negre *et al.*, 2008:1032). During this study, the parameters of the SeDeM EDS were determined for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and TCC, as well as furosemide, paracetamol, and pyridoxine. The results obtained for each of the twelve parameters can be seen in tables 4.1 and 4.2, while the converted SeDeM EDS radial values are represented in tables 4.3 and 4.4.

Table 4.1: Twelve basic SeDeM EDS parameters for fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and tricalcium citrate)

Parameter	Fillers						
	Avicel®	**Combi-Lac®**	**Emcom-press®**	**Flow-Lac®**	**Microce-Lac®**	**Tablet-tose®**	**Tricalcium citrate®**
Bulk density (g/cm^3)	0.375	0.502	0.909	0.610	0.521	0.713	0.516
Tapped density (g/cm^3)	0.448	0.618	1.199	0.774	0.623	0.923	0.677
Inter-particle porosity	0.433	0.373	0.266	0.347	0.339	0.319	0.306
Carr's index	16.233	18.736	21.174	21.172	17.645	22.752	17.165
Cohesion Index (N)	367.3	343.4	156.5	223.6	338.9	91.3	442.8
Hausner ratio	1.194	1.231	1.318	1.269	1.214	1.295	1.207
Angle of repose (°)	22.720	21.563	20.575	20.475	21.469	22.741	23.328
Flow rate (s)	8.499	7.000	4.000	8.100	7.667	5.300	7.433
Loss on drying (%)	5.531	2.664	2.675	0.299	1.824	0.316	5.713
Hygro-scopicity (%)	8.150	4.426	0.066	0.132	3.306	0.099	3.023
Particles < 50 µm (%)	6.430	18.46	17.39	29.67	16.22	4.86	6.810
Homogeneity index ($x10^{-3}$)	5.539	6.458	6.470	6.373	6.949	10.690	25.051

Table 4.2: Twelve basic SeDeM EDS parameters for APIs (furosemide, paracetamol, and pyridoxine)

Parameter	APIs		
	Furosemide	**Paracetamol**	**Pyridoxine**
Bulk density (g/cm^3)	0.329	0.401	0.592
Tapped density (g/cm^3)	0.512	0.728	0.820
Inter-particle porosity	1.087	1.118	0.469
Carr's index	35.749	44.871	27.792
Cohesion Index (N)	92.0	2.4	14.3
Hausner ratio	1.556	1.814	1.385
Angle of repose (°)	46.359	49.354	27.562
Flow rate (s)	∞	∞	∞
Loss on drying (%)	0.432	0.264	0.050
Hygroscopicity (%)	0.263	0.062	0.067
Particles < 50 µm (%)	64.94	61.25	12.22
Homogeneity index ($x10^{-3}$)	8.764	13.376	6.237

Where ∞ represents an undefined flow time due to no powder flow

Table 4.3: SeDeM EDS radial values for the basic parameters for fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and tricalcium citrate)

Parameter	Fillers						
	Avicel®	**Combi-Lac®**	**Emcom-press®**	**Flow-Lac®**	**Microce-Lac®**	**Tablet-tose®**	**Tricalcium citrate®**
Bulk density	3.752	5.020	9.094	6.100	5.208	7.128	5.607
Tapped density	4.479	6.177	10.000	7.739	6.323	9.228	6.768
Inter-particle porosity	3.606	3.110	2.215	2.892	2.824	2.660	2.551
Carr's index	3.247	3.747	4.835	4.234	3.529	4.550	3.433
Cohesion Index	10.000	10.000	7.825	10.000	10.000	4.565	10.000
Hausner ratio	6.021	5.898	5.604	5.771	5.952	5.685	5.976
Angle of repose	5.456	5.687	5.885	5.905	5.706	5.452	5.334
Flow rate	5.750	6.500	8.000	5.950	6.167	7.350	6.283
Loss on drying	4.469	7.336	7.325	9.701	8.175	9.684	4.286
Hygro-scopicity	5.925	7.787	9.967	9.934	8.347	9.950	8.489
Particles < 50 µm	8.714	6.308	6.522	4.066	6.756	9.028	8.638
Homogeneity index	2.769	3.229	3.235	3.186	3.475	5.345	10.000

Table 4.4: SeDeM EDS radial values for the basic parameters for APIs (furosemide, paracetamol, and pyridoxine)

Parameter	APIs		
	Furosemide	Paracetamol	Pyridoxine
Bulk density	3.290	4.014	5.919
Tapped density	5.120	7.281	8.197
Inter-particle porosity	9.055	9.315	3.913
Carr's index	7.150	8.974	5.558
Cohesion Index (N)	4.600	0.120	0.715
Hausner ratio	4.812	3.954	5.384
Angle of repose	0.728	0.129	4.488
Flow rate	0.000	0.000	0.000
Loss on drying	9.568	9.736	9.950
Hygroscopicity	9.868	9.969	9.967
Particles < 50 µm	0.000	0.000	7.556
Homogeneity index	4.382	6.688	3.118

4.2.2 SeDeM EDS profiles for fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and tricalcium citrate)

An advantage of the SeDeM EDS is that the parameter values as given in table 4.1 can be mathematically converted to radial values and used to construct a polygon for each powder or powder mixture. This has the advantage that a graphical overview of a powder profile can be obtained (Sune-Negre *et al.*, 2008:1032-1033). The passing criteria for each parameter according to the SeDeM EDS is a minimum radial value of five per parameter. Each filler and API were analysed, and the results are presented in figures 4.1 to 4.7 and figures 4.14 to 4.16.

4.2.2.1 Avicel® PH200

The SeDeM EDS profile for Avicel® PH200 can be seen in figure 4.1. When considering the parameters of Avicel® PH200, the bulk (3.752) and tapped (4.479) densities as well as the inter-particle porosity (3.606), Carr's index (3.247), loss on drying (4.469), and homogeneity index (2.769) did not achieve a SeDeM EDS radial value of ≥ 5. When comparing Avicel® PH200 to the other fillers tested, it was the only filler that did not obtain a passing SeDeM EDS radial value in the bulk and tapped density parameters. Avicel® PH200 obtained the second lowest value of all the fillers tested in the loss on drying parameter (4.469), having a mean moisture content of 5.531%. Avicel® PH200 also showed the highest hygroscopicity (5.952) of all the fillers tested with a mean moisture weight gain of 8.151% over 24 hours. Avicel® PH200 also obtained the lowest of all the fillers analysed in the homogeneity parameter (2.769). This is due to Avicel PH200®'s particles distributed over a greater range than the other fillers tested.

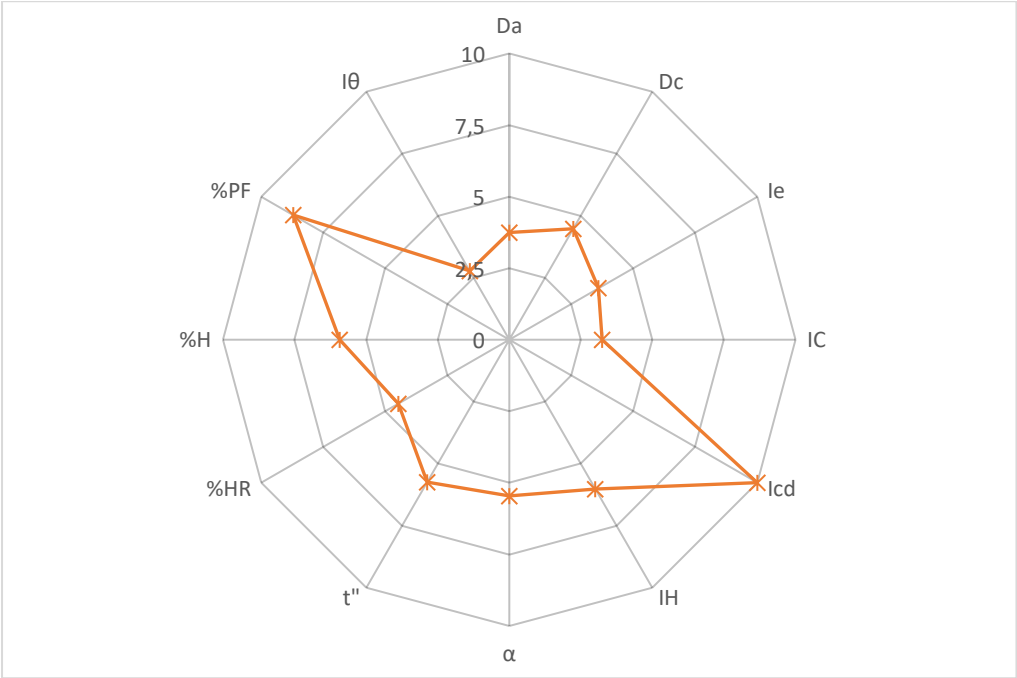

Figure 4.1: SeDeM EDS polygon representing Avicel® PH200

4.2.2.2 CombiLac

The SeDeM EDS profile of CombiLac® can be seen in figure 4.2. CombiLac® obtained a SeDeM EDS radial value of less than five, in three parameters, namely inter-particle porosity (3.11), Carr's index (3.743), and homogeneity index (3.229). The reason for these results can be linked to the difference between CombiLac's® bulk and tapped densities. A greater difference in densities results in higher radial values for both Carr's index and inter-particle

porosity. The inter-particle porosity and Carr's index results, indicate that CombiLac® may potentially present undesirable powder flowability.

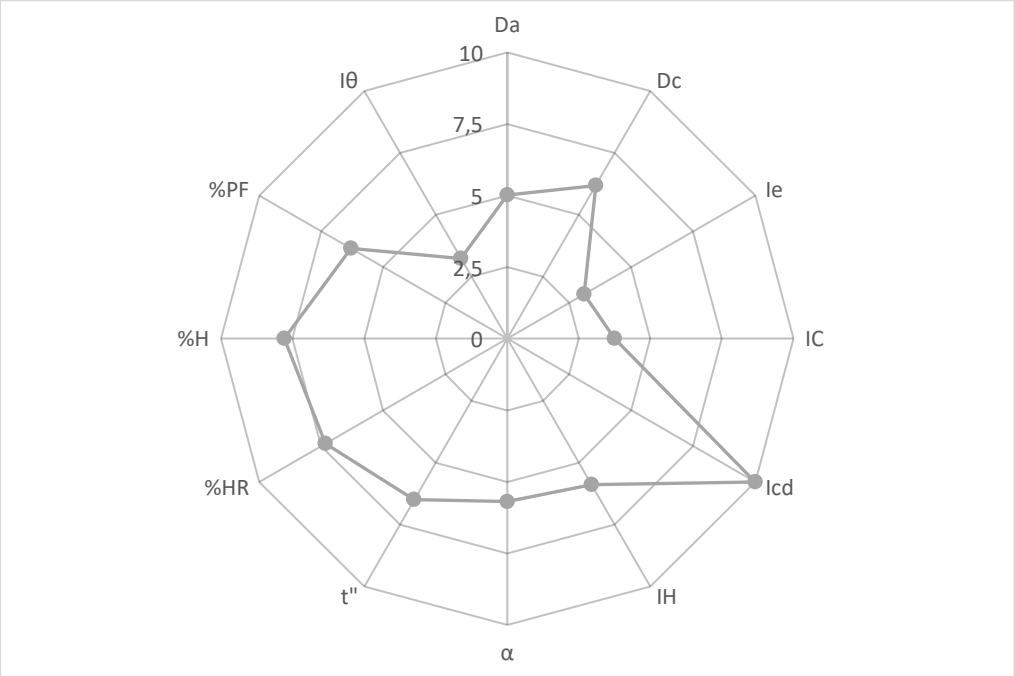

Figure 4.2: SeDeM EDS polygon representing CombiLac®

4.2.2.3 Emcompress®

Emcompress® presented the highest hygroscopicity radial value of all the fillers tested in this study, with a mean mass gain of only 0.082% over 24 hours. This can be explained by the chemical composition of Emcompress®. Emcompress® consists of dicalcium phosphate which is practically insoluble in water (Moreton, 2017:151,152). Emcompress® also presented with the highest bulk (9.094) and tapped (10) density radial values of the fillers tested. This implies that tablets with a higher weight, formulated with Emcompress® as a filler, will occupy a smaller volume, leading to a smaller tablet when compared to other fillers with higher densities. The SeDeM EDS profile for Emcompress® can be seen in figure 4.3. Emcompress® presented with the fastest flow time, obtaining a mean SeDeM EDS radial value of 8, the highest of the fillers tested in this study. A fast flow rate enables the powder to fill the die completely, and generally leading to a higher uniformity in mass of the tablets produced, as well as enabling a faster tabletting speed due to faster die filling (Yaginuma *et al.*, 2007:209).

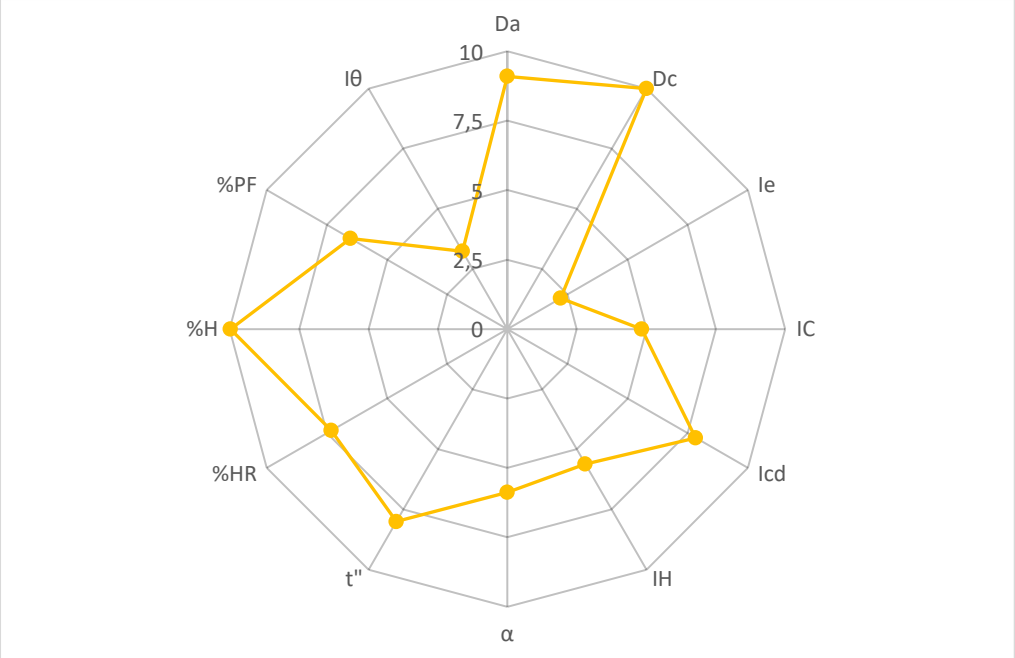

Figure 4.3: SeDeM EDS polygon representing Emcompress®

4.2.2.4 FlowLac®

It is evident from figure 4.4 that FlowLac® presented with four parameters including the percentage of particles smaller than 50 µm (4.066), homogeneity index (3.186), inter-particle porosity (2.892), and Carr's index (4.434) that did not pass the SeDeM criteria of a minimum value of 5.

FlowLac® presented with the lowest angle of repose value of the fillers tested with an angle of 20.475°, making it the filler with the highest SeDeM EDS radial value in the angle of repose parameter, obtaining a radial value of 5.905. This angle of repose result indicates that FlowLac® is likely to possess good powder flow. This can, however, only be compared to other fillers when considering the other parameters related to flowability. FlowLac® also presented with the lowest moisture content of the fillers tested with a mean moisture content of 0.299%. This enabled FlowLac® to also obtain the highest in the loss on drying SeDeM EDS parameter with a radial value of 9.701.

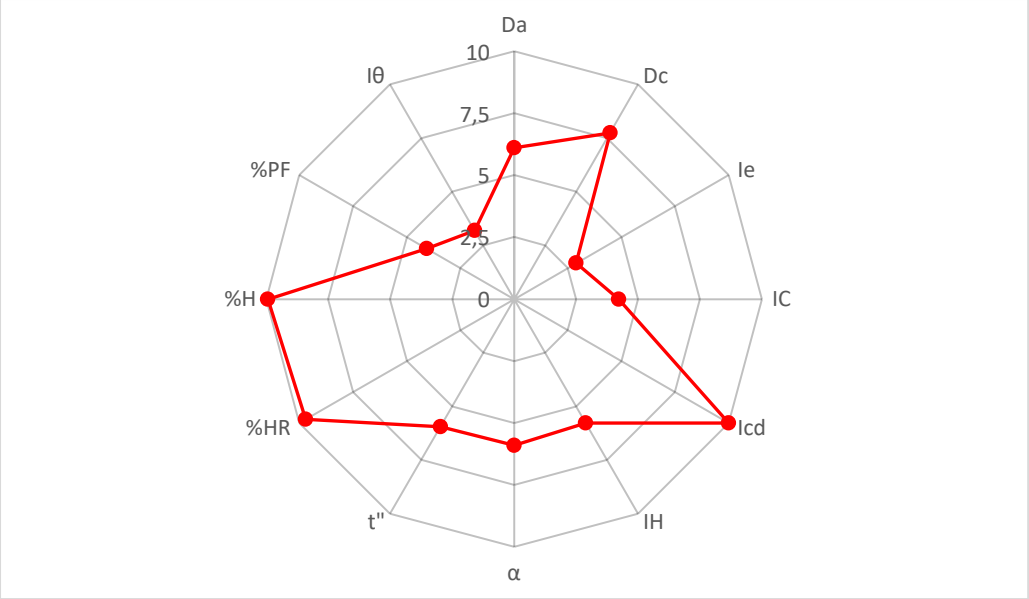

Figure 4.4: SeDeM EDS representation of FlowLac®

4.2.2.5 MicroceLac®

Similar to CombiLac®, MicroceLac® obtained a SeDeM EDS radial value of less than 5 in three parameters including its inter-particle porosity (2.824), Carr's index (3.529) and homogeneity index (3.475). The reason for the homogeneity index to obtain a low radial value of 3.475 can be explained by MicroceLac®'s particle size distribution being spread over a greater range than some of the other fillers tested in this study. MicroceLac® was, however able to obtain a radial value of 10 for the cohesion index parameter, indicating that it can produce tablets of sufficient hardness. The SeDeM EDS profile for MicroceLac® can be seen in figure 4.5.

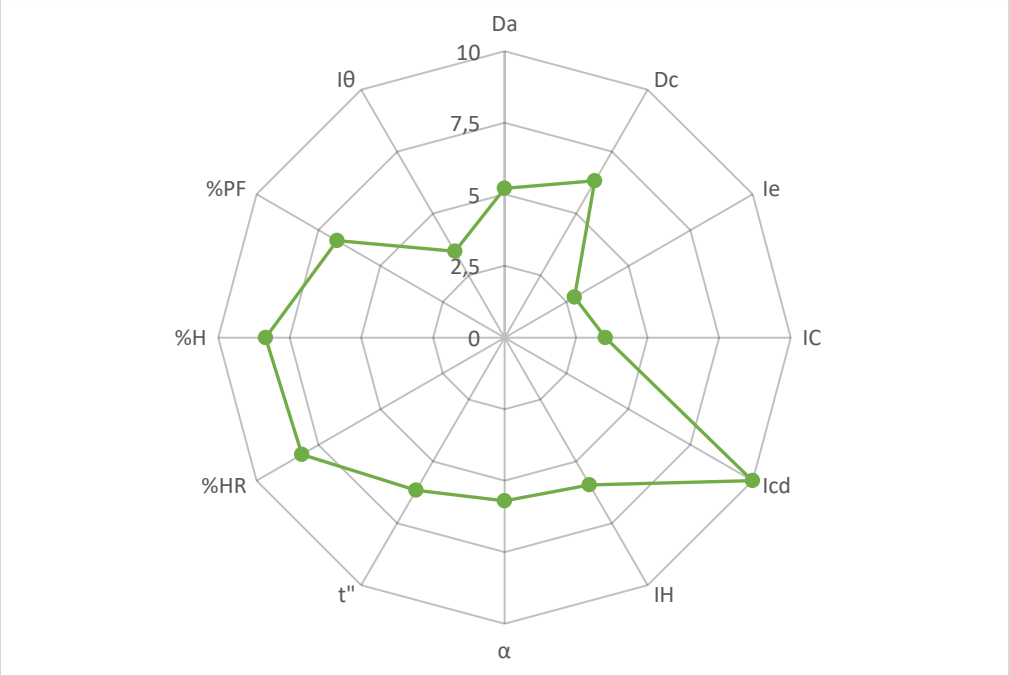

Figure 4.5: SeDeM EDS representation of MicroceLac®

4.2.2.6 Tablettose®

Tablettose® was the only filler tested in this study that produced tablets of insufficient hardness based on the cohesion index parameter (4.565). With a mean maximum tablet hardness of 91.3 N, which, while still within the range of 80 – 120 N as suggested by the BP (2021), the cohesion index parameter value for Tablettose® less than the SeDeM EDS requirement of 5. This cohesion index radial value is, however, only slightly lower than the requirement of 5. The rest of the parameters influencing compressibility should therefore also be considered before making a final conclusion regarding the compressibility of Tablettose®. Tablettose® also did not pass the SeDeM EDS requirement of 5 in the Carr's index (4.55) and inter-particle porosity (2.66) parameters, due to the difference in the bulk and tapped density values of the powder. Tablettose® did, however present with the second highest loss on drying SeDeM EDS radial value (9.684), containing the least moisture, with a mean moisture content of 0.316%. Tablettose® also had the second highest hygroscopicity radial value of 9.95, which indicates a very small amount of moisture (0.099%) was absorbed from the environment during a 24 h period. Tablettose® consists of α-lactose monohydrate which can exist in either an anhydrous or normal form. The anhydrous form, which only exists when the substance has been exposed to temperatures of at least 120˚C, is more hygroscopic than its normal form (Listiohadi *et al.*, 2008:127). Tablettose® was not exposed to these temperatures so the lower hygroscopicity is to be expected. The SeDeM EDS profile for Tablettose® can be seen in figure 4.6.

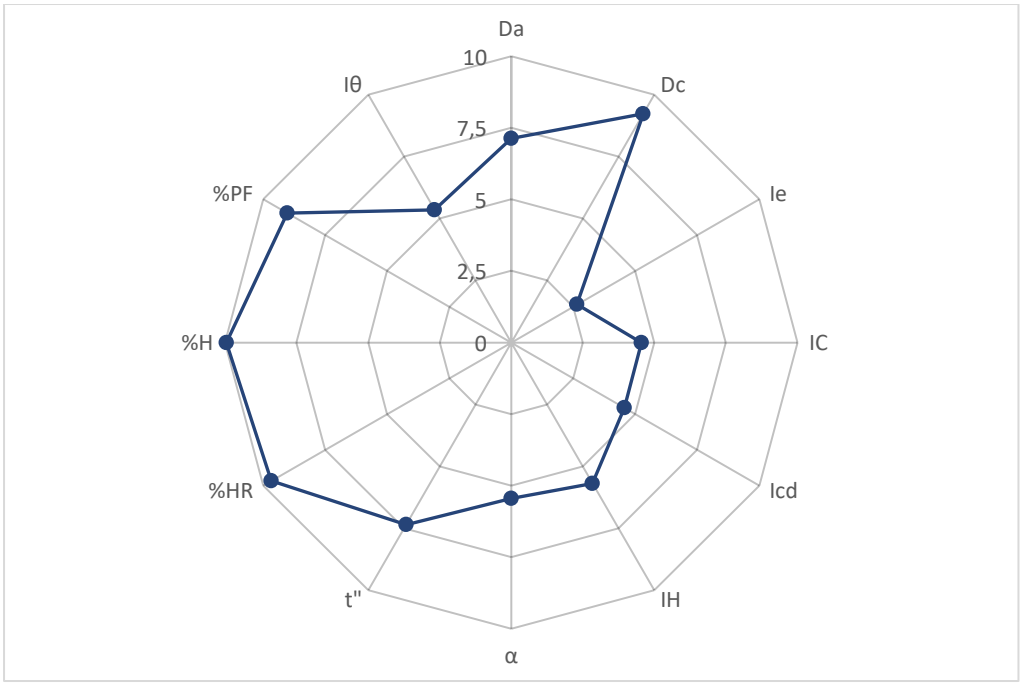

Figure 4.6: SeDeM EDS representation of Tablettose®

4.2.2.7 Tricalcium citrate

During the SeDeM EDS characterisation of TCC, it presented with the highest moisture content (5.714%) of all the fillers tested in this study. It did not, however, exhibit the highest moisture absorption (hygroscopicity) with a mean value of 3.023% mass gain over 24 h, obtaining a SeDeM EDS radial value of 8.489 in the hygroscopicity parameter. This led to TCC having the lowest SeDeM EDS radial value in the loss on drying parameter with a SeDeM EDS radial value of 4.286. This high moisture content can affect the stability of the final product negatively by interacting with other ingredients in the mixture such as moisture sensitive APIs. A high moisture content may also affect powder flow negatively as the particles tends to form stronger bonds between each other (Sandler *et al.*, 2010:277). TCC was also able to produce tablets with the highest crushing strength of the fillers tested. With a mean tablet hardness of 442.8 N, consequently, TCC achieved the highest radial value in the SeDeM EDS cohesion index parameter with a radial value limited to the maximum value of 10. TCC also obtained the highest in the homogeneity index parameter with a radial value of 10. This indicates that most of TCC's particles, falls within a narrower particle size distribution range than the rest of the fillers tested in this study. TCC did, however, not succeed in obtaining a radial value of 5 in its Carr's index (3.433), inter-particle porosity (2.551) and, as previously mentioned, its loss on drying parameters. The SeDeM EDS profile of TCC can be seen in figure 4.7.

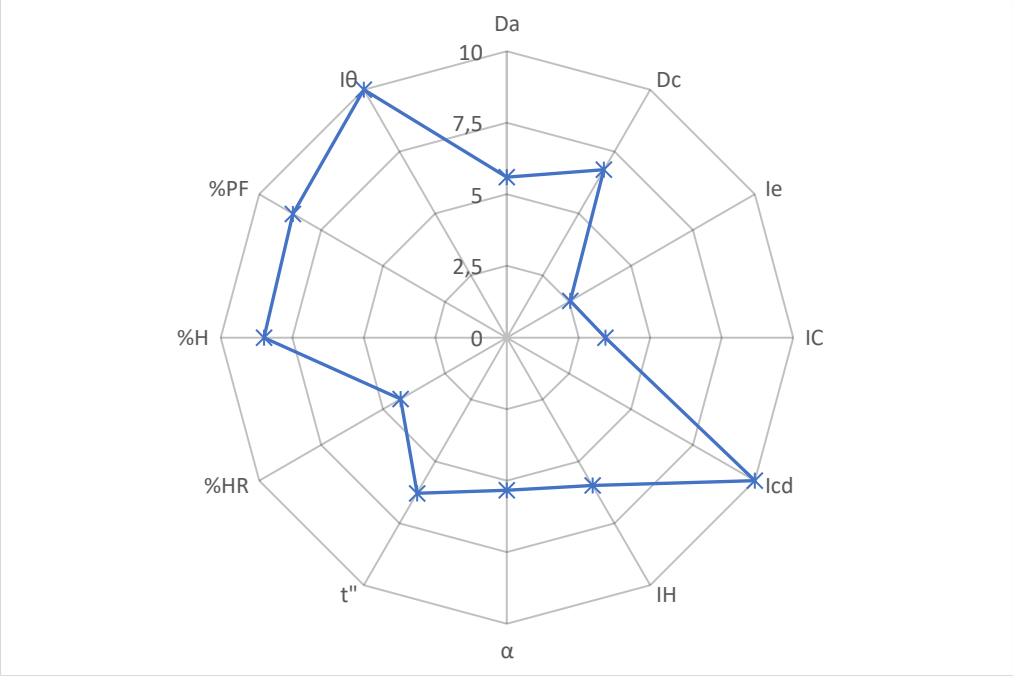

Figure 4.7: SeDeM EDS representation of tricalcium citrate

4.2.3 Comparative summary of the SeDeM EDS parameters of tricalcium citrate versus other fillers using SeDeM EDS polygons

SeDeM EDS can be used to compare different pharmaceutical powders using their theoretical ability to be used for the formulation of directly compressible tablets (Sune-Negre *et al.*, 2008:1031). The SeDeM EDS use twelve basic parameters to characterise a powder including bulk density, tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner ratio, angle of response, powder flow, percentage loss on drying, hygroscopicity, percentage of particles smaller than 50 µm, and the homogeneity index (Sune-Negre *et al.*, 2008:1031). Using these parameters, SeDeM EDS polygons could be drawn which enables us to easily compare the different aspects of each filler to TCC. The comparison graphs between TCC and the other fillers can be found in figure 4.8 – 4.13.

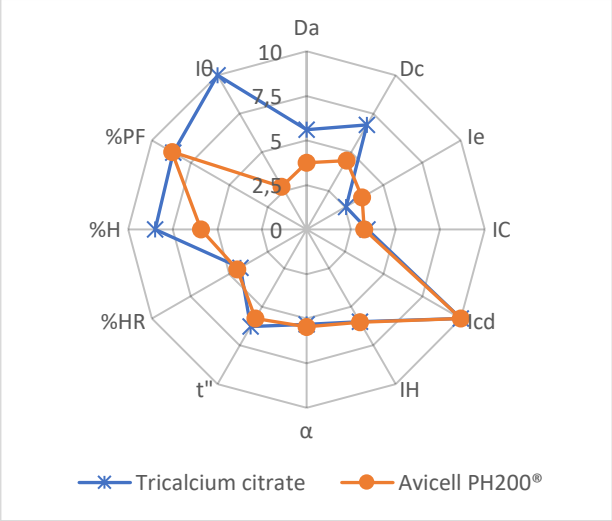

Figure 4.8: Comparison of SeDeM EDS polygons of tricalcium citrate and Avicel® PH200

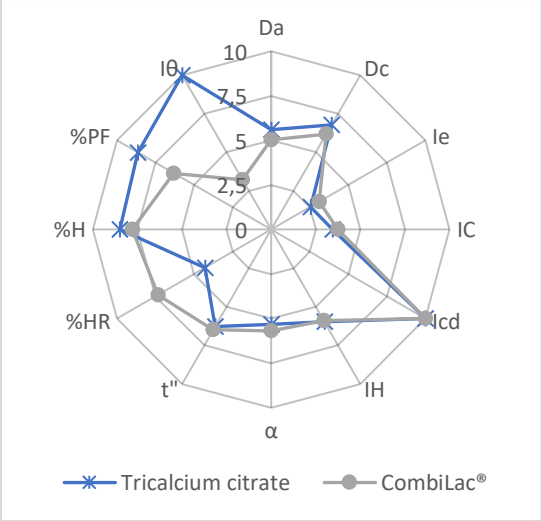

Figure 4.9: Comparison of SeDeM EDS polygons of tricalcium citrate and CombiLac®

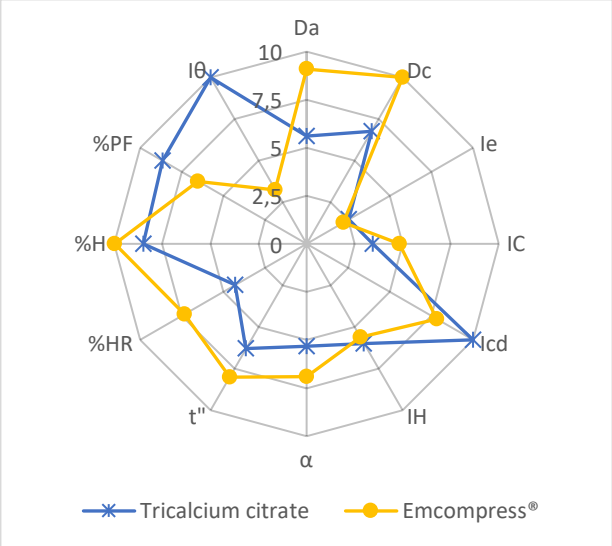

Figure 4.10: Comparison of SeDeM EDS polygons of tricalcium citrate and Emcompress®

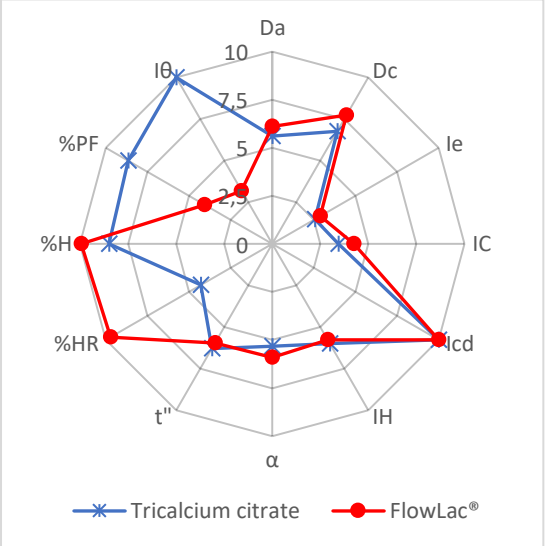

Figure 4.11: Comparison of SeDeM EDS polygons of tricalcium citrate and FlowLac®

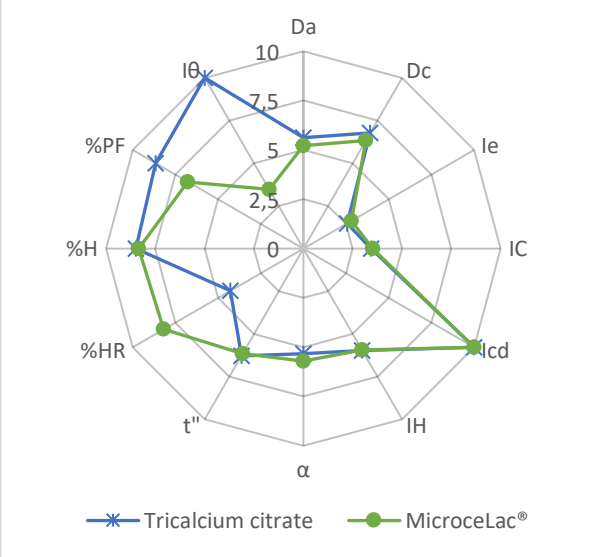

Figure 4.12: Comparison of SeDeM EDS polygons of tricalcium citrate and MicroceLac®

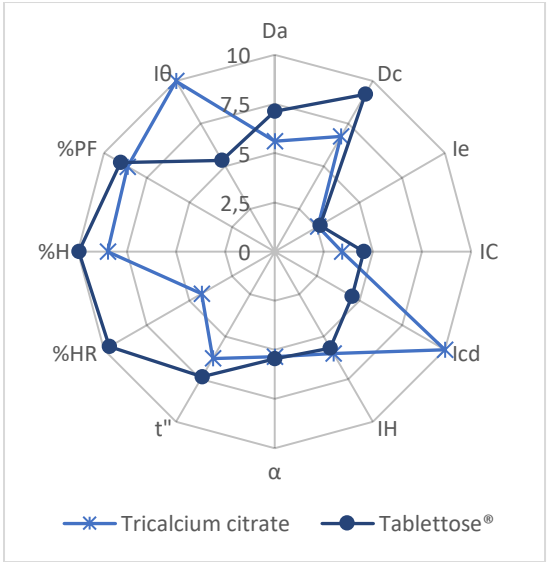

Figure 4.13: Comparison of SeDeM EDS polygons of tricalcium citrate and Tablettose®

As can be seen in the SeDeM EDS polygons, TCC obtained higher SeDeM EDS radial values than all the other fillers tested in the category for homogeneity index. This indicates that TCC possessed the narrowest particle sized distribution as this is reflected in the highest radial value (10.0) for the homogeneity index. (Aguilar-Díaz *et al.*, 2009:417; Dai *et al.*, 2019:520).

TCC also exhibited results either higher or at least on par with the other fillers with respect to the radial value when comparing the cohesion index parameter. This can be explained by TCC's character to produce tablets with a hardness of linear relation to the compression force used to produce the tablets (Hagelstein *et al.*, 2018:1643). While both Emcompress® and TCC use brittle fraction as a bonding mechanism, TCC's particles shifts in an orientation which maximises surface contact and therefore Van der Waals forces which might be the reason for TCC to produce harder tablets than Emcompress® (Doldán *et al.*, 1995:72; Hagelstein *et al.*, 2018:1634).

For the rest of the parameters TCC either obtained a result on par or slightly lower to the comparative filler. These parameters should, however, not be considered without considering how they interact with each other as illustrated by the comprehensive SeDeM EDS factors or incidences (Dai *et al.*, 2019:518-519; Suñé-Negre *et al.*, 2011:465).

4.2.4 SeDeM EDS profiles for APIs including furosemide, paracetamol, and pyridoxine

When analysing APIs with the SeDeM EDS, the same basic parameters is still used. In contrast to the results obtained for the different fillers, all three of the APIs presented with deficient results related to powder flow and compressibility, indicating a trend towards poor tabletability as well as compressibility. The SeDeM EDS results of the three APIs will be discussed in the following subsections.

4.2.4.1 Furosemide

When comparing furosemide to the other APIs tested in this study, the results indicates that furosemide is the powder with the least potential for direct compression. With only five parameters passing the SeDeM EDS's minimum required radial value of 5, furosemide fails with regards to its bulk density (3.290), cohesion index (4.6), Hausner ratio (4.812), angle of repose (0.728), flowability (0), percentage of particles smaller than 50 µm (0), and the homogeneity index (4.382) parameters. Furosemide obtained a SeDeM EDS radial value of 0 in flowability for no powder flow occurred during testing. Furthermore, furosemide can also be classified as a fairly fine powder with 64.94% of its particles smaller than 50 µm, resulting in a SeDeM EDS radial value of 0. When comparing the APIs used in this study, furosemide does have the potential to form the hardest tablets of the APIs tested, indicated by its cohesion index represented by a radial value of 4.60, which is higher than both paracetamol and pyridoxine's. Furosemide's SeDeM EDS profile can be seen in figure 4.14.

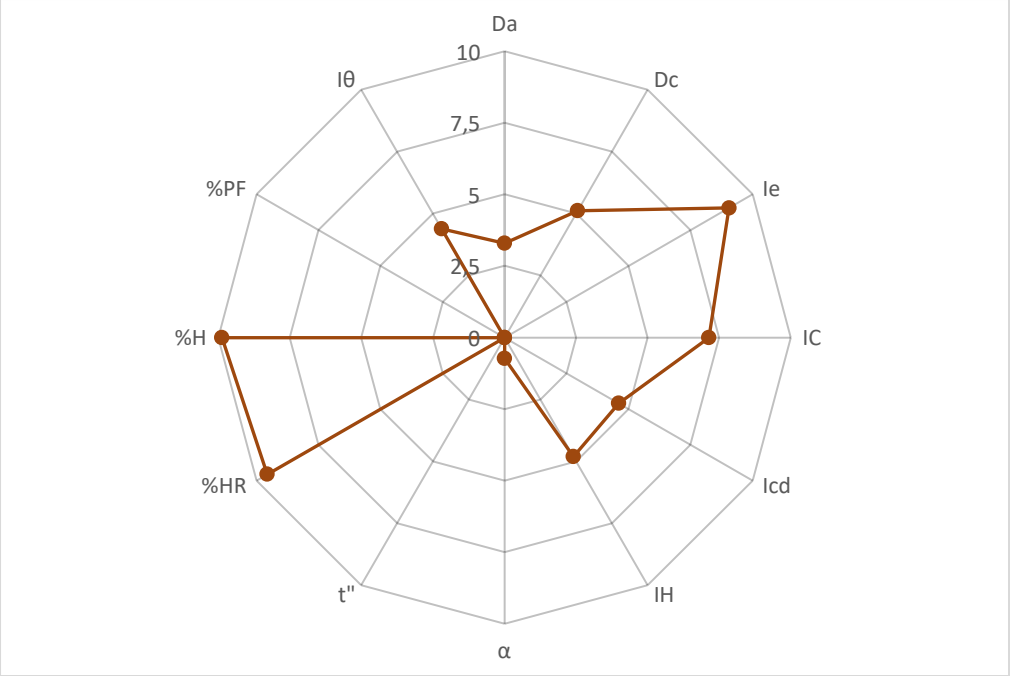

Figure 4.14: SeDeM EDS representation of furosemide

4.2.4.2 Paracetamol

During the SeDeM EDS analysis of paracetamol, six basic parameters, including its bulk density (4.014), cohesion index (0.120), Hausner ratio (3.953), angle of repose (0.129), flow time (0) and percentage of particles smaller than 50 µm (0), did not present with a minimum required radial value of 5. The SeDeM EDS profile for paracetamol can be seen in figure 4.15. Paracetamol presented with no observable powder flow resulting in a SeDeM EDS radial value of 0 being awarded for this parameter. This poor flowability may stem from paracetamol's particle size. Smaller particles have larger surface area which in turn increases the intermolecular forces between the particles (Kudo *et al.*, 2020:126). While paracetamol also achieved the highest radial value of the APIs tested in the homogeneity index parameter, it exceeded the 50% limit placed on the percentage of particles smaller than 50 µm. By having a result of 61.25% of its particles being smaller than 50 µm, paracetamol obtained a SeDeM EDS radial value of 0. With a mean angle of repose of 49.354°, paracetamol exhibited the lowest angle of repose radial value (0.129) of the APIs tested. Of the three APIs tested, paracetamol showed the lowest hygroscopicity with a mass gain of only 0.062% over 24 hours.

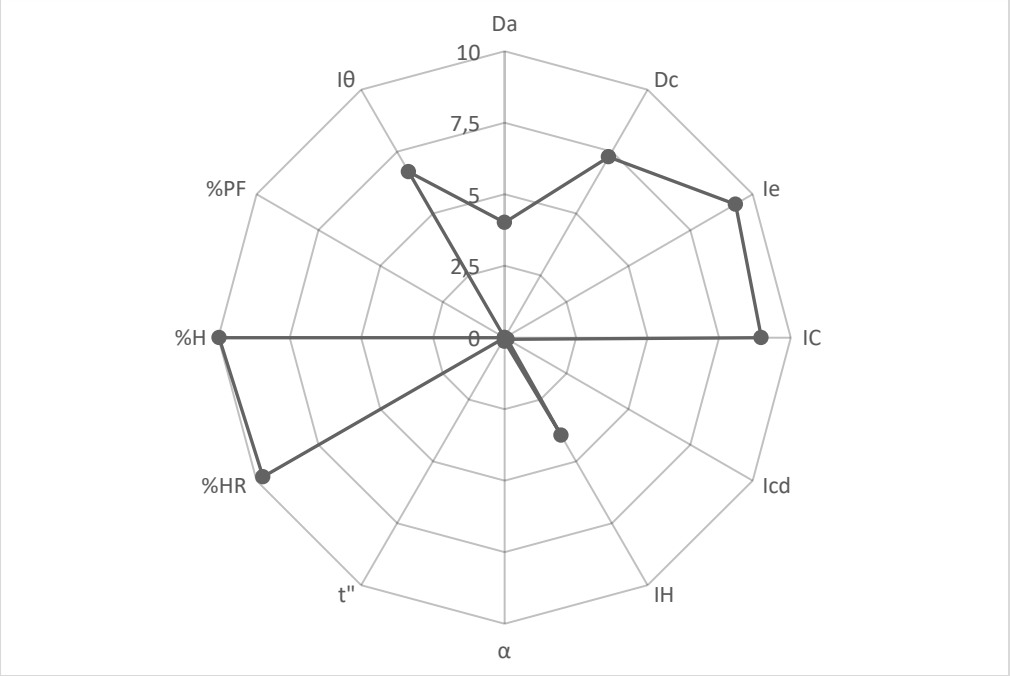

Figure 4.15: SeDeM EDS representation of paracetamol

4.2.4.3 Pyridoxine

With seven parameters passing the SeDeM EDS criteria, pyridoxine performed the best of the three APIs tested in this study. Even though it performed the best according to the passing rate of basic parameters, the SeDeM EDS profile still does not recommend pyridoxine to be solely used for the direct compression of tablets. Inter-particle porosity (3.913), cohesion index (0.715), angle of repose (4.488), flow rate (0), and the homogeneity index (3.118) were parameters presenting with radial values ≤ 5. With a flow rate represented by a SeDeM EDS radial value of 0, pyridoxine did not present with any observable powder flow similar to the two other APIs tested in this study. As powder flow is critical to render direct compressible tablets, it is evident that pyridoxine is highly likely to present with powder flow problems during direct compression. Pyridoxine obtained an angle of repose value of 27.56°, corresponding to a SeDeM EDS radial value of 4.488, indicating that pyridoxine have the highest potential flowability rate when comparing it with furosemide and paracetamol based on the angle of repose data. The angle of repose and flow time parameter results contradicts each other. It is therefore important to consider both these factors together, using the flowability factor as will be discussed in a later subsection. The cohesion index, with a radial value of 0.715, while slightly higher than paracetamol, still indicates that tablets formed with pyridoxine as the only ingredient, is highly likely to fail the friability test. Pyridoxine, however, exhibited the lowest moisture content of the APIs tested, with a mean mass loss of 0.05%, obtaining a radial value of 9.950 in the loss on drying parameter, while having a 0.067% increase in mass, resulting in

a radial value of 9.967 in the hygroscopicity parameter, which is slightly higher than the value obtained for paracetamol. Pyridoxine also exhibited the highest bulk and tapped density values, which implies that a higher dose can be reached with a smaller tablet volume. Pyridoxine was also the only API which did not receive a SeDeM EDS radial value of 0 on its percentage particles smaller than 50 µm parameter obtaining a value of 7.555. The SeDeM EDS profile for pyridoxine can be seen in figure 4.16.

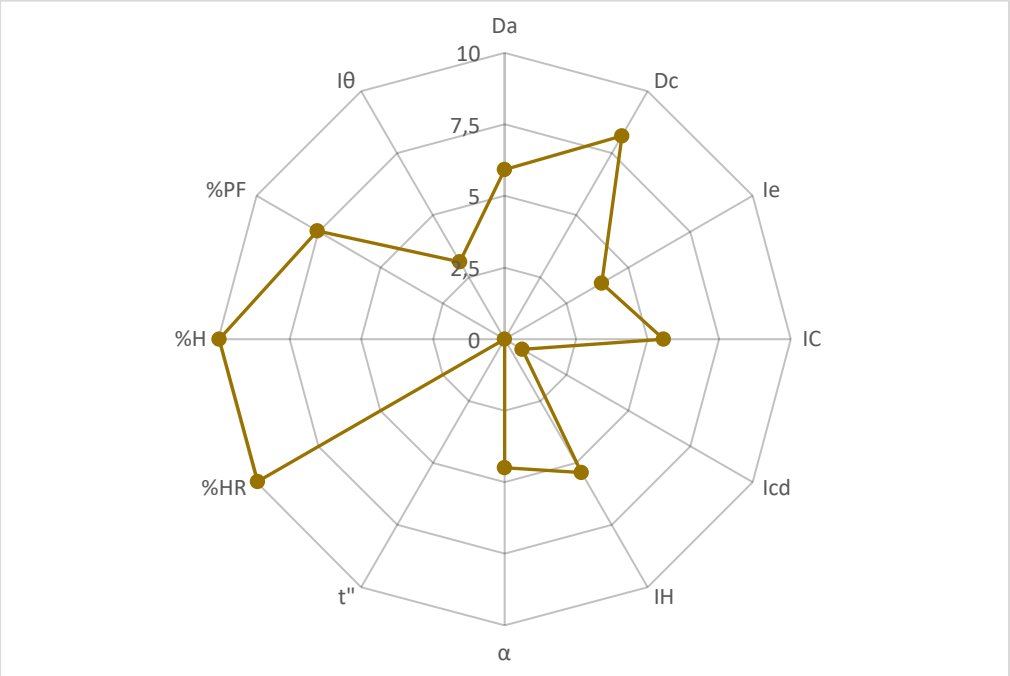

Figure 4.16: SeDeM EDS representation of pyridoxine

4.2.5 Dimension-, Compressibility-, Flowability-, Lubricity/Stability-, and Lubricity/Dosage factors

The twelve basic SeDeM parameters may be grouped into five different groups also called factors or incidences. These five factors or incidences include the dimensional factor, flowability factor, compressibility factor, lubricity/dosage factor and the lubricity/stability factor (Dai *et al.*, 2019:520). Each of these factors were determined for each filler as well as each active ingredient studied and can be seen in table 4.5. The acceptance value for each of these five factors is ≥ 5 as per SeDeM specification (Suñé-Negre *et al.*, 2011:468). A comparison of these five factors for each filler is graphically depicted in figure 4.17, while a comparison between the APIs is depicted in figure 4.18.

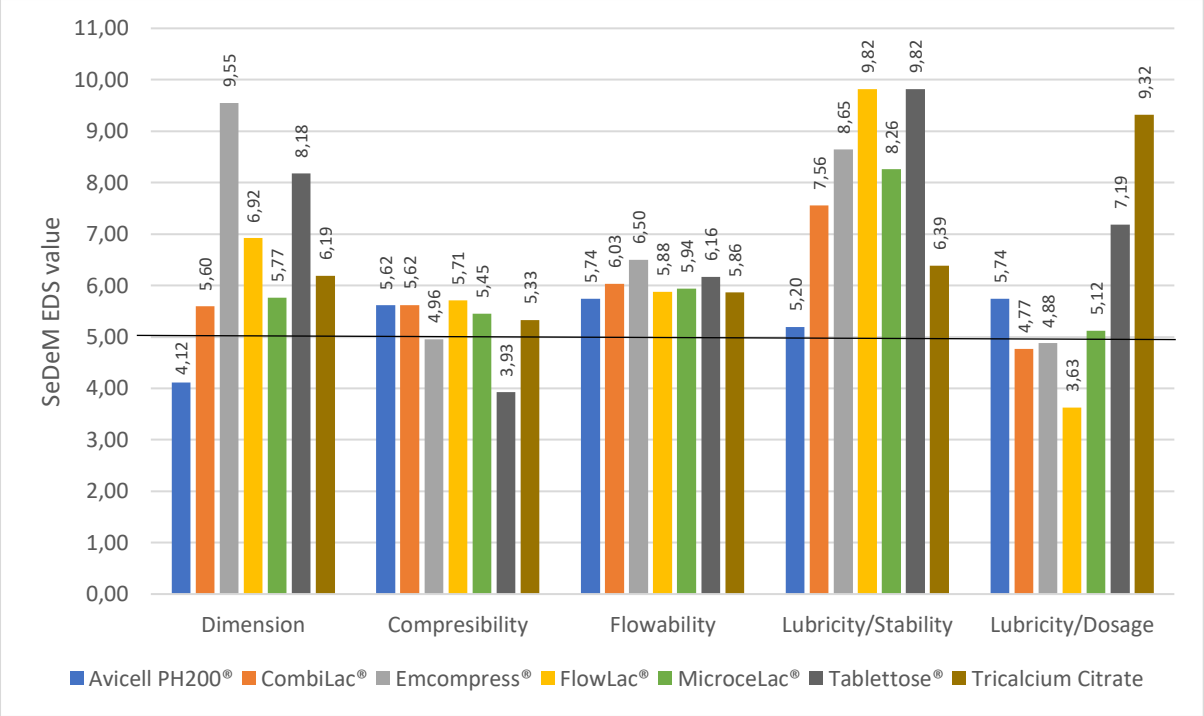

Figure 4.17: Dimension, compressibility, flowability, lubricity/stability, and lubricity/dosage factor values of Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate

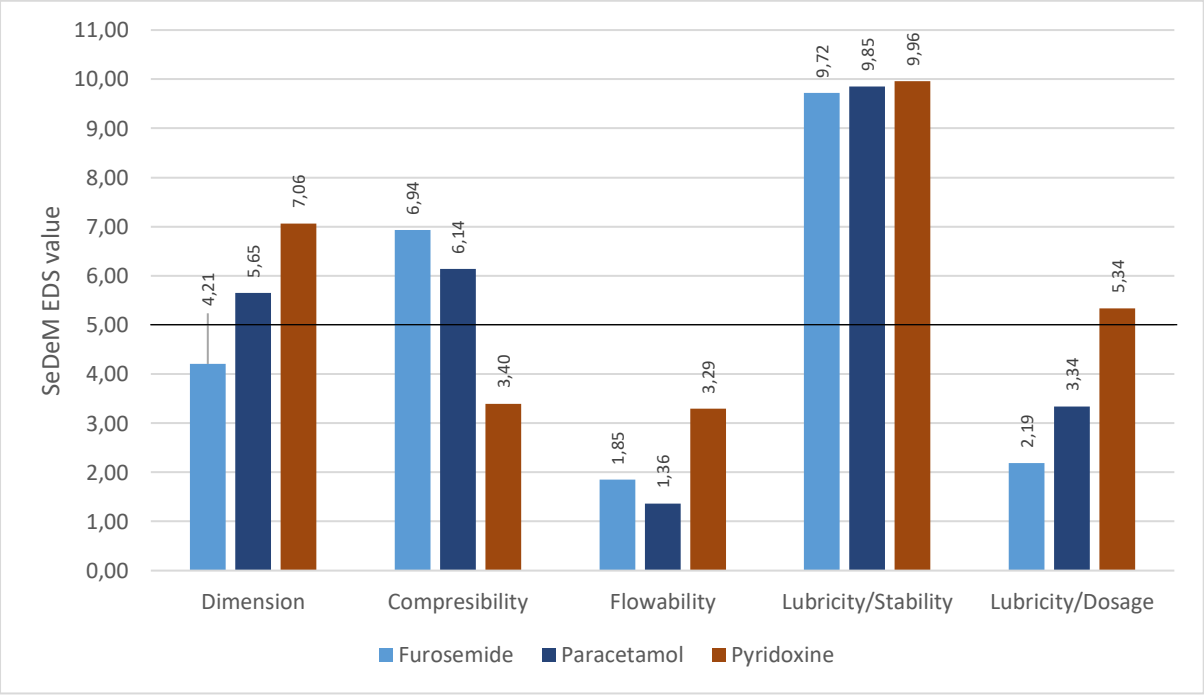

Figure 4.18: SeDeM EDS dimension-, compressibility-, flowability-, lubricity/stability-, and lubricity/dosage factors of furosemide, paracetamol, and pyridoxine

Table 4.5: Dimension-, flowability-, compressibility-, lubricity/stability, and lubricity/dosage factors of Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate

	Dimension factor	Compressibility factor	Flowability factor	Lubricity / Stability factor	Lubricity / Dosage factor
Avicel® PH200	4.115	5.618	5.742	5.197	5.742
CombiLac®	5.599	5.619	6.028	7.561	4.769
Emcompress®	9.547	4.958	6.496	8.646	4.878
FlowLac®	6.92	5.709	5.875	9.818	3.626
MicroceLac®	5.765	5.451	5.942	8.261	5.115
Tablettose®	8.178	3.925	6.162	9.817	7.187
Tricalcium citrate	6.188	5.328	5.865	6.387	9.319

4.2.5.2 Dimensional factor

The dimension factor, which represents a powder's ability to pile up, was calculated using the bulk density and tapped density radial values as reported in table 4.3 (Dai *et al.*, 2019:518; Perez *et al.*, 2006:354).

The acceptance value for SeDeM EDS factors is ≥ 5 (Suñé-Negre *et al.*, 2011:468). Taking this acceptance value into consideration, six of the seven fillers tested passed the dimensional factor according to the SeDeM EDS. Emcompress® exhibited the highest dimensional factor with a value of 9.547, while Avicel® PH200 is the only filler tested that, with a value of 4.115, did not comply with a minimum value of 5. TCC obtained a value of 6.188 for the dimensional factor and therefore possesses a modest ability or capacity to act as a corrective excipient for a powder or powder mixture exhibiting a deficiency with regard to the dimensional factor. The following ranking order for the fillers regarding the dimensional factor could be established: Emcompress® (9.547) > Tablettose® (8.178) > FlowLac® (6.92) > TCC (6.188) > MicroceLac® (5.765) > CombiLac® (5.599) > Avicel® PH200 (4.115). The dimensional factor may also be linked to the flowability factor for several parameters that is used to calculate the dimensional factor is also used to calculate the parameters used in the flowability factor. An example of such parameters is the tapped and bulk densities which are used to calculate the Carr's index used in the flowability factor.

4.2.5.3 Compressibility factor

To calculate the SeDeM EDS compressibility factor, the powders' inter-particle porosity, Carr's index, and cohesion index radial values, which can be seen in table 4.3, were used (Perez *et al.*, 2006:354). The compressibility factor provides information regarding a powder's compressibility and therefore the powders' ability to be compressed into tablets of sufficient hardness.

A higher cohesion index radial value tends to increase the compressibility factor notably. Two of the fillers tested namely Emcompress® and Tablettose®, did not pass the compressibility factor's criteria. Tablettose® obtained the lowest value of 3.925 while FlowLac® obtained the highest value of 5.709. TCC obtained a compressibility value of 5.328 indicating that it might be used as a corrective excipient in a powder or powder mixture that is deficient in its compressibility ability. TCC did, however, show the highest cohesion index by being able to form tablets with a hardness of 442.8 N. This data is supported by the fact that TCC demonstrates a near linear relationship between its hardness and the force used to compress the powder into tablets (Hagelstein *et al.*, 2018:1634). The results for TCC pertaining to the compressibility factor, may be an indication that tablets compressed with TCC as a filler, might have less mass loss during the friability test when compared to tablets formulated using other fillers. The following ranking order can be established for the fillers tested in this study: FlowLac® (5.709) > CombiLac® (5.619) > Avicel® PH200 (5.618) > MicroceLac® (5.451) > TCC (5.328) > Emcompress® (4.958) > Tablettose® (3.925).

4.2.5.4 Flowability factor

The SeDeM EDS flowability factor is calculated using the Hausner ratio, angle of repose, and powder flow time (Perez *et al.*, 2006:353). The radial values of the respective parameters used to calculate the flowability factor is given in table 4.3. Given that tablets are usually manufactured on high-speed rotary presses (Sinka *et al.*, 2003:33), or presses that uses gravity feed mechanics, fillers with good flow properties are needed to maintain the speed while still acquiring sufficient die filling. It is thus essential that a powder or powder mixture intended for tableting exhibits good powder flow.

When considering the results collected, all the fillers tested in this study, obtained a radial value ≥ 5 for the SeDeM EDS flowability factor with values ranging from 5.742 – 6.835. TCC, exhibited a value of 5.865, and while still being considered as a powder with good flow, were on the bottom spectrum of the seven fillers tested with only Avicel® PH200 exhibiting a lower value of 5.742. It is therefore evident that all of these fillers will exhibit the ability or capacity to

act as a corrective excipient for a powder with a deficient flowability factor albeit to a different extent (Dai *et al.*, 2019:521). During the tabletting process, TCC also repeatedly filled the die completely indicating that the flow properties are sufficient to be used as a direct compression filler. Overall Emcompress® exhibited the best results regarding flow rate with a rate of 25 g/s while Avicel® PH200 exhibited the slowest flow rate of 11.765 g/s and therefore obtaining a radial value of 5.750. A fast flow rate is also beneficial in terms of production time as a faster rate, will lead to a decreased production time per unit, and consequently, the tableting process can be completed faster (Wu *et al.*, 2003:26). The fillers studied can be organised into the following ranking order based on their flowability factor: Emcompress® (6.835) > Tablettose® (6.162) > CombiLac® (6.028) > MicroceLac® (5.942) > FlowLac® (5.875) > TCC (5.865) > Avicel® PH200 (5.742).

Flowability can also be affected by the powder's density. A powder with a higher bulk density have weaker intermolecular bonds and should therefore have a better flow rate (Abdullah & Geldart, 1999:156). Particle size plays a role in this phenomenon for bigger particles tends to form a powder with a greater difference between bulk and tapped densities (Abdullah & Geldart, 1999:156). This is incorporated into the SeDeM EDS via the Hausner ratio. This correlation between powder density and flowability can also be seen in the SeDeM EDS data, when comparing the flowability factor for each filler with the dimensional factor. Powders with a higher dimensional factor, have a higher flowability factor and vice versa. For example, Tablettose® have a dimensional factor greater than TCC while also presenting a higher flowability factor. This correlation between the dimensional and flowability factors is only present while the powder's particles are of such a size that the Van der Waals interactions between the particles is affected by the distance between the particles (Abdullah & Geldart, 1999:156). This means that if the particles are closer to each other, the Van der Waals interactions between the particles are stronger thus impeding powder flow. Bigger particles correspond to the surfaces of each particle being further removed from each other, thus leading to weaker interactions and better flowability. This increase of flowability is, however, only noticeable if the particles are still close enough to each other for the Van der Waals interactions to affect their bonding strength. If there are sufficient space between the particles (big particles) there will not be a noticeable change in the interaction forces between the particles and the flowability would remain technically unchanged.

4.2.5.5 Lubricity/Stability factor

To calculate the lubricity/stability factor for each filler, the loss on drying and hygroscopicity of each filler was used (Sune-Negre *et al.*, 2008:1031). The radial values for these parameters

are given in table 4.3 while the calculated lubricity/stability factor value is presented in table 4.5.

From the data presented in table 4.5 and figure 4.17, it can be seen that Avicel® PH200 and TCC expressed the highest loss during drying. This indicates that during normal atmospheric conditions, these powders contain more moisture than the rest of the fillers tested. Hygroscopicity tests showed that Avicel® PH200 also absorbed the most moisture from the atmosphere with a mass gain of 8.150% compared to the rest of the fillers tested. The lubricity/stability factor indicates that all of the fillers tested is suitable for direct compression, for their values were ≥ 5 (Perez *et al.*, 2006:353). This indicates that all the fillers tested can be used as a corrective excipient for mixtures expressing a deficiency in their lubricity/stability factor. FlowLac® presented with the highest value of 9.818, while Avicel® PH200 obtained the lowest value of 5.197. Even though TCC achieved the second lowest radial value of 6.387, the results obtained are still within the acceptable range according to the SeDeM EDS (Sune-Negre *et al.*, 2008:1031). The following ranking order in terms of the lubricity/stability factor could be established: FlowLac® (9.819) > Tablettose® (9.817) > Emcompress® (8.646) > MicroceLac® (8.216) > CombiLac® (7.561) > TCC (6.387) > Avicel® PH200 (5.197).

4.2.5.6 Lubricity/Dosage factor

The lubricity/dosage factor was calculated using the percentage of particles smaller than 50 µm as well as the homogeneity index parameters (Perez *et al.*, 2006:353; Sune-Negre *et al.*, 2008:1031). The radial value results obtained for these parameters can be seen in table 4.3 while the calculated lubricity/dosage factor values are given in table 4.5.

As can be seen in table 4.3 the more uniform the filler's particle size, indicated by a higher homogeneity index value, the higher the lubricity/dosage factor value. Of the seven fillers tested, TCC exhibited the most uniform particle size distribution as well as a relatively small percentage of particles smaller than 50 µm which is reflected in the lubricity/dosage factor value. FlowLac® exhibited the lowest value of 3.626 for the lubricity/dosage factor. This can be attributed to the fact that FlowLac® possessed a high percentage of particles smaller than 50 µm. A consequence for powders that possess a wide particle size distribution, i.e., a powder with a low homogeneity is that it is likely to exhibit higher segregation rates (Abdullah & Geldart, 1999:160). This occurs because the fine particles tend to fill the voids between the bigger particles on the bottom of the container more easily than the voids towards the top (Abdullah & Geldart, 1999:160). This separation, especially when mixing two powders with different particle sizes may cause segregation which may lead to a difference in the pharmaceutical composition of the final product. This segregation occurs more frequently, the

bigger the difference between particle sizes are. The studied fillers can be ranked according to their lubricity/dosage factor values as follows: TCC (9.319) > Tablettose® (7.187) > Avicel® PH200 (5.742) > MicroceLac® (5.115) > Emcompress® (4.878) > CombiLac® (4.769) > FlowLac® (3.626).

4.2.6 Index of Good Compressibility (IGC), Parameter Index (IP) and Index of Profile Parameter (IPP)

The SeDeM EDS also provides three additional indices that can be calculated to analyse a powder or powder mixture's suitability for direct compression. These three indices are the Index of Good Compressibility (IGC), Parameter Index (IP) and Index of Profile Parameter (IPP) (Perez *et al.*, 2006:353-354). These indices are more inclusive, for they combine the results of the five SeDeM incidences or factors, which simplifies the comparison of powders in terms of their suitability for direct compression. Figure 4.19 gives a graphical representation of the values for each of these indices for the seven fillers tested during this study.

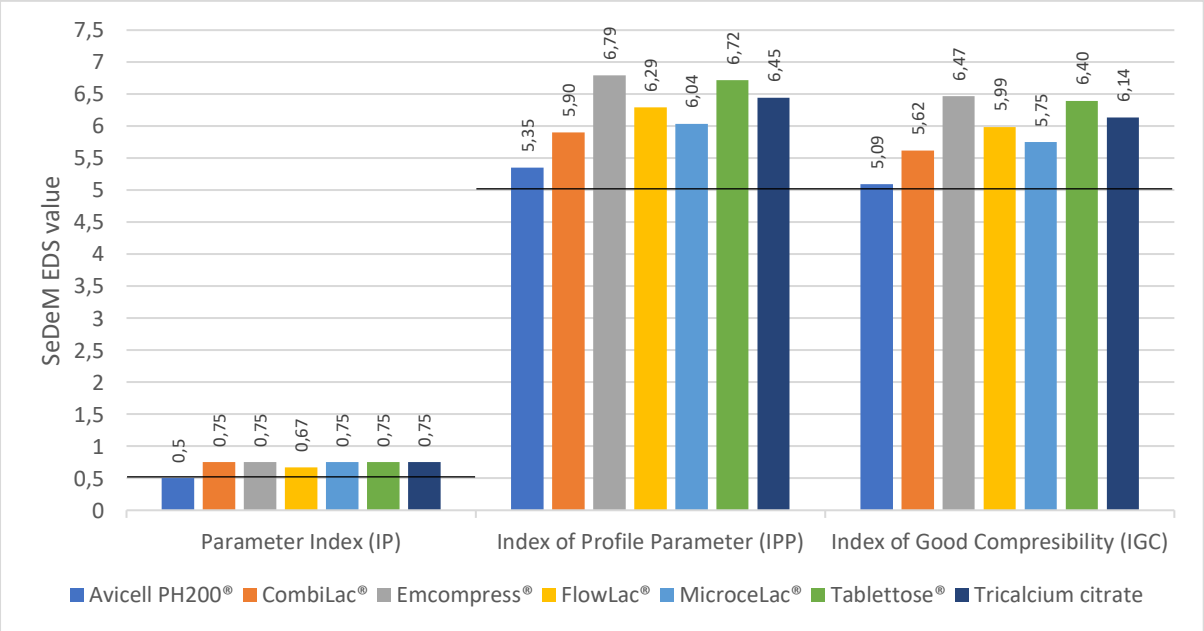

Figure 4.19: SeDeM EDS additional indices (IP, IPP & IGC) for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and Tricalcium citrate

To interpret the results of these indices, the acceptability criteria need to be known. For the IP, the acceptability criterium is a value ≥ 0.5, while the acceptability criteria for the IPP and IGC are values ≥ 5 (Perez *et al.*, 2006:354). When considering the results obtained, a higher value corresponds to a theoretical better filler to use in direct compression of tablets. From the data presented in figure 4.19, it can be seen that all the fillers tested are suitable for direct compression. The results for the IP ranged between 0.50 – 0.75, while the IPP and IGC were

within the ranges of 5.35 – 6.79 and 5.09 – 6.47, respectively. The fillers can also be ranked using these indices. The ranking for the IP is as follows: Emcompress®, Tablettose®, TCC, MicroceLac® and CombiLac® > FlowLac® > Avicel® PH200, while the IPP and IGC can both be ranked as: Emcompress® > Tablettose® > TCC > FlowLac® > MicroceLac® > CombiLac® >Avicel® PH200.

When comparing the additional index results obtained from analysing the APIs (furosemide, paracetamol, and pyridoxine) the conclusion can be reached that two of these three APIs (furosemide & paracetamol) were not suitable for direct compression without the addition of a corrective excipient according to the SeDeM EDS. These indices are presented in figure 4.20. Furosemide's SeDeM EDS profile is the poorest with no indices passing the criteria mentioned above. While paracetamol passed the IP as well as the IPP criteria's, it failed to pass the IGC acceptable criterium with a value of 4.77. Pyridoxine on the other hand, passed all three additional indices, which indicated that it might be possible to directly compress tablets using only pyridoxine powder.

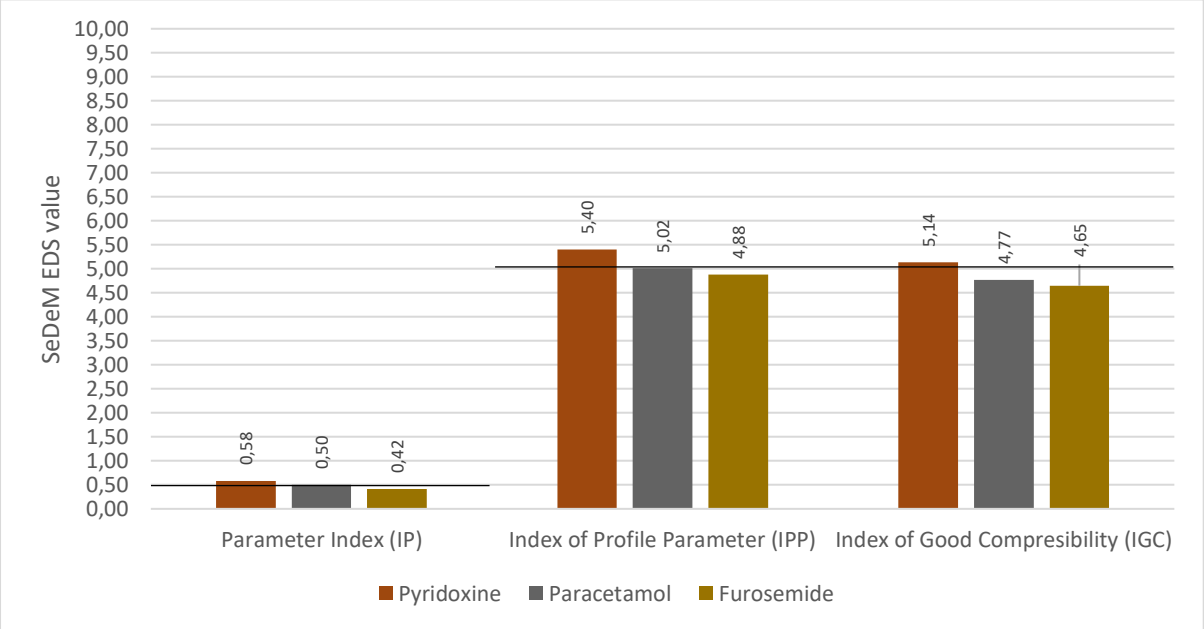

Figure 4.20: SeDeM EDS additional indices (IP, IPP & IGC) for furosemide, paracetamol, and pyridoxine

4.3 Phase 2: Theoretical dilution potential according to SeDeM EDS

The aim of performing dilution potential studies on a pharmaceutical filler is to determine the amount of API (or a powder mixture of APIs) that can be incorporated into the specific filler, while still acquiring a tablet of acceptable quality (Habib *et al.*, 1996:206). The theoretical

dilution potential can be determined using the SeDeM EDS's corrective excipient calculations (Sune-Negre *et al.*, 2008:1032).

From the API factor values, the conclusion can be drawn that these APIs (furosemide, paracetamol and pyridoxine), are not suitable for direct compression without the addition of a corrective agent, which is to be expected as the flow properties as well as the compression properties of APIs are generally not suitable for direct compression, hence the need for excipients such as fillers.

The percentage corrective excipient was calculated for each of the filler (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and TCC) and API (furosemide, paracetamol, and pyridoxine) combinations The theoretical amount of filler needed to correct each of these APIs according to SeDeM EDS is given in tables 4.6 to 4.8, while a comparative presentation is given in figure 4.21. Due to practicality reasons, a percentage of 100 or greater should be regarded as impossible to correct. This stems from the reason that 100% represents a powder mixture of only filler and no API, which is unacceptable due to rendering no therapeutic effect as the tablet will not contain any pharmacologically active compound. Using this principle, FlowLac®, Emcompress® and CombiLac® are theoretically unsuitable to produce tablets containing paracetamol and furosemide, while Tablettose® and Emcompress are theoretically unsuitable to produce tablets containing pyridoxine. It should, however, be noted that these values were obtained using only a filler and the API in the formulations. In the pharmaceutical industry, additional excipients, such as a lubricant and disintegrant would be added (Jivraj *et al.*, 2000:59), thus theoretically allowing these unsuitable fillers to be able to produce acceptable tablets.

Table 4.6: Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible furosemide formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)**
Avicel® PH200	**Dimension**	4.115	4.205	∞	80.95
	Compressibility	5.618	6.935	NCN	
	Flowability	5.742	1.847	80.95	
	Lubricity/Dosage	5.742	2.191	79.11	
	Lubricity/Stability	5.197	9.718	NCN	
CombiLac®	**Dimension**	5.599	4.205	57.05	108.97
	Compressibility	5.619	6.935	NCN	
	Flowability	6.028	1.847	75.41	
	Lubricity/Dosage	4.769	2.191	108.97	
	Lubricity/Stability	7.561	9.718	NCN	
Emcompress®	**Dimension**	9.547	4.205	14.88	104.52
	Compressibility	4.958	6.935	NCN	
	Flowability	6.835	1.847	67.82	
	Lubricity/Dosage	4.878	2.191	104.52	
	Lubricity/Stability	8.646	9.718	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

Table 4.6: (Continued) Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible furosemide formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)
FlowLac®	**Dimension**	6.920	4.205	29.28	195.73
	Compressibility	5.709	6.935	NCN	
	Flowability	5.875	1.847	78.27	
	Lubricity/Dosage	3.626	2.191	195.73	
	Lubricity/Stability	9.818	9.718	NCN	
MicroceLac®	**Dimension**	5.765	4.205	50.94	96.06
	Compressibility	5.451	6.935	NCN	
	Flowability	5.942	1.847	77.00	
	Lubricity/Dosage	5.115	2.191	96.06	
	Lubricity/Stability	8.261	9.718	NCN	
Tablettose®	**Dimension**	8.178	4.205	20.01	73.07
	Compressibility	3.925	6.935	NCN	
	Flowability	6.162	1.847	73.07	
	Lubricity/Dosage	7.187	2.191	56.23	
	Lubricity/Stability	9.817	9.718	NCN	
Tricalcium citrate	**Dimension**	6.188	4.205	40.10	78.48
	Compressibility	5.328	6.935	NCN	
	Flowability	5.865	1.847	78.48	
	Lubricity/Dosage	9.319	2.191	39.41	
	Lubricity/Stability	6.387	9.718	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

Table 4.7: Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible paracetamol formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)
Avicel® PH200	**Dimension**	4.115	5.648	NCN	83.06
	Compressibility	5.618	6.136	NCN	
	Flowability	5.742	1.361	83.06	
	Lubricity/Dosage	5.742	3.344	69.07	
	Lubricity/Stability	5.197	9.852	NCN	
CombiLac®	**Dimension**	5.599	5.648	NCN	116.25
	Compressibility	5.619	6.136	NCN	
	Flowability	6.028	1.361	77.97	
	Lubricity/Dosage	4.769	3.344	116.25	
	Lubricity/Stability	7.561	9.852	NCN	
Emcompress®	**Dimension**	9.547	5.648	NCN	107.92
	Compressibility	4.958	6.136	NCN	
	Flowability	6.835	1.361	70.86	
	Lubricity/Dosage	4.878	3.344	107.92	
	Lubricity/Stability	8.646	9.852	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

Table 4.7: (Continued) Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible paracetamol formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)
FlowLac®	**Dimension**	6.920	5.648	NCN	586.95
	Compressibility	5.709	6.136	NCN	
	Flowability	5.875	1.361	80.61	
	Lubricity/Dosage	3.626	3.344	586.95	
	Lubricity/Stability	9.818	9.852	NCN	
MicroceLac®	**Dimension**	5.765	5.648	NCN	93.49
	Compressibility	5.451	6.136	NCN	
	Flowability	5.942	1.361	79.44	
	Lubricity/Dosage	5.115	3.344	93.49	
	Lubricity/Stability	8.261	9.852	NCN	
Tablettose®	**Dimension**	8.178	5.648	NCN	75.79
	Compressibility	3.925	6.136	NCN	
	Flowability	6.162	1.361	75.79	
	Lubricity/Dosage	7.187	3.344	43.10	
	Lubricity/Stability	9.817	9.852	NCN	
Tricalcium citrate	**Dimension**	6.188	5.648	NCN	80.80
	Compressibility	5.328	6.136	NCN	
	Flowability	5.865	1.361	80.80	
	Lubricity/Dosage	9.319	3.344	27.71	
	Lubricity/Stability	6.387	9.852	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

Table 4.8: Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible pyridoxine formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)
Avicel® PH200	**Dimension**	4.115	7.058	NCN	72.21
	Compressibility	5.618	3.395	72.21	
	Flowability	5.742	3.290	69.73	
	Lubricity/Dosage	5.742	5.337	NCN	
	Lubricity/Stability	5.197	9.958	NCN	
CombiLac®	**Dimension**	5.599	7.058	NCN	72.16
	Compressibility	5.619	3.395	72.16	
	Flowability	6.028	3.290	62.44	
	Lubricity/Dosage	4.769	5.337	NCN	
	Lubricity/Stability	7.561	9.958	NCN	
Emcompress®	**Dimension**	9.547	7.058	NCN	102.67
	Compressibility	4.958	3.395	102.67	
	Flowability	6.835	3.290	53.32	
	Lubricity/Dosage	4.878	5.337	NCN	
	Lubricity/Stability	8.646	9.958	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

Table 4.8: (Continued) Corrective excipient data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate to produce compressible pyridoxine formulations

Filler	SeDeM EDS Factor	SeDeM EDS value: Filler	SeDeM EDS value: API	Corrective excipient (filler) as per SeDeM EDS Factor (%)	Total Corrective Excipient (%)
FlowLac®	**Dimension**	6.920	7.058	NCN	69.36
	Compressibility	5.709	3.395	69.36	
	Flowability	5.875	3.290	66.13	
	Lubricity/Dosage	3.626	5.337	NCN	
	Lubricity/Stability	9.818	9.958	NCN	
MicroceLac®	**Dimension**	5.765	7.058	NCN	78.06
	Compressibility	5.451	3.395	78.06	
	Flowability	5.942	3.290	64.48	
	Lubricity/Dosage	5.115	5.337	NCN	
	Lubricity/Stability	8.261	9.958	NCN	
Tablettose®	**Dimension**	8.178	7.058	NCN	302.92
	Compressibility	3.925	3.395	302.92	
	Flowability	6.162	3.290	59.53	
	Lubricity/Dosage	7.187	5.337	NCN	
	Lubricity/Stability	9.817	9.958	NCN	
Tricalcium citrate	**Dimension**	6.188	7.058	NCN	83.02
	Compressibility	5.328	3.395	83.02	
	Flowability	5.865	3.290	66.41	
	Lubricity/Dosage	9.319	5.337	NCN	
	Lubricity/Stability	6.387	9.958	NCN	

** – Percentage obtained by taking the largest percentage filler calculated for the five factors

∞ – Represents a value that was impossible to calculate because both the filler and API radial values are below five

NCN – No correction required (the API already has a radial value > 5)

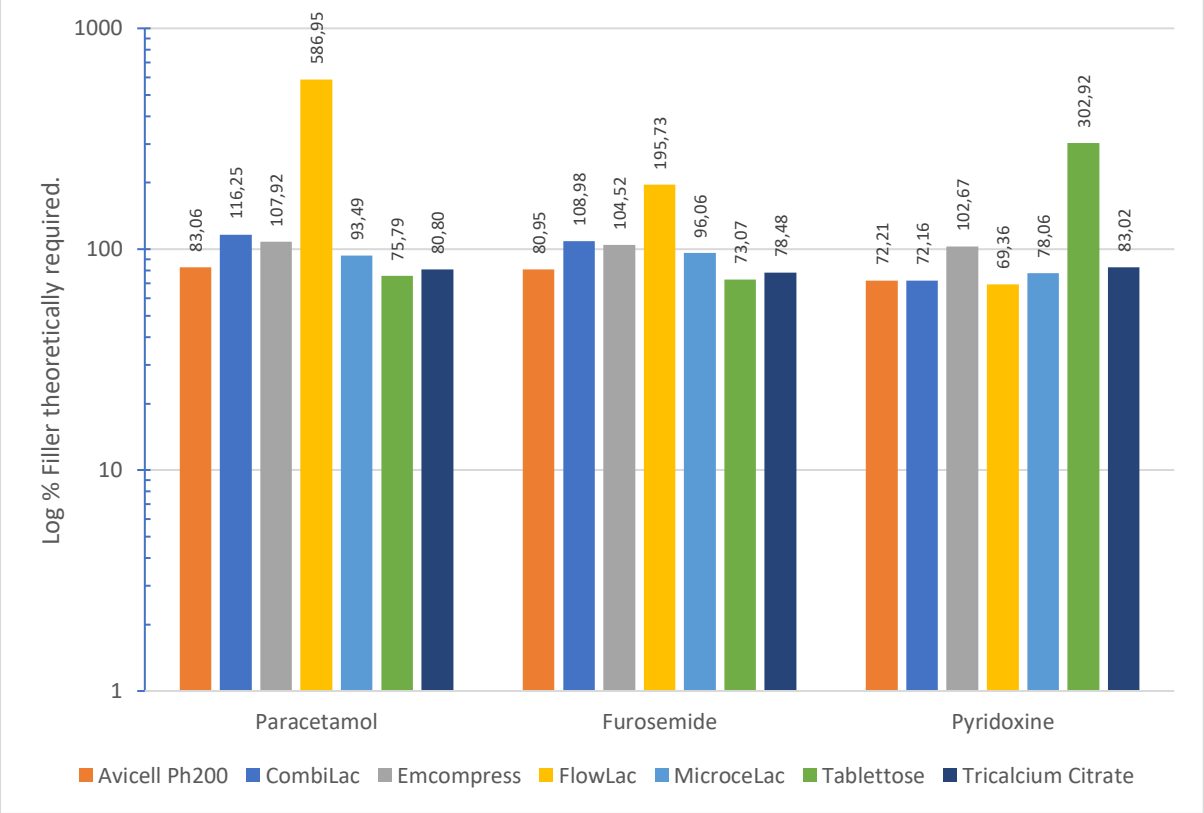

Figure 4.21: Theoretical percentage of Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and Tricalcium citrate needed to correct the properties of paracetamol, furosemide, and pyridoxine using SeDeM EDS respectively.

According to the theoretical calculations, the filler most suitable for paracetamol and furosemide is Tablettose®, while for pyridoxine it is FlowLac®. The reasoning behind these suggestions, is that when performing the corrective excipient calculations, these fillers resulted in the lowest amount of corrective excipient needed to correct all the deficient SeDeM EDS factors of the APIs. Concentrations of 75.79% and 73.07% of Tablettose® are required to correct paracetamol and furosemide respectively, while only 69.36% FlowLac® is needed to correct the poor flow and compressibility of pyridoxine. This indicates that a higher concentration API might be incorporated into the formulation. TCC is suitable to correct all three APIs tested, with an average ratio of 20 % API to 80 % filler. Paracetamol needs 80.8% TCC, which indicated that TCC can incorporate 19.2% paracetamol. Furosemide needs 78.48% TCC, while pyridoxine needs 83.02% TCC, which indicated that TCC can incorporate 21.52% furosemide and 16.98% pyridoxine in directly compressible tablets. When considering paracetamol and furosemide, TCC is theoretically the second-best filler to use when comparing the fillers tested in this study, with only Tablettose® providing a higher dilution potential. A ranking order of fillers can be drafted for each of the APIs according to their

theoretical dilution potential. This ranking order for paracetamol and furosemide is as follows: Tablettose® > TCC > Avicel® PH200 > MicroceLac® > Emcompress® > CombiLac® > FlowLac®. The ranking order for pyridoxine is: FlowLac® > CombiLac® > Avicel® PH200 > MicroceLac® > TCC > Emcompress® > Tablettose®.

4.4 Phase 3: Experimental dilution potential results

To determine dilution potential, tablets were formulated and compressed using known and fixed concentration ranges of API (Habib *et al.*, 1996:206). These tablets were also evaluated for their pharmaceutical acceptability. The friability and uniformity of mass were considered when evaluating the dilution potential of each filler (Salim *et al.*, 2022:182; Scholtz *et al.*, 2017:226). The dilution potential values can be seen in figure 4.22.

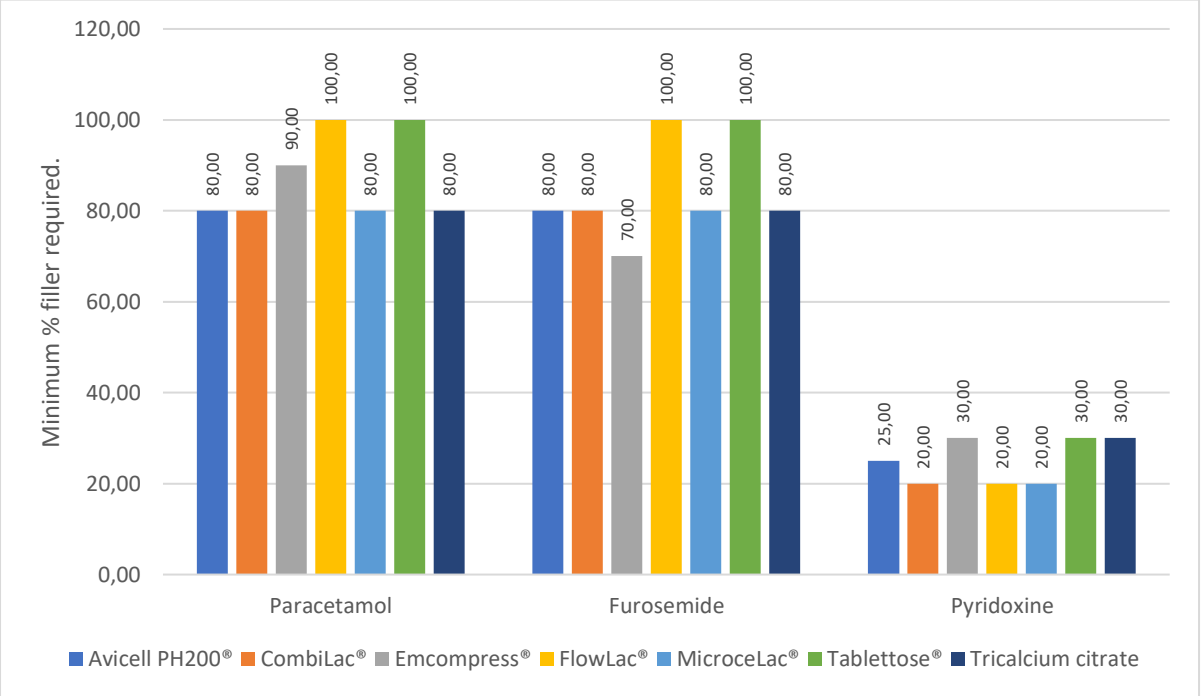

Figure 4.22: Minimum amount of filler needed to produce acceptable tablets using Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose® and tricalcium citrate together with paracetamol, furosemide, and pyridoxine respectively

When interpreting these results, a lower value of filler needed corresponds to a higher dilution potential of the filler. Results of 100% or higher, indicates that no tablets of sufficient quality could be compressed using the specific filler. These included the mixtures of FlowLac® and Tablettose® containing paracetamol and furosemide. The reason for these failures were a friability of higher than the 1% allowed as specified in official criteria (BP, 2021).

The SeDeM EDS's reliability factor is 0.952, which means that a deviation of more than 10% between the theoretical and real results is considered significant (Scholtz *et al.*, 2017:226). When taking this into consideration, the SeDeM prediction of the amount of TCC needed to formulate both paracetamol and furosemide were not only within the acceptable range, but also smaller than the deviations obtained from the other fillers tested. Pyridoxine on the other hand showed a significant deviation from the prediction when using all seven fillers. This might be explained by pyridoxine's IP, IPP and IGC passing the SeDeM EDS criteria, indicating that the API itself may be directly compressible. Pyridoxine also showed greater potential when comparing powder flow to the other APIs, which would cause better die filling and consequently higher quality tablets (Wu *et al.*, 2003:26-29). When trying to compress pyridoxine on its own, however, tablets could not be manufactured due to poor flowability. FlowLac®'s inability to produce tablets containing paracetamol and furosemide, was correctly predicted by the SeDeM EDS analysis.

When comparing TCC's dilution potential to the other fillers tested, no other filler exceeded TCC's dilution potential for paracetamol and furosemide. When considering pyridoxine, TCC, while still performing well with a ratio of 30:70 filler to API, performed equal to or worse than the other fillers tested.

4.5 Tablet evaluation results using quality tests

The results of the quality evaluation tests, together with the concentration range were used to determine the real or true dilution potential of the different fillers. The ratio of API to filler were further increased in intervals of 5% per formulation when the evaluation tests indicated that tablets did not comply with specifications. Table 4.9, 4.10 and 4.11 provide the tablet evaluation test results for the different formulations used to determine the dilution potential for different filler (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and TCC) and API (furosemide, paracetamol, and pyridoxine) combinations. The two tests most important for dilution potential includes uniformity of mass and friability. Crushing strength were also considered, but it is classified as an unofficial test (BP, 2021) and could therefore only be used as a guideline.

Table 4.9: Evaluation test results used for determination of dilution potential of different fillers for furosemide

Filler	Filler : API	Uniformity of mass	Friability	Mean crushing strength (N)	Crushing strength standard deviation (N)
Avicel® PH200	**90:10**	✓	✓	103.2	19.05
	80:20	✓	✓	54.9	8.74
	75:25	✓	×	11.85	1.77
CombiLac®	**90:10**	✓	✓	126.3	35.15
	80:20	✓	✓	91.7	8.81
	70:30	✓	×	0	0
Emcompress®	**90:10**	✓	✓	102.0	41.75
	80:20	✓	✓	106.1	23.95
	70:30	✓	✓	117.0	13.65
	60:40	×	×	60.3	15.49
FlowLac®	**95:5**	×	×	0	0
MicroceLac®	**90:10**	✓	✓	160.8	16.48
	80:20	✓	✓	81.8	15.86
	70:30	✓	×	74.1	21.88
Tablettose®	**90:10**	×	×	44.4	28.45
Tricalcium citrate	**90:10**	✓	✓	382.3	24.85
	80:20	✓	✓	255.5	21.41
	70:30	×	✓	123.7	23.58

The highlighted rows are the highest dilution potential reached for each filler and API combination

Table 4.10: Evaluation test results used for determination of dilution potential of different fillers for paracetamol

Filler	Filler : API	Uniformity of mass	Friability	Mean crushing strength (N)	Crushing strength standard deviation (N)
Avicel® PH200	**90:10**	✓	✓	61.6	3.84
	80:20	✓	✓	42.3	4.95
	75:25	×	×	0	0
CombiLac®	**90:10**	✓	✓	349.9	20.12
	80:20	✓	✓	295.7	14.31
	70:30	✓	×	0	0
Emcompress®	**90:10**	✓	✓	140.0	24.45
	85:15	×	✓	130	20.36
	80:20	×	✓	125.9	16.51
FlowLac®	**95:5**	✓	×	38.6	10.24
MicroceLac®	**90:10**	✓	✓	270.4	47.61
	80:20	✓	✓	119.2	6.51
	70:30	×	×	44.78	21.05
Tablettose®	**90:10**	×	×	78.2	32.78
Tricalcium citrate	**90:10**	✓	✓	440.7	34.58
	80:20	✓	✓	340.3	51.88
	75:25	×	×	242.3	14.37
	70:30	✓	×	220.4	36.00
	60:40	✓	×	82.0	10.09

The highlighted rows are the highest dilution potential reached for each filler and API combination

Table 4.11: Evaluation test results used for determination of dilution potential of different fillers for pyridoxine

Filler	Filler : API	Uniformity of mass	Friability	Mean crushing strength (N)	Crushing strength standard deviation (N)
Avicel® PH200	**70:30**	✓	✓	374.8	15.21
	30:70	✓	✓	109.5	3.5
	25:75	✓	✓	0	0
	20:80	✓	×	65.0	2.36
CombiLac®	**70:30**	✓	✓	260.9	7.56
	20:80	✓	✓	53.3	2.7
	10:90	✓	×	30.2	2.35
Emcompress®	**90:10**	✓	✓	124.0	22.52
	30:70	✓	✓	75.0	8.23
	25:75	✓	×	38.3	22.87
	20:80	✓	×	45.8	5.05
FlowLac®	**90:10**	✓	✓	161.0	32.06
	60:40	✓	✓	85.0	11.41
	40:60	✓	✓	80.6	6.65
	20:80	✓	✓	41.5	2.64
	10:90	✓	×	20.2	2.78
MicroceLac®	**70:30**	✓	✓	279.9	23.14
	20:80	✓	✓	61.5	1.43
	10:90	✓	×	64.7	4.35
Tablettose®	**90:10**	✓	✓	111.8	29.79
	40:60	✓	✓	42.7	4.6
	30:70	✓	✓	29.8	3.08
	25:75	✓	×	24.9	1.45
	20:80	×	×	25.4	2.8
Tricalcium citrate	**80:20**	✓	✓	331.5	86.53
	30:70	✓	✓	99.5	6.95
	25:75	✓	×	30.1	7.28
	20:80	×	×	45.7	7.86

The highlighted rows are the highest dilution potential reached for each filler and API combination

4.5.1.2 Uniformity of mass

Uniformity of mass is used to determine the deviation of each tablet's mass from the mean mass of the batch of tablets (BP, 2021). Using table 4.9 to 4.11 it can be seen that pyridoxine was able to reach a much higher API content (up to 90% pyridoxine using CombiLac®, FlowLac® and MicroceLac®) than either paracetamol or furosemide, while still complying with the uniformity of mass requirements as stipulated in the BP (2021).

Furosemide was able to reach an API content of 20% for all fillers except Tablettose® and FlowLac®. Tablettose and FlowLac® were unable to produce any tablets containing furosemide, which complied with the BP's uniformity of mass specifications. TCC was able to produce tablets containing 20% furosemide, while still complying with the uniformity of mass specifications.

Emcompress® and FlowLac® were not able to produce a tablet with a paracetamol concentration of 20%. Tablettose® was unable to produce tablets containing paracetamol, while FlowLac® could incorporate 5% paracetamol and Emcompress® were able to produce tablets containing 10% paracetamol while still complying with the BP specifications.

Variation in uniformity of mass as well as crushing strength as indicated by standard deviation, which can be seen in tables 4.9 to 4.11, might be directly linked to the flow rate of a powder as a higher variation might be caused by poor flowability leading to incomplete die filling. This incomplete die filling might also cause higher deviations in tablet mass as the amount of powder used to produce each tablet might differ from each other (Bhowmik *et al.*, 2014:24373; Chavan *et al.*, 2018:61-62).

4.5.1.3 Friability

Friability together with crushing strength, are used to determine the amount of mass lost during handling of the tablet as well as ensure that no broken tablets ends in the final product used by the patients (Osei-Yeboah & Sun, 2015:146-147). Friability can be linked to tablet hardness. Usually the mechanically stronger tablets, presents a lower friability. According to the BP (2021) standards, a tablet must have less than 1% friability. As with the uniformity of mass results, friability limits of tablets containing pyridoxine is in general reached at a higher concentration of API (80%) than either paracetamol (20%) or pyridoxine (30%), while still complying with the BP friability specification.

Furosemide and paracetamol were able to reach average concentrations of 20% with all fillers tested in this study except for FlowLac® and Tablettose®, which both could not produce any

tablets containing furosemide or paracetamol, while still complying with friability specifications. Both Emcompress® and TCC were able to reach a furosemide concentration of 30%, while still complying with the BP's friability requirements.

4.5.1.4 Tensile strength

Tensile strength provides a more inclusive value for comparing tablets' mechanical strength than the crushing strength (BP, 2021). The reason for this, is that this parameter also considers the tablet's dimensions. The tensile strength values for each formulation tested in this study can be seen in tables 4.12 to 4.14.

Table 4.12: Tensile strength data for formulations containing furosemide

Filler	Filler : API	Mean tablet thickness (mm)	Mean tablet diameter (mm)	Mean crushing strength (N)	Mean tensile strength (N/mm^2)
Avicel® PH200	**90:10**	4.62	12.06	103.2	1.18
	80:20	4.72	12.04	54.9	0.62
	75:25	5.86	11.78	11.85	0.11
CombiLac®	**90:10**	3.4	12.03	126.3	1.97
	80:20	3.55	12.04	91.7	1.37
	70:30	4.62	3.53	0	0.00
Emcompress®	**90:10**	2.15	12.27	102	2.46
	80:20	2.3	11.83	106.1	2.48
	70:30	2.32	11.79	117.0	2.72
	60:40	2.79	12.02	60.3	1.14
FlowLac®	**95:5**	0	0	0	0.00
MicroceLac®	**90:10**	3.41	12.09	160.8	2.48
	80:20	3.58	12.05	81.8	1.21
	70:30	3.47	12.04	74.1	1.13
Tablettose®	**90:10**	3.14	12.09	44.4	0.74
Tricalcium citrate	**90:10**	2.86	12.06	382.3	7.06
	80:20	2.95	12.06	255.5	4.57
	70:30	3.07	11.09	123.7	2.31

Table 4.13: Tensile strength data for formulations containing paracetamol

Filler	Filler : API	Mean tablet thickness (mm)	Mean tablet diameter (mm)	Mean crushing strength (N)	Mean tensile strength (N/mm^2)
Avicel® PH200	**90:10**	5.69	12.03	61.6	0.57
	80:20	5.22	12.03	42.3	0.43
	75:25	6.07	4.38	0	0.00
CombiLac®	**90:10**	3.08	12.02	349.9	6.02
	80:20	3.23	12.03	295.7	4.84
	70:30	4.36	3.22	0	0.00
Emcompress®	**90:10**	2.32	12.08	140	3.18
	85:15	2.71	12.01	65.8	1.29
	80:20	2.45	12.04	125.9	2.72
FlowLac®	**95:5**	3.28	12.04	38.6	0.62
MicroceLac®	**90:10**	3.23	12.2	270.4	4.37
	80:20	3.44	12.08	119.2	1.83
	70:30	3.52	12.07	44.78	0.67
Tablettose®	**90:10**	3.19	12.11	78.2	1.29
Tricalcium citrate	**90:10**	2.77	12.03	440.7	8.42
	80:20	2.99	12.04	340.3	6.02
	75:25	4.09	12.04	242.3	3.13
	70:30	3.25	12.04	220.4	3.59
	60:40	3.28	12.06	82.0	1.32

Table 4.14: Tensile strength data for formulations containing pyridoxine.

Filler	Filler : API	Mean tablet thickness (mm)	Mean tablet diameter (mm)	Mean crushing strength (N)	Mean tensile strength (N/mm^2)
Avicel® PH200	**70:30**	3.24	11.95	374.8	6.16
	30:70	3.31	12.03	109.5	1.75
	25:75	3.35	10.93	0	0.00
	20:80	3.36	12.04	65.0	1.02
CombiLac®	**70:30**	3.16	11.98	260.9	4.39
	20:80	3.37	12.05	53.3	0.84
	10:90	3.45	12.03	30.2	0.46
Emcompress®	**90:10**	2.4	11.88	124	2.77
	30:70	3.08	12.05	75	1.29
	25:75	3.2	12.02	38.3	0.63
	20:80	3.09	12.04	45.8	0.78
FlowLac®	**90:10**	3.19	12	161	2.68
	60:40	3.41	12.16	85	1.31
	40:60	3.26	12.04	80.6	1.31
	20:80	3.36	12.03	41.5	0.65
	10:90	3.42	12.02	20.2	0.31
MicroceLac®	**70:30**	3.21	11.7	279.9	4.74
	20:80	3.44	12.03	61.5	0.95
	10:90	3.46	12.04	64.7	0.99
Tablettose®	**90:10**	3.22	12.09	111.8	1.83
	40:60	3.31	12.06	42.7	0.68
	30:70	3.44	12.05	29.8	0.46
	25:75	3.31	12.03	24.9	0.40
	20:80	3.4	12.05	25.4	0.39
Tricalcium citrate	**80:20**	3.19	12.06	331.5	5.49
	30:70	3.19	12.04	99.5	1.65
	25:75	3.49	12.05	30.1	0.46
	20:80	3.23	12.04	45.7	0.75

When comparing results from the friability test with the tensile strength results, it can be seen that a higher tensile strength almost always corresponds to a passable friability result. TCC was also able to obtain higher tensile strength values than the other fillers tested in this study. This might be due to TCC being able to form harder tablets than the other fillers tested.

4.6 Summary

SeDeM EDS characterisation was performed on various selected fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and TCC), as well as selected APIs (furosemide, paracetamol, and pyridoxine). Each filler and API was analysed based on the twelve SeDeM EDS parameters including bulk density, tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner ratio, angle of response, powder flow, percentage loss on drying, hygroscopicity, percentage of particles smaller than 50 µm, and the homogeneity index (Sune-Negre *et al.*, 2008:1031). It is not ideal to draw any conclusions using only these parameters, therefore, the parameters were grouped into five incidences or factors and three additional indices were also calculated (Dai *et al.*, 2019:520-521,523).

Based on the SeDeM EDS results obtained, including the five incidence factors and three additional indices, it was evident that it was unlikely to compress tablets consisting of only the APIs. The SeDeM EDS can provide a solution for this problem by predicting the theoretical amount of a corrective excipient that should be added to the formulation for it to be directly compressible (Dai *et al.*, 2019:523). To evaluate the accuracy of this corrective excipient value, experimental dilution studies were performed on the API – filler mixtures.

When comparing the results of the SeDeM EDS performed on the fillers, TCC and MicroceLac® were the only fillers to pass all five SeDeM incidence factors, as well as all three additional indices. This should theoretically indicate that TCC and MicroceLac® are suitable for direct compression of tablets without adding any extra ingredients to the formulation. However, tablets should contain at least one API to produce a therapeutic effect.

When the selected APIs were added to the fillers, Avicel® PH200, CombiLac®, Emcompress®, MicroceLac® and TCC were able to produce acceptable tablets according to the BP (2021) specifications for furosemide, paracetamol, and pyridoxine. FlowLac® and Tablettose®, however, were only able to produce tablets containing pyridoxine. Avicel® PH200 was able to incorporate 20% furosemide and paracetamol, as well as 75% pyridoxine. CombiLac® and MicroceLac® produced tablets containing 20% furosemide and paracetamol and could also incorporate 80% pyridoxine. Emcompress® could produce tablets containing 10%, 70% and 30% furosemide, paracetamol, and pyridoxine respectively. FlowLac® and Tablettose® could only produce tablets containing 80% and 70% pyridoxine respectively. TCC could incorporate 20% furosemide and paracetamol as well as 70% pyridoxine.

The SeDeM EDS were also able to predict, within 5%, the amount of TCC needed to successfully produce tablets containing furosemide (80.8% TCC needed) and paracetamol

(78.48% TCC needed). Pyridoxine, however, exceeded the SeDeM EDS prediction of 83.02% TCC needed, producing tablets containing only 30% TCC and 70% pyridoxine.

CHAPTER 5:
SUMMARY AND FUTURE PROSPECTS

5.1 Summary

Since tablets was introduced to the market as solid oral dosage forms, it has become the most commonly used dosage form (Sun, 2011:213). Tablets are manufactured by using one of several manufacturing methods such as wet granulation, dry granulation, and direct compression (Bhowmik *et al.*, 2014:24369). Each of these methods have different advantages as well as disadvantages but one factor that all these methods have in common is that it needs a pharmaceutical powder mixture constituted of different pharmaceutical excipients each with a specific function (Abrantes *et al.*, 2016:2019). Direct compression is a method that uses these pharmaceutical powder mixtures and directly compress them into tablets. This enables the manufacturing of tablets containing substances that are thermo-labile or moisture sensitive (Jivraj *et al.*, 2000:58).

To determine the suitability of a pharmaceutical powder to be used during direct compression, the SeDeM EDS was developed (Suñé-Negre *et al.*, 2011:464). This system takes several powder properties such as bulk density, tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner ratio, angle of repose, powder flow, loss on drying, hygroscopicity, particle size and the homogeneity into consideration (Suñé-Negre *et al.*, 2011:464). After values for these properties are determined, the SeDeM EDS also combines them into five incidence factors including compressibility factor, flowability factor, dimensional factor, lubricity/dosage factor and the lubricity/stability factor (Suñé-Negre *et al.*, 2011:465). These can then be further combined into three additional indices, which include the index parameter, index of good compressibility, and the index of profile parameter (Dai *et al.*, 2019:521). Using these values, pharmaceutical powders can be compared in terms of their ability to be directly compressed. The SeDeM EDS also provides the means to calculate the amount of a corrective excipient, which should be added to a powder mixture to render the mixture suitable for direct compression (Dai *et al.*, 2019:521).

TCC, a fairly new filler was characterised according to the SeDeM EDS and compared to commonly used direct compressible excipients/fillers (Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac® and Tablettose®). Three APIs namely furosemide, paracetamol, and pyridoxine were also characterised according to the SeDeM EDS. Furthermore, the fillers were also characterised with respect to their dilution potential using the three APIs respectively.

When comparing the overall results obtained during this study, TCC performed remarkably well. Only TCC and MicroceLac® passed all five SeDeM EDS factors as well as the three SeDeM EDS additional indices. The other fillers failed in at least one SeDeM EDS incidence factor or additional index. TCC also exhibited the highest radial value (10) for the homogeneity index, indicating that its particle size distribution range is the smallest of the powders tested during this study. TCC also produced the hardest tablets, requiring the strongest force in order to break the tablets during the execution of the crushing strength test. This resulted in TCC tablets presenting the highest tensile strength as well as obtaining the highest radial value in in the cohesion index parameter (10).

When taking all the results obtained in this study into consideration, the conclusion can be made that TCC is indeed suitable as a filler to be used during the direct compression of tablets containing the selected APIs. When considering the fillers tested during this study, two ranking orders can be assigned based on their SeDeM EDS additional indices. The ranking for the IP is as follows: Emcompress®, Tablettose®, TCC, MicroceLac® and CombiLac® > FlowLac® > Avicel® PH200, while the IPP and IGC can both be ranked as: Emcompress® > Tablettose® > TCC > FlowLac® > MicroceLac® > CombiLac® >Avicel® PH200 When considering both of these ranking orders, TCC is within the top three of the fillers tested, based on its suitability for direct compression, according to the SeDeM EDS.

5.2 Outcomes

The aim of this study was to analyse TCC's suitability as a filler when using direct compression as a means to produce pharmaceutical tablets as well as comparing TCC to other commonly used fillers using the SeDeM Expert Diagram System.

When considering the objectives as given in section 1.3, the following objectives were met:

- The bulk density, tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner ratio, angle of response, powder flow, loss on drying, hygroscopicity, homogeneity index as well as the percentage of particles smaller than 50 µm were determined for the selected fillers namely Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose ®, and TCC, as well as the selected APIs namely furosemide, paracetamol, and pyridoxine.
- The selected fillers and APIs were successfully characterised with regards to its SeDeM EDS profile using the abovementioned properties of each powder respectively.
- Tablets were successfully compressed using the abovementioned APIs and fillers, making use of the direct compression manufacturing method.

- The dilution potential for the selected fillers were successfully determined for furosemide, paracetamol, and pyridoxine and the results compared to the SeDeM EDS theoretical prediction.
- Tablets compressed using the abovementioned APIs and fillers were successfully evaluated in respect to mass variation, friability and crushing strength according to the specifications as stipulated in the BP (BP, 2021).

5.3 Future prospects

Based on the results and findings or the study, the following recommendations can be made for future investigation:

- Investigate other drug delivery systems, or dosage forms, prepared from TCC such as beads and granules. These delivery systems could also be analysed and compared to beads and granules prepared from other fillers, using the SeDeM EDS.
- The list of fillers that are characterised using the SeDeM EDS and compared to TCC can be expanded.
- Final direct compressible tablet formulations, containing TCC, an API, a disintegrant, a lubricant or a binder, or all of the previously mentioned excipients should be prepared and evaluated according to the standards and specifications as stipulated in the BP (2021) to investigate the performance and suitability of TCC as tableting excipient.
- The dilution potential of TCC could be determined for other commonly used APIs such as ibuprofen.

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Annexture A:

Cohesion index data for pure fillers and APIs

Table A-1 and A-2 contains the tablet hardness data used to determine the cohesion index of each filler and API during the SeDeM EDS characterisation. Ten randomly selected tablets were tested, and the average hardness were used in the calculations as discussed in chapter 3. Values indicated as N/A indicates that the resulting tablet's hardness could not be determined for the tablet was too soft.

Table A-1: Tablet hardness (cohesion index) data for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, and MicroceLac®.

	Avicel® PH200	**CombiLac®**	**Emcompress®**	**FlowLac®**	**MicroceLac®**
T_1	378 N	340 N	158 N	224 N	337 N
T_2	365 N	354 N	157 N	235 N	334 N
T_3	364 N	287 N	149 N	209 N	349 N
T_4	366 N	354 N	158 N	220 N	340 N
T_5	366 N	347 N	158 N	234 N	343 N
T_6	367 N	341 N	163 N	231 N	348 N
T_7	362 N	335 N	151 N	211 N	341 N
T_8	367 N	356 N	150 N	214 N	327 N
T_9	369 N	360 N	157 N	206 N	328 N
T_{10}	369 N	360 N	164 N	252 N	342 N
Average	367.30 N	343.40 N	156.50 N	223.60 N	338.9 N

Table A-2: Tablet hardness (cohesion index) data for Tablettose®, tricalcium citrate, furosemide, paracetamol, and pyridoxine.

	Tablettose®	**Tricalcium citrate**	**Furosemide**	**Paracetamol**	**Pyridoxine**
T_1	105 N	432 N	125 N	24 N	14 N
T_2	66 N	432 N	76 N	N/A	14 N
T_3	94 N	457 N	85 N	N/A	13 N
T_4	95 N	456 N	102 N	N/A	15 N
T_5	94 N	472 N	81 N	N/A	14 N
T_6	100 N	387 N	62 N	N/A	14 N
T_7	105 N	453 N	93 N	N/A	14 N
T_8	92 N	446 N	83 N	N/A	14 N
T_9	95 N	445 N	89 N	N/A	17 N
T_{10}	67 N	448 N	124 N	N/A	14 N
Average	91.30 N	442.80 N	92.00 N	24.00 N	14.30 N

Annexture B:
Powder particle size analysis data for pure fillers and APIs, obtained from the Malvern Mastersizer

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Figure B-1 up to figure B-10 contains the particle size analysis data obtained from a Malvern® mastersizer 3000 (Malvern®, Heusenstamm, Germany). This data was used to determine two of the SeDeM EDS basic parameters including the homogeneity index as well as the percentage of particles smaller than 50 µm as described in chapter 3.

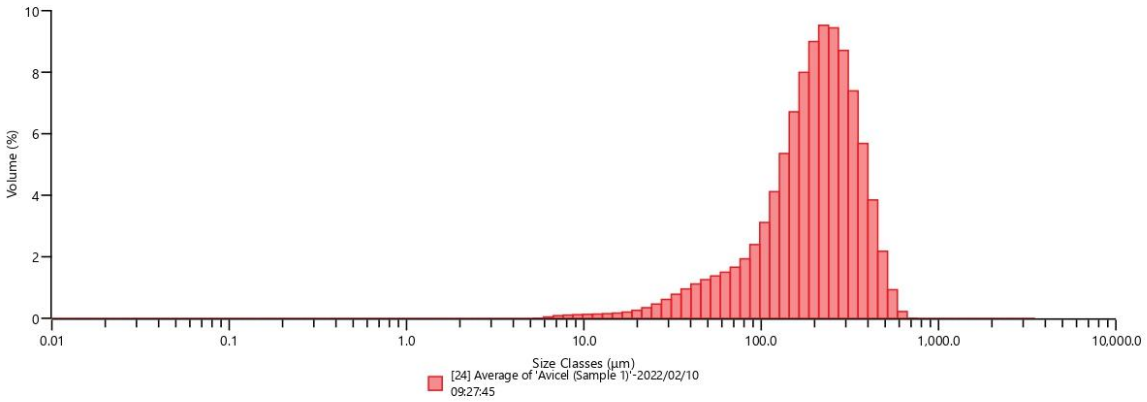
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Avicel (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:27:45
Measurement Date Time	2022/02/10 09:27:45
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,67 %
Laser Obscuration	0,18 %

Result	
Concentration	0,0029 %
Span	1,498
Uniformity	0,449
Specific Surface Area	47,56 m²/kg
D [3,2]	126,148 µm
D [4,3]	216,315 µm
Dv (10)	67,988 µm
Dv (50)	204,929 µm
Dv (90)	375,015 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	0,15	76,006	1,93	453,960	2,18	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	0,17	86,355	2,40	515,772	0,93	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	0,20	98,114	3,11	586,001	0,22	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	0,26	111,473	4,12	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,00	21,205	0,34	126,652	5,36	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,00	24,092	0,46	143,897	6,71	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,00	27,373	0,61	163,490	7,99	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,00	31,100	0,78	185,752	9,00	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,04	35,335	0,95	211,044	9,52	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,08	40,146	1,12	239,780	9,44	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,10	45,613	1,26	272,430	8,71	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,12	51,823	1,38	309,525	7,39	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,13	58,880	1,50	351,670	5,68	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	0,14	66,897	1,66	399,555	3,85	2386,415	0,00		

Figure 1-1: Particle size data for Avicel PH200®

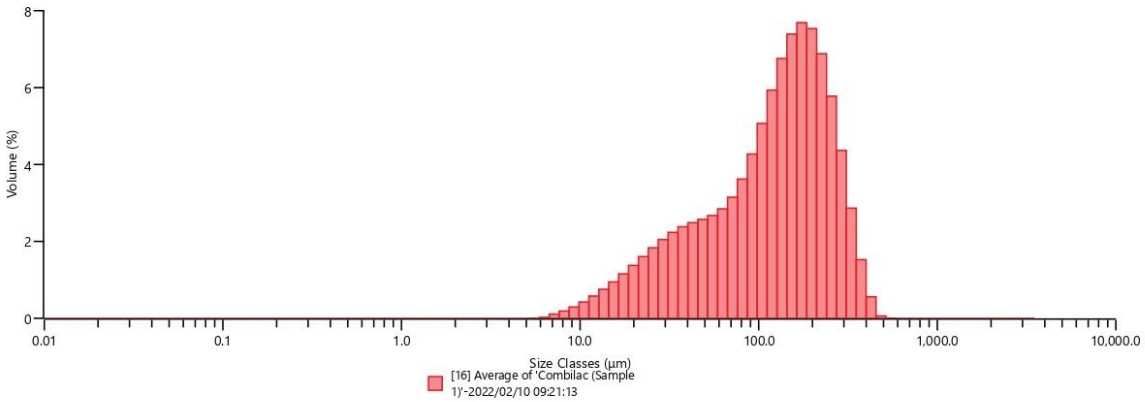
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Combilac (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:21:13
Measurement Date Time	2022/02/10 09:21:13
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,50 %
Laser Obscuration	0,72 %

Result	
Concentration	0,0062 %
Span	1,846
Uniformity	0,576
Specific Surface Area	87,63 m²/kg
D [3,2]	68,467 µm
D [4,3]	140,557 µm
Dv (10)	28,595 µm
Dv (50)	130,067 µm
Dv (90)	268,708 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	0,75	76,006	3,62	453,960	0,06	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	0,95	86,355	4,27	515,772	0,00	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	1,16	98,114	5,07	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	1,38	111,473	5,93	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,00	21,205	1,61	126,652	6,76	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,00	24,092	1,83	143,897	7,39	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,00	27,373	2,05	163,490	7,69	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,00	31,100	2,24	185,752	7,53	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,02	35,335	2,38	211,044	6,88	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,11	40,146	2,49	239,780	5,78	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,19	45,613	2,57	272,430	4,37	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,29	51,823	2,67	309,525	2,86	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,43	58,880	2,85	351,670	1,53	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	0,58	66,897	3,15	399,555	0,56	2386,415	0,00		

Figure 1-2: Particle size data for CombiLac®

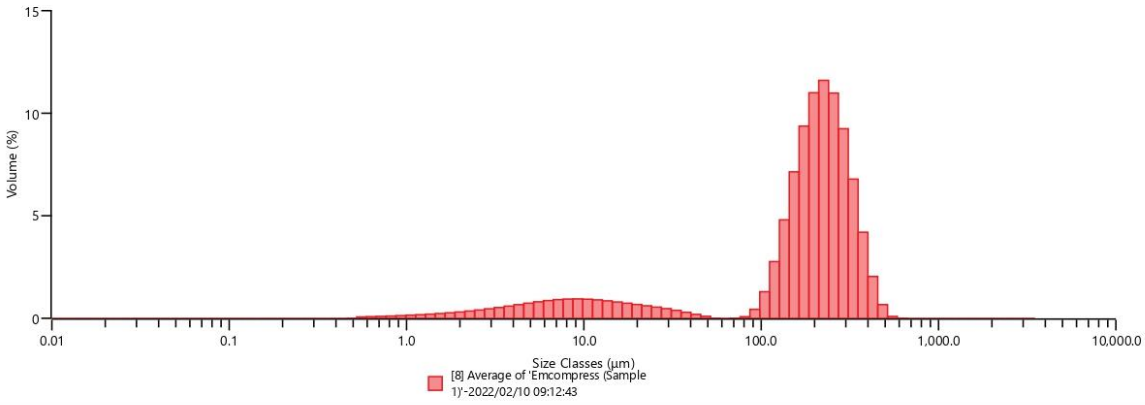
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Emcompress (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:12:43
Measurement Date Time	2022/02/10 09:12:43
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,60 %
Laser Obscuration	2,98 %

Result	
Concentration	0,0084 %
Span	1,608
Uniformity	0,431
Specific Surface Area	246,1 m²/kg
D [3,2]	24,384 µm
D [4,3]	194,187 µm
Dv (10)	9,832 µm
Dv (50)	200,564 µm
Dv (90)	332,342 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,35	12,726	0,85	76,006	0,08	453,960	0,67	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,40	14,458	0,80	86,355	0,44	515,772	0,09	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,46	16,427	0,73	98,114	1,30	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,07	3,125	0,53	18,664	0,67	111,473	2,77	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,08	3,550	0,59	21,205	0,61	126,652	4,80	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,09	4,034	0,67	24,092	0,54	143,897	7,14	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,11	4,583	0,74	27,373	0,47	163,490	9,37	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,13	5,207	0,81	31,100	0,39	185,752	11,00	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,15	5,916	0,86	35,335	0,29	211,044	11,60	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,17	6,722	0,91	40,146	0,19	239,780	10,98	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,20	7,637	0,94	45,613	0,10	272,430	9,24	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,23	8,677	0,94	51,823	0,00	309,525	6,79	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,27	9,858	0,93	58,880	0,00	351,670	4,20	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,31	11,201	0,90	66,897	0,00	399,555	2,04	2386,415	0,00		

Figure 1-3: Particle size data for Emcompress®

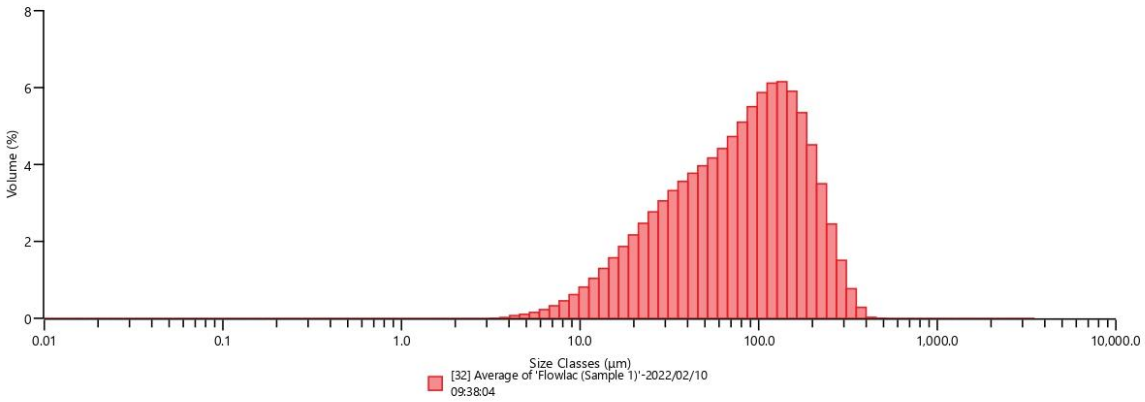
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Flowlac (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:38:04
Measurement Date Time	2022/02/10 09:38:04
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,61 %
Laser Obscuration	1,18 %

Result	
Concentration	0,0069 %
Span	2,221
Uniformity	0,700
Specific Surface Area	129,1 m²/kg
D [3,2]	46,470 µm
D [4,3]	98,583 µm
Dv (10)	20,316 µm
Dv (50)	82,035 µm
Dv (90)	202,508 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	1,30	76,006	5,10	453,960	0,00	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	1,57	86,355	5,50	515,772	0,00	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	1,87	98,114	5,87	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	2,17	111,473	6,12	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,02	21,205	2,47	126,652	6,15	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,07	24,092	2,77	143,897	5,91	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,10	27,373	3,05	163,490	5,35	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,15	31,100	3,32	185,752	4,51	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,23	35,335	3,56	211,044	3,50	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,33	40,146	3,77	239,780	2,45	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,45	45,613	3,97	272,430	1,51	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,62	51,823	4,17	309,525	0,77	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,81	58,880	4,41	351,670	0,28	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	1,04	66,897	4,73	399,555	0,03	2386,415	0,00		

Figure 1-4: Particle size data for FlowLac®

Analysis

Malvern Instruments

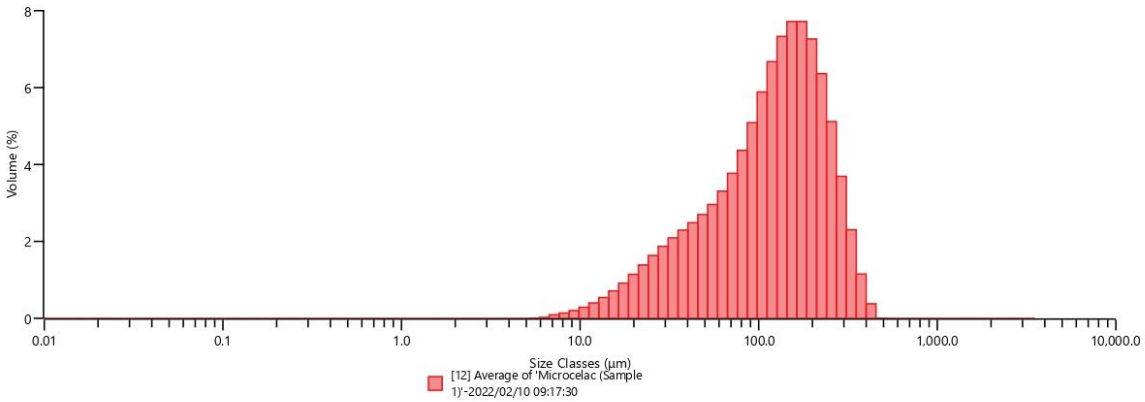
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Microcelac (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:17:30
Measurement Date Time	2022/02/10 09:17:30
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,39 %
Laser Obscuration	0,56 %

Result	
Concentration	0,0052 %
Span	1,799
Uniformity	0,555
Specific Surface Area	82,59 m²/kg
D [3,2]	72,644 µm
D [4,3]	135,815 µm
Dv (10)	32,376 µm
Dv (50)	124,339 µm
Dv (90)	256,119 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	0,54	76,006	4,37	453,960	0,00	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	0,71	86,355	5,09	515,772	0,00	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	0,91	98,114	5,89	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	1,14	111,473	6,67	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,00	21,205	1,39	126,652	7,33	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,00	24,092	1,63	143,897	7,72	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,00	27,373	1,87	163,490	7,72	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,00	31,100	2,09	185,752	7,26	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,02	35,335	2,29	211,044	6,36	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,09	40,146	2,49	239,780	5,11	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,14	45,613	2,70	272,430	3,69	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,20	51,823	2,96	309,525	2,30	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,29	58,880	3,31	351,670	1,15	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	0,40	66,897	3,77	399,555	0,38	2386,415	0,00		

Figure 1-5: Particle size data for MicroceLac®

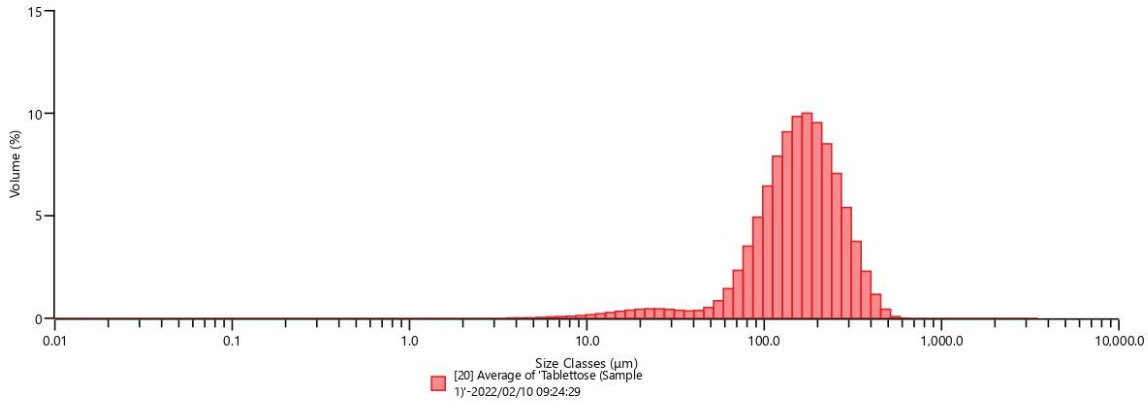
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Tablettose (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:24:29
Measurement Date Time	2022/02/10 09:24:29
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,47 %
Laser Obscuration	0,46 %

Result	
Concentration	0,0063 %
Span	1,360
Uniformity	0,426
Specific Surface Area	55,78 m²/kg
D [3,2]	107,571 µm
D [4,3]	173,063 µm
Dv (10)	75,999 µm
Dv (50)	159,839 µm
Dv (90)	293,435 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	0,28	76,006	3,52	453,960	0,44	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	0,34	86,355	4,93	515,772	0,08	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	0,40	98,114	6,45	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	0,44	111,473	7,90	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,02	21,205	0,46	126,652	9,09	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,02	24,092	0,46	143,897	9,84	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,02	27,373	0,43	163,490	10,00	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,04	31,100	0,39	185,752	9,54	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,07	35,335	0,36	211,044	8,51	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,08	40,146	0,38	239,780	7,06	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,10	45,613	0,52	272,430	5,40	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,13	51,823	0,86	309,525	3,75	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,17	58,880	1,45	351,670	2,29	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	0,22	66,897	2,34	399,555	1,17	2386,415	0,00		

Figure 1-6: Particle size data for Tablettose®

Analysis

Malvern Instruments

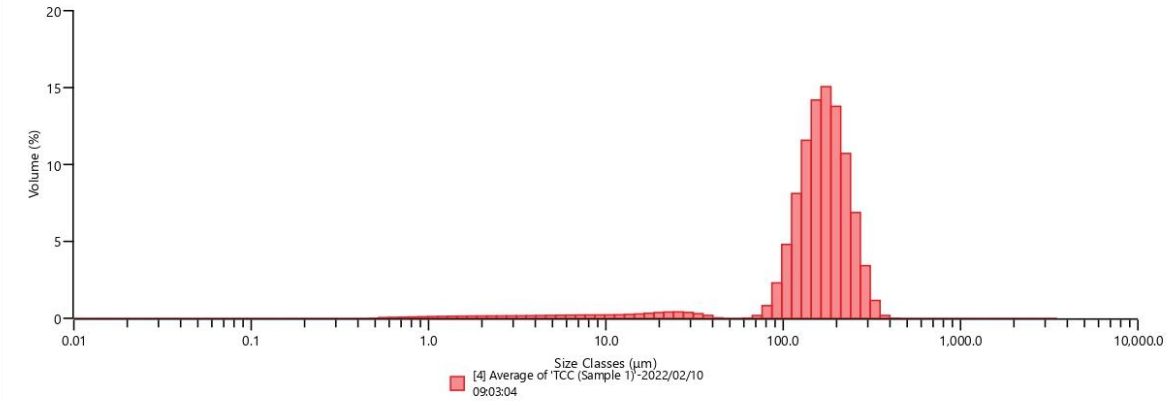
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'TCC (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:03:04
Measurement Date Time	2022/02/10 09:03:04
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,66 %
Laser Obscuration	0,58 %

Result	
Concentration	0,0029 %
Span	0,906
Uniformity	0,302
Specific Surface Area	138,6 m²/kg
D [3,2]	43,289 µm
D [4,3]	165,564 µm
Dv (10)	97,544 µm
Dv (50)	165,176 µm
Dv (90)	247,225 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,15	12,726	0,25	76,006	0,82	453,960	0,00	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,16	14,458	0,28	86,355	2,30	515,772	0,00	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,16	16,427	0,33	98,114	4,80	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,05	3,125	0,16	18,664	0,37	111,473	8,12	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,06	3,550	0,17	21,205	0,41	126,652	11,57	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,07	4,034	0,18	24,092	0,42	143,897	14,19	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,09	4,583	0,19	27,373	0,38	163,490	15,06	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,10	5,207	0,20	31,100	0,30	185,752	13,78	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,11	5,916	0,20	35,335	0,19	211,044	10,72	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,12	6,722	0,21	40,146	0,03	239,780	6,88	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,13	7,637	0,21	45,613	0,00	272,430	3,42	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,14	8,677	0,21	51,823	0,00	309,525	1,16	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,15	9,858	0,22	58,880	0,01	351,670	0,18	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,15	11,201	0,23	66,897	0,18	399,555	0,00	2386,415	0,00		

Figure 1-7: Particle size data for tricalcium citrate

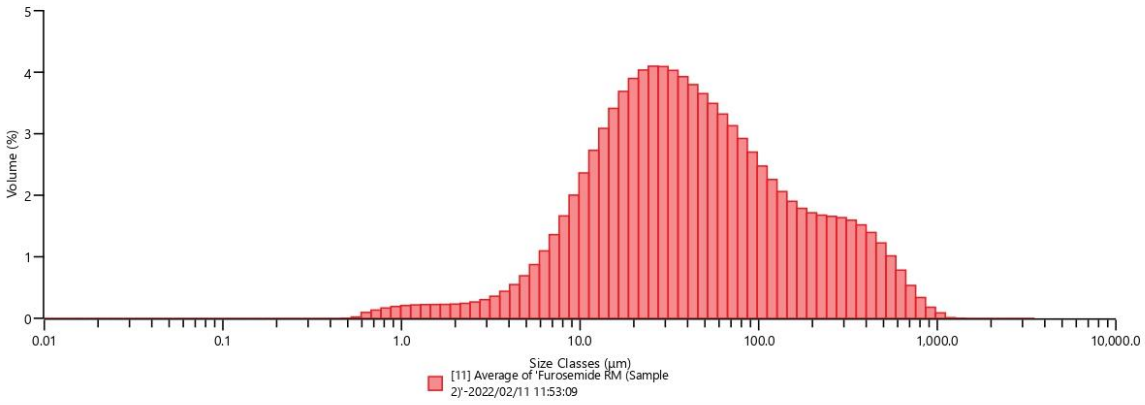
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Furosemide RM (Sample 2)'
SOP File Name	ManualAccessory.cfg

Measurement Details	
Analysis Date Time	2022/02/14 09:17:51
Measurement Date Time	2022/02/11 11:53:09
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Rutile)
Particle Refractive Index	2,680
Particle Absorption Index	0,010
Dispersant Name	Water
Dispersant Refractive Index	1,330
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,15 %
Laser Obscuration	10,65 %

Result	
Concentration	0,0222 %
Span	6,990
Uniformity	2,030
Specific Surface Area	359,5 m²/kg
D [3,2]	16,691 µm
D [4,3]	96,803 µm
Dv (10)	8,801 µm
Dv (50)	38,688 µm
Dv (90)	279,246 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,24	12,726	3,09	76,006	2,92	453,960	1,22	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,27	14,458	3,41	86,355	2,70	515,772	1,01	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,30	16,427	3,69	98,114	2,47	586,001	0,78	3500,000	
0,015	0,00	0,088	0,00	0,523	0,02	3,125	0,36	18,664	3,90	111,473	2,26	665,793	0,53		
0,017	0,00	0,100	0,00	0,594	0,09	3,550	0,44	21,205	4,04	126,652	2,06	756,449	0,34		
0,019	0,00	0,113	0,00	0,675	0,13	4,034	0,55	24,092	4,10	143,897	1,90	859,450	0,18		
0,022	0,00	0,128	0,00	0,767	0,17	4,583	0,69	27,373	4,09	163,490	1,79	976,475	0,09		
0,024	0,00	0,146	0,00	0,872	0,19	5,207	0,87	31,100	4,03	185,752	1,71	1109,435	0,01		
0,028	0,00	0,166	0,00	0,991	0,21	5,916	1,10	35,335	3,93	211,044	1,68	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,22	6,722	1,36	40,146	3,80	239,780	1,66	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,22	7,637	1,66	45,613	3,65	272,430	1,64	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,22	8,677	2,00	51,823	3,49	309,525	1,60	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,23	9,858	2,36	58,880	3,32	351,670	1,52	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,23	11,201	2,73	66,897	3,13	399,555	1,40	2386,415	0,00		

Figure 1-8: Particle size data for furosemide

Analysis

Malvern Instruments

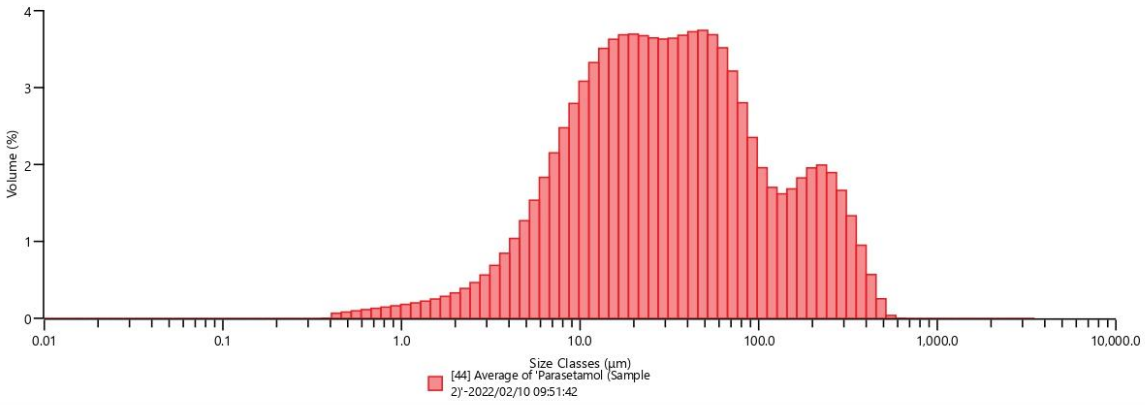
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Parasetamol (Sample 2)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:51:42
Measurement Date Time	2022/02/10 09:51:42
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,59 %
Laser Obscuration	4,64 %

Result	
Concentration	0,0071 %
Span	6,070
Uniformity	1,682
Specific Surface Area	464,5 m²/kg
D [3,2]	12,916 µm
D [4,3]	65,853 µm
Dv (10)	6,317 µm
Dv (50)	30,889 µm
Dv (90)	193,812 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,39	12,726	3,51	76,006	2,80	453,960	0,25	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,07	2,421	0,46	14,458	3,63	86,355	2,35	515,772	0,04	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,08	2,750	0,56	16,427	3,69	98,114	1,96	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,10	3,125	0,69	18,664	3,70	111,473	1,70	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,11	3,550	0,85	21,205	3,67	126,652	1,62	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,13	4,034	1,04	24,092	3,65	143,897	1,68	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,15	4,583	1,27	27,373	3,63	163,490	1,83	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,16	5,207	1,54	31,100	3,64	185,752	1,96	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,18	5,916	1,83	35,335	3,68	211,044	1,99	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,20	6,722	2,15	40,146	3,73	239,780	1,89	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,22	7,637	2,48	45,613	3,74	272,430	1,66	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,25	8,677	2,79	51,823	3,69	309,525	1,33	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,29	9,858	3,08	58,880	3,52	351,670	0,95	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,33	11,201	3,33	66,897	3,22	399,555	0,57	2386,415	0,00		

Figure 1-9: Particle size data for paracetamol

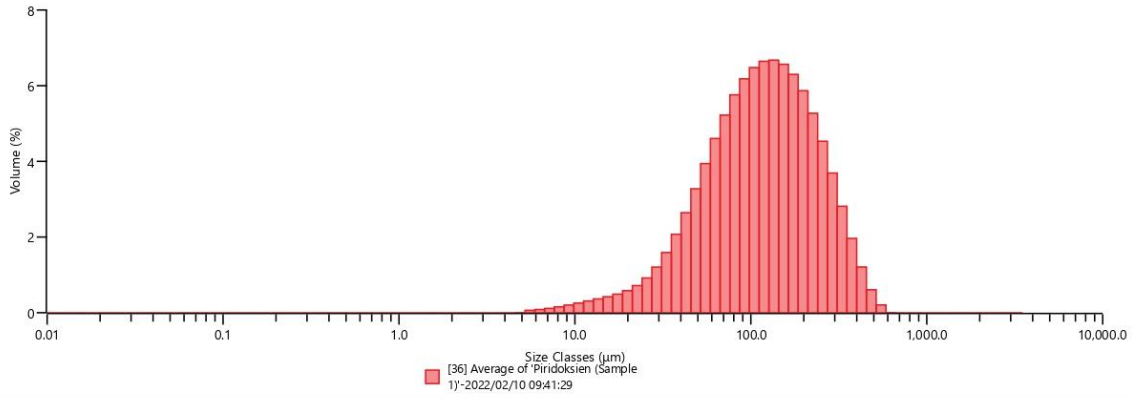
Measurement Details	
Operator Name	Neil Barnard
Sample Name	Average of 'Piridoksien (Sample 1)'
SOP File Name	SOP KK 18 Nov 21.msop

Measurement Details	
Analysis Date Time	2022/02/10 09:41:29
Measurement Date Time	2022/02/10 09:41:29
Result Source	Averaged

Analysis	
Particle Name	Titanium Dioxide TiO2 (Amorphous)
Particle Refractive Index	2,493
Particle Absorption Index	0,010
Dispersant Name	Dry dispersion
Dispersant Refractive Index	1,000
Scattering Model	Mie
Analysis Model	General Purpose
Weighted Residual	0,49 %
Laser Obscuration	0,42 %

Result	
Concentration	0,0041 %
Span	2,024
Uniformity	0,626
Specific Surface Area	77,34 m²/kg
D [3,2]	77,580 µm
D [4,3]	140,727 µm
Dv (10)	41,025 µm
Dv (50)	116,609 µm
Dv (90)	277,098 µm

Histogram



Result

Size (µm)	% Volume In	Size (µm)	% Volume In	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	0,060	0,00	0,357	0,00	2,131	0,00	12,726	0,36	76,006	5,76	453,960	0,61	2711,357	0,00
0,011	0,00	0,068	0,00	0,405	0,00	2,421	0,00	14,458	0,42	86,355	6,18	515,772	0,21	3080,544	0,00
0,013	0,00	0,077	0,00	0,460	0,00	2,750	0,00	16,427	0,49	98,114	6,48	586,001	0,00	3500,000	
0,015	0,00	0,088	0,00	0,523	0,00	3,125	0,00	18,664	0,58	111,473	6,64	665,793	0,00		
0,017	0,00	0,100	0,00	0,594	0,00	3,550	0,00	21,205	0,72	126,652	6,68	756,449	0,00		
0,019	0,00	0,113	0,00	0,675	0,00	4,034	0,00	24,092	0,92	143,897	6,56	859,450	0,00		
0,022	0,00	0,128	0,00	0,767	0,00	4,583	0,00	27,373	1,21	163,490	6,30	976,475	0,00		
0,024	0,00	0,146	0,00	0,872	0,00	5,207	0,06	31,100	1,59	185,752	5,87	1109,435	0,00		
0,028	0,00	0,166	0,00	0,991	0,00	5,916	0,08	35,335	2,07	211,044	5,27	1260,499	0,00		
0,032	0,00	0,188	0,00	1,125	0,00	6,722	0,11	40,146	2,64	239,780	4,53	1432,133	0,00		
0,036	0,00	0,214	0,00	1,279	0,00	7,637	0,15	45,613	3,28	272,430	3,69	1627,136	0,00		
0,041	0,00	0,243	0,00	1,453	0,00	8,677	0,20	51,823	3,94	309,525	2,81	1848,692	0,00		
0,046	0,00	0,276	0,00	1,651	0,00	9,858	0,25	58,880	4,60	351,670	1,96	2100,416	0,00		
0,053	0,00	0,314	0,00	1,875	0,00	11,201	0,31	66,897	5,22	399,555	1,21	2386,415	0,00		

Figure 1-10: Particle size data for pyridoxine

Annexture C:

Tablet evaluation test data used for the determination of each filler's dilution potential.

Table C-1 to table C-65 provides the tablet quality test data and results determined and calculated according to the methods found in the BP (2021) and briefly described in chapter 3. The tables include uniformity of mass, disintegration, friability, and tablet hardness data for filler – API mixtures of increased ratio API to filler for Avicel® PH200, CombiLac®, Emcompress®, FlowLac®, MicroceLac®, Tablettose®, and tricalcium citrate in combination with furosemide, paracetamol, and pyridoxine respectively. These data were used to determine each fillers respective dilution potential for each of the abovementioned APIs.

Table C-1: Avicel® PH200: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.510	0.513	0.516	0.513	0.514
	0.516	0.507	0.512	0.518	0.515
	0.510	0.511	0.511	0.517	0.514
	0.515	0.515	0.507	0.510	0.520
Average tablet mass (g)	0.513				
Lower Limit (g)	0.488				
Upper Limit (g)	0.539				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.624	0.039	0.546	0.039	0.156
	0.546	1.208	0.234	0.935	0.351
	0.624	0.429	0.429	0.740	0.156
	0.351	0.351	1.208	0.624	1.325
Friability Initial Mass (g)	6.671				
Friability Final Mass (g)	6.668				
Friability Mass Lost (%)	0.045				
Tablet hardness data (N)	111.000	74.000	107.000	89.000	121.000
	118.000	133.000	109.000	88.000	82.000
Average Tablet Hardness (N)	103.200				

Table C-2: Avicel® PH200: Furosemide (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.507	0.500	0.505	0.508	0.506
	0.504	0.503	0.503	0.502	0.510
	0.480	0.506	0.505	0.503	0.503
	0.500	0.503	0.502	0.502	0.506
Average tablet mass (g)	0.503				
Lower Limit (g)	0.478				
Upper Limit (g)	0.528				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.815	0.577	0.418	1.014	0.616
	0.219	0.020	0.020	0.179	1.412
	4.554	0.616	0.418	0.020	0.020
	0.577	0.020	0.179	0.179	0.616
Friability Initial Mass (g)	6.565				
Friability Final Mass (g)	6.549				
Friability Lost (%)	0.244				
Tablet hardness data (N)	55.000	52.000	63.000	67.000	51.000
	42.000	65.000	43.000	51.000	60.000
Average Tablet Hardness (N)	54.900				

Table C-3: Avicel® PH200: Furosemide (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.508	0.494	0.509	0.501	0.503
	0.507	0.502	0.502	0.514	0.500
	0.526	0.514	0.503	0.503	0.503
	0.497	0.506	0.500	0.504	0.508
Average tablet mass (g)	0.505				
Lower Limit (g)	0.480				
Upper Limit (g)	0.530				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.554	2.217	0.752	0.831	0.435
	0.356	0.633	0.633	1.742	1.029
	4.117	1.742	0.435	0.435	0.435
	1.623	0.158	1.029	0.238	0.554
Friability Initial Mass (g)	6.456				
Friability Final Mass (g)	5.783				
Friability Lost (%)	10.424				
Tablet hardness data (N)	13.000	14.000	N/A	10.000	14.000
	N/A	11.000	10.000	11.000	N/A
Average Tablet Hardness (N)	11.857				

Table C-4: Avicel® PH200: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.538	0.542	0.542	0.544	0.548
	0.546	0.545	0.541	0.560	0.546
	0.545	0.525	0.543	0.545	0.543
	0.543	0.542	0.541	0.541	0.575
Average tablet mass (g)	0.545				
Lower Limit (g)	0.518				
Upper Limit (g)	0.572				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.239	0.505	0.505	0.138	0.597
	0.229	0.046	0.688	2.799	0.229
	0.046	3.626	0.321	0.046	0.321
	0.321	0.505	0.688	0.688	5.553
Friability Initial Mass (g)	6.525				
Friability Final Mass (g)	6.519				
Friability Lost (%)	0.092				
Tablet hardness data (N)	58.000	68.000	62.000	62.000	58.000
	58.000	65.000	57.000	62.000	66.000
Average Tablet Hardness (N)	61.600				

Table C-5: Avicel® PH200: Paracetamol (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.493	0.508	0.503	0.504	0.508
	0.503	0.520	0.491	0.503	0.509
	0.521	0.507	0.506	0.557	0.509
	0.505	0.509	0.496	0.505	0.512
Average tablet mass (g)	0.508				
Lower Limit (g)	0.483				
Upper Limit (g)	0.534				
Allowed Deviation (%)	5				
Mass Deviations (%)	3.039	0.089	1.072	0.875	0.089
	1.072	2.272	3.432	1.072	0.108
	2.468	0.285	0.482	9.549	0.108
	0.679	0.108	2.449	0.679	0.698
Friability Initial Mass (g)	6.67				
Friability Final Mass (g)	6.622				
Friability Lost (%)	0.720				
Tablet hardness data (N)	39.000	37.000	46.000	49.000	44.000
	49.000	34.000	40.000	42.000	43.000
Average Tablet Hardness (N)	42.300				

Table C-6: Avicel® PH200: Paracetamol (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.431	0.454	0.470	0.461	0.468
	0.454	0.485	0.468	0.454	0.458
	0.477	0.474	0.469	0.407	0.452
	0.461	0.478	0.428	0.412	0.463
Average tablet mass (g)	0.456				
Lower Limit (g)	0.433				
Upper Limit (g)	0.479				
Allowed Deviation (%)	5				
Mass Deviations (%)	5.524	0.482	3.025	1.052	2.587
	0.482	6.313	2.587	0.482	0.395
	4.559	3.902	2.806	10.785	0.921
	1.052	4.779	6.181	9.689	1.491
Friability Initial Mass (g)	6.341				
Friability Final Mass (g)	0				
Friability Lost (%)	100.000				
Tablet hardness data (N)	0.000	0.000	0.000	0.000	0.000
	0.000	0.000	0.000	0.000	0.000
Average Tablet Hardness (N)	0.000				

Table C-7: Avicel® PH200: Pyridoxine (30:70) tablet test data and results for determination of dilution potential.

30 : 70					
API Ratio	70	Theoretical Total Mass (g)			100.00
Filler Ratio	30.00	Actual Total Mass (g)			50.00
Actual API Mass	35.00				
Actual Filler Mass	15.00	Theoretical API Mass (g)			70
Mass Modifier	1.00	Theoretical Filler Mass (g)			30
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	4.00			Result #	0.66666667
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.492	0.495	0.499	0.504	0.502
	0.499	0.502	0.499	0.504	0.494
	0.485	0.503	0.508	0.510	0.493
	0.494	0.503	0.499	0.502	0.501
Average tablet mass (g)	0.499				
Lower Limit (g)	0.474				
Upper Limit (g)	0.524				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.482	0.881	0.080	0.921	0.521
	0.080	0.521	0.080	0.921	1.081
	2.883	0.721	1.722	2.123	1.282
	1.081	0.721	0.080	0.521	0.320
Friability Initial Mass (g)	6.472				
Friability Final Mass (g)	6.469				
Friability Lost (%)	0.046				
Tablet hardness data (N)	103.000	108.000	109.000	108.000	109.000
	107.000	111.000	112.000	116.000	112.000
Average Tablet Hardness (N)	109.500				

Table C-8: Avicel® PH200: Pyridoxine (25:75) tablet test data and results for determination of dilution potential.

25:75					
API Ratio	75	Theoretical Total Mass (g)			100.00
Filler Ratio	25.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			75
Mass Modifier	1.00	Theoretical Filler Mass (g)			25
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.500	0.496	0.492	0.500	0.496
	0.446	0.493	0.496	0.495	0.489
	0.499	0.498	0.497	0.495	0.495
	0.498	0.506	0.483	0.497	0.497
Average tablet mass (g)	0.493				
Lower Limit (g)	0.469				
Upper Limit (g)	0.518				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.338	0.527	0.284	1.338	0.527
	9.607	0.081	0.527	0.324	0.892
	1.135	0.932	0.730	0.324	0.324
	0.932	2.554	2.108	0.730	0.730
Friability Initial Mass (g)	6.398				
Friability Final Mass (g)	6.387				
Friability Lost (%)	0.172				
Tablet hardness data (N)	500.000	0.000	0.000	0.000	0.000
	0.000	0.000	0.000	0.000	0.000
Average Tablet Hardness (N)	50.000				

Table C-9: Avicel® PH200: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	4.00			Result #	0.66666667
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.520	0.518	0.510	0.508	0.520
	0.505	0.506	0.498	0.511	0.514
	0.511	0.518	0.500	0.516	0.517
	0.503	0.505	0.513	0.519	0.506
Average tablet mass (g)	0.511				
Lower Limit (g)	0.485				
Upper Limit (g)	0.536				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.781	1.390	0.176	0.568	1.781
	1.155	0.959	2.525	0.020	0.607
	0.020	1.390	2.133	0.998	1.194
	1.546	1.155	0.411	1.585	0.959
Friability Initial Mass (g)	6.657				
Friability Final Mass (g)	6.456				
Friability Lost (%)	3.019				
Tablet hardness data (N)	66.000	64.000	67.000	62.000	66.000
	63.000	66.000	68.000	61.000	67.000
Average Tablet Hardness (N)	65.000				

Table C-10: CombiLac®: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.525	0.489	0.486	0.513	0.488
	0.489	0.488	0.490	0.487	0.483
	0.483	0.490	0.489	0.493	0.488
	0.510	0.485	0.485	0.484	0.486
Average tablet mass (g)	0.492				
Lower Limit (g)	0.467				
Upper Limit (g)	0.516				
Allowed Deviation (%)	5				
Mass Deviations (%)	6.805	0.519	1.129	4.364	0.722
	0.519	0.722	0.315	0.926	1.739
	1.739	0.315	0.519	0.295	0.722
	3.753	1.333	1.333	1.536	1.129
Friability Initial Mass (g)	6.351				
Friability Final Mass (g)	6.344				
Friability Lost (%)	0.110				
Tablet hardness data (N)	116.000	110.000	97.000	112.000	108.000
	208.000	106.000	172.000	117.000	117.000
Average Tablet Hardness (N)	126.300				

Table C-11: CombiLac®: Furosemide (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.503	0.500	0.509	0.498	0.512
	0.498	0.504	0.511	0.498	0.514
	0.505	0.499	0.507	0.508	0.501
	0.511	0.502	0.504	0.503	0.504
Average tablet mass (g)	0.505				
Lower Limit (g)	0.479				
Upper Limit (g)	0.530				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.307	0.902	0.882	1.298	1.477
	1.298	0.109	1.278	1.298	1.873
	0.089	1.100	0.486	0.684	0.704
	1.278	0.505	0.109	0.307	0.109
Friability Initial Mass (g)	6.537				
Friability Final Mass (g)	6.524				
Friability Lost (%)	0.199				
Tablet hardness data (N)	94.000	97.000	98.000	99.000	83.000
	78.000	99.000	79.000	101.000	89.000
Average Tablet Hardness (N)	91.700				

Table C-12: CombiLac®: Furosemide (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.487	0.486	0.466	0.484	0.483
	0.492	0.473	0.447	0.499	0.488
	0.480	0.477	0.465	0.481	0.481
	0.472	0.483	0.474	0.479	0.475
Average tablet mass (g)	0.479				
Lower Limit (g)	0.455				
Upper Limit (g)	0.503				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.755	1.546	2.633	1.128	0.919
	2.800	1.170	6.603	4.262	1.964
	0.293	0.334	2.842	0.501	0.501
	1.379	0.919	0.961	0.084	0.752
Friability Initial Mass (g)	6.222				
Friability Final Mass (g)	0				
Friability Lost (%)	100.000				
Tablet hardness data (N)	0.000	0.000	0.000	0.000	0.000
	0.000	0.000	0.000	0.000	0.000
Average Tablet Hardness (N)	0.000				

Table C-13: CombiLac®: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.502	0.496	0.496	0.487	0.496
	0.494	0.495	0.498	0.496	0.499
	0.492	0.495	0.495	0.506	0.498
	0.498	0.496	0.495	0.493	0.495
Average tablet mass (g)	0.496				
Lower Limit (g)	0.471				
Upper Limit (g)	0.521				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.189	0.020	0.020	1.834	0.020
	0.423	0.222	0.383	0.020	0.585
	0.826	0.222	0.222	1.996	0.383
	0.383	0.020	0.222	0.625	0.222
Friability Initial Mass (g)	6.543				
Friability Final Mass (g)	6.543				
Friability Lost (%)	0.000				
Tablet hardness data (N)	312.000	346.000	367.000	364.000	317.000
	358.000	361.000	367.000	346.000	361.000
Average Tablet Hardness (N)	349.900				

Table C-14: CombiLac®: Paracetamol (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.506	0.514	0.507	0.497	0.509
	0.520	0.513	0.506	0.499	0.519
	0.511	0.506	0.499	0.499	0.517
	0.501	0.486	0.497	0.491	0.497
Average tablet mass (g)	0.505				
Lower Limit (g)	0.479				
Upper Limit (g)	0.530				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.258	1.843	0.456	1.526	0.852
	3.032	1.645	0.258	1.129	2.833
	1.248	0.258	1.129	1.129	2.437
	0.733	3.705	1.526	2.714	1.526
Friability Initial Mass (g)	6.423				
Friability Final Mass (g)	6.417				
Friability Lost (%)	0.093				
Tablet hardness data (N)	291.000	287.000	297.000	268.000	304.000
	320.000	302.000	283.000	306.000	299.000
Average Tablet Hardness (N)	295.700				

Table C-15: CombiLac®: Paracetamol (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.486	0.474	0.464	0.472	0.475
	0.489	0.463	0.461	0.506	0.484
	0.469	0.459	0.462	0.456	0.463
	0.457	0.459	0.481	0.484	0.468
Average tablet mass (g)	0.472				
Lower Limit (g)	0.448				
Upper Limit (g)	0.495				
Allowed Deviation (%)	5				
Mass Deviations (%)	3.053	0.509	1.612	0.085	0.721
	3.690	1.824	2.248	7.294	2.629
	0.551	2.672	2.036	3.308	1.824
	3.096	2.672	1.993	2.629	0.763
Friability Initial Mass (g)	6.687				
Friability Final Mass (g)	0				
Friability Lost (%)	100.000				
Tablet hardness data (N)	0.000	0.000	0.000	0.000	0.000
	0.000	0.000	0.000	0.000	0.000
Average Tablet Hardness (N)	0.000				

Table C-16: CombiLac®: Pyridoxine (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	180.00			Result Time	0.20
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.521	0.489	0.502	0.494	0.492
	0.490	0.494	0.490	0.492	0.494
	0.485	0.485	0.505	0.491	0.491
	0.487	0.488	0.496	0.489	0.497
Average tablet mass (g)	0.494				
Lower Limit (g)	0.469				
Upper Limit (g)	0.518				
Allowed Deviation (%)	5				
Mass Deviations (%)	5.551	0.932	1.702	0.081	0.324
	0.729	0.081	0.729	0.324	0.081
	1.742	1.742	2.310	0.527	0.527
	1.337	1.135	0.486	0.932	0.689
Friability Initial Mass (g)	6.419				
Friability Final Mass (g)	6.417				
Friability Lost (%)	0.031				
Tablet hardness data (N)	277.000	255.000	258.000	264.000	266.000
	260.000	260.000	252.000	265.000	252.000
Average Tablet Hardness (N)	260.900				

Table C-17: CombiLac®: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20 : 80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	180.00			Result Time	0.20
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.513	0.505	0.485	0.510	0.498
	0.512	0.516	0.511	0.511	0.511
	0.504	0.506	0.504	0.507	0.513
	0.511	0.516	0.509	0.508	0.510
Average tablet mass (g)	0.508				
Lower Limit (g)	0.483				
Upper Limit (g)	0.533				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.984	0.591	4.528	0.394	1.969
	0.787	1.575	0.591	0.591	0.591
	0.787	0.394	0.787	0.197	0.984
	0.591	1.575	0.197	0.000	0.394
Friability Initial Mass (g)	6.584				
Friability Final Mass (g)	6.573				
Friability Lost (%)	0.167				
Tablet hardness data (N)	57.000	52.000	49.000	56.000	54.000
	54.000	54.000	52.000	54.000	56.000
Average Tablet Hardness (N)	53.800				

Table C-18: CombiLac®: Pyridoxine (10:90) tablet test data and results for determination of dilution potential.

10:90					
API Ratio	90	Theoretical Total Mass (g)			100.00
Filler Ratio	10.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			90
Mass Modifier	1.00	Theoretical Filler Mass (g)			10
Disintegration Time (s)	180.00			Result Time	0.20
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.522	0.518	0.513	0.513	0.511
	0.516	0.519	0.516	0.512	0.517
	0.513	0.507	0.513	0.512	0.517
	0.509	0.519	0.508	0.514	0.519
Average tablet mass (g)	0.514				
Lower Limit (g)	0.489				
Upper Limit (g)	0.540				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.477	0.700	0.272	0.272	0.661
	0.311	0.894	0.311	0.467	0.505
	0.272	1.439	0.272	0.467	0.505
	1.050	0.894	1.244	0.078	0.894
Friability Initial Mass (g)	6.689				
Friability Final Mass (g)	6.569				
Friability Lost (%)	1.794				
Tablet hardness data (N)	28.000	34.000	32.000	31.000	27.000
	29.000	33.000	28.000	29.000	31.000
Average Tablet Hardness (N)	30.200				

Table C-19: Emcompress®: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.494	0.491	0.496	0.471	0.479
	0.494	0.496	0.492	0.496	0.496
	0.494	0.491	0.496	0.507	0.474
	0.494	0.496	0.506	0.465	0.502
Average tablet mass (g)	0.492				
Lower Limit (g)	0.467				
Upper Limit (g)	0.516				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.509	0.102	0.916	4.171	2.543
	0.509	0.916	0.102	0.916	0.916
	0.509	0.102	0.916	3.154	3.561
	0.509	0.916	2.950	5.392	2.136
Friability Initial Mass (g)	6.378				
Friability Final Mass (g)	6.377				
Friability Lost (%)	0.016				
Tablet hardness data (N)	139.000	141.000	98.000	20.000	83.000
	66.000	127.000	69.000	135.000	142.000
Average Tablet Hardness (N)	102.000				

Table C-20: Emcompress®: Furosemide (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.505	0.527	0.507	0.486	0.494
	0.485	0.486	0.513	0.482	0.503
	0.511	0.515	0.515	0.505	0.499
	0.491	0.487	0.510	0.484	0.469
Average tablet mass (g)	0.499				
Lower Limit (g)	0.474				
Upper Limit (g)	0.524				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.263	5.675	1.664	2.547	0.942
	2.747	2.547	2.867	3.349	0.862
	2.466	3.268	3.268	1.263	0.060
	1.544	2.346	2.266	2.948	5.955
Friability Initial Mass (g)	6.519				
Friability Final Mass (g)	6.5				
Friability Lost (%)	0.291				
Tablet hardness data (N)	115.000	126.000	110.000	148.000	73.000
	128.000	75.000	95.000	99.000	92.000
Average Tablet Hardness (N)	106.100				

Table C-21: Emcompress®: Furosemide (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.497	0.468	0.498	0.480	0.470
	0.495	0.466	0.499	0.480	0.492
	0.497	0.485	0.488	0.480	0.465
	0.486	0.497	0.506	0.494	0.460
Average tablet mass (g)	0.485				
Lower Limit (g)	0.461				
Upper Limit (g)	0.509				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.447	3.531	2.653	1.057	3.119
	2.035	4.026	2.859	1.057	1.416
	2.447	0.027	0.592	1.057	4.149
	0.179	2.447	4.302	1.828	5.180
Friability Initial Mass (g)	6.315				
Friability Final Mass (g)	6.301				
Friability Lost (%)	0.222				
Tablet hardness data (N)	105.000	124.000	101.000	107.000	121.000
	98.000	133.000	119.000	124.000	138.000
Average Tablet Hardness (N)	117.000				

Table C-22: Emcompress®: Furosemide (60:40) tablet test data and results for determination of dilution potential.

60:40					
API Ratio	40	Theoretical Total Mass (g)			100.00
Filler Ratio	60.00	Actual Total Mass (g)			50.00
Actual API Mass	20.00				
Actual Filler Mass	30.00	Theoretical API Mass (g)			40
Mass Modifier	1.00	Theoretical Filler Mass (g)			60
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.512	0.527	0.513	0.523	0.490
	0.527	0.536	0.519	0.497	0.530
	0.502	0.591	0.518	0.492	0.517
	0.512	0.521	0.551	0.501	0.512
Average tablet mass (g)	0.520				
Lower Limit (g)	0.494				
Upper Limit (g)	0.546				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.453	1.434	1.261	0.664	5.688
	1.434	3.166	0.106	4.340	2.011
	3.378	13.752	0.298	5.303	0.491
	1.453	0.279	6.053	3.570	1.453
Friability Initial Mass (g)	6.782				
Friability Final Mass (g)	6.375				
Friability Lost (%)	6.001				
Tablet hardness data (N)	60.000	39.000	37.000	55.000	62.000
	51.000	69.000	87.000	70.000	73.000
Average Tablet Hardness (N)	60.300				

Table C-23: Emcompress®: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.477	0.489	0.508	0.487	0.506
	0.512	0.506	0.510	0.506	0.510
	0.502	0.509	0.503	0.508	0.504
	0.508	0.512	0.509	0.508	0.493
Average tablet mass (g)	0.503				
Lower Limit (g)	0.478				
Upper Limit (g)	0.529				
Allowed Deviation (%)	5				
Mass Deviations (%)	5.235	2.851	0.924	3.248	0.526
	1.718	0.526	1.321	0.526	1.321
	0.268	1.122	0.070	0.924	0.129
	0.924	1.718	1.122	0.924	2.056
Friability Initial Mass (g)	6.526				
Friability Final Mass (g)	6.509				
Friability Lost (%)	0.260				
Tablet hardness data (N)	141.000	148.000	97.000	161.000	157.000
	113.000	151.000	109.000	161.000	162.000
Average Tablet Hardness (N)	140.000				

Table C-24: Emcompress®: Paracetamol (85:15) tablet test data and results for determination of dilution potential.

85:15					
API Ratio		Theoretical Total Mass (g)			0.00
Filler Ratio		Actual Total Mass (g)			0.00
Actual API Mass					
Actual Filler Mass		Theoretical API Mass (g)			0
Mass Modifier	1.00	Theoretical Filler Mass (g)			0
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.491	0.492	0.498	0.489	0.492
	0.497	0.493	0.494	0.500	0.491
	0.498	0.501	0.494	0.487	0.493
	0.493	0.490	0.497	0.497	0.491
Average tablet mass (g)	0.494				
Lower Limit (g)	0.469				
Upper Limit (g)	0.519				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.587	0.385	0.830	0.992	0.385
	0.628	0.182	0.020	1.235	0.587
	0.830	1.438	0.020	1.397	0.182
	0.182	0.790	0.628	0.628	0.587
Friability Initial Mass (g)	6.425				
Friability Final Mass (g)	4.908				
Friability Lost (%)	23.611				
Tablet hardness data (N)	77.000	81.000	57.000	56.000	89.000
	58.000	63.000	62.000	58.000	57.000
Average Tablet Hardness (N)	65.800				

Table C-25: Emcompress®: Paracetamol (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.493	0.506	0.502	0.497	0.509
	0.436	0.506	0.509	0.508	0.509
	0.502	0.509	0.508	0.459	0.451
	0.504	0.500	0.504	0.509	0.513
Average tablet mass (g)	0.497				
Lower Limit (g)	0.472				
Upper Limit (g)	0.522				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.745	1.872	1.067	0.060	2.476
	12.221	1.872	2.476	2.275	2.476
	1.067	2.476	2.275	7.590	9.201
	1.470	0.664	1.470	2.476	3.282
Friability Initial Mass (g)	6.407				
Friability Final Mass (g)	6.375				
Friability Lost (%)	0.499				
Tablet hardness data (N)	112.000	111.000	124.000	93.000	132.000
	133.000	141.000	148.000	138.000	127.000
Average Tablet Hardness (N)	125.900				

Table C-26: Emcompress®: Paracetamol (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.486	0.458	0.428	0.480	0.482
	0.480	0.432	0.497	0.485	0.434
	0.482	0.482	0.443	0.469	0.469
	0.424	0.448	0.467	0.485	0.481
Average tablet mass (g)	0.466				
Lower Limit (g)	0.442				
Upper Limit (g)	0.489				
Allowed Deviation (%)	5				
Mass Deviations (%)	4.381	1.632	8.076	3.093	3.522
	3.093	7.216	6.744	4.167	6.787
	3.522	3.522	4.854	0.730	0.730
	8.935	3.780	0.301	4.167	3.308
Friability Initial Mass (g)	6.236				
Friability Final Mass (g)	5.077				
Friability Lost (%)	18.586				
Tablet hardness data (N)	42.000	52.000	70.000	92.000	41.000
	81.000	36.000	48.000	95.000	65.000
Average Tablet Hardness (N)	62.200				

Table C-27: Emcompress®: Paracetamol (60:40) tablet test data and results for determination of dilution potential.

60:40					
API Ratio	40	Theoretical Total Mass (g)			100.00
Filler Ratio	60.00	Actual Total Mass (g)			50.00
Actual API Mass	20.00				
Actual Filler Mass	30.00	Theoretical API Mass (g)			40
Mass Modifier	1.00	Theoretical Filler Mass (g)			60
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.510	0.480	0.439	0.454	0.493
	0.504	0.501	0.488	0.499	0.499
	0.508	0.465	0.491	0.491	0.485
	0.492	0.487	0.471	0.503	0.440
Average tablet mass (g)	0.485				
Lower Limit (g)	0.461				
Upper Limit (g)	0.509				
Allowed Deviation (%)	5				
Mass Deviations (%)	5.155	1.031	9.485	6.392	1.649
	3.918	3.299	0.619	2.887	2.887
	4.742	4.124	1.237	1.237	0.000
	1.443	0.412	2.887	3.711	9.278
Friability Initial Mass (g)	6.217				
Friability Final Mass (g)	4.869				
Friability Lost (%)	21.682				
Tablet hardness data (N)	34.000	36.000	40.000	49.000	38.000
	41.000	35.000	28.000	36.000	41.000
Average Tablet Hardness (N)	37.800				

Table C-28: Emcompress®: Pyridoxine (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.508	0.505	0.491	0.509	0.502
	0.508	0.498	0.487	0.497	0.498
	0.496	0.494	0.500	0.492	0.501
	0.485	0.500	0.508	0.501	0.486
Average tablet mass (g)	0.498				
Lower Limit (g)	0.473				
Upper Limit (g)	0.523				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.947	1.345	1.465	2.147	0.743
	1.947	0.060	2.268	0.261	0.060
	0.462	0.863	0.341	1.264	0.542
	2.669	0.341	1.947	0.542	2.468
Friability Initial Mass (g)	6.505				
Friability Final Mass (g)	6.493				
Friability Lost (%)	0.184				
Tablet hardness data (N)	126.000	85.000	119.000	121.000	89.000
	122.000	147.000	147.000	148.000	136.000
Average Tablet Hardness (N)	124.000				

Table C-29: Emcompress®: Pyridoxine (30:70) tablet test data and results for determination of dilution potential.

30 : 70					
API Ratio	70	Theoretical Total Mass (g)			100.00
Filler Ratio	30.00	Actual Total Mass (g)			50.00
Actual API Mass	35.00				
Actual Filler Mass	15.00	Theoretical API Mass (g)			70
Mass Modifier	1.00	Theoretical Filler Mass (g)			30
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.528	0.511	0.519	0.517	0.519
	0.516	0.516	0.517	0.510	0.513
	0.510	0.514	0.521	0.519	0.505
	0.497	0.514	0.504	0.517	0.525
Average tablet mass (g)	0.515				
Lower Limit (g)	0.489				
Upper Limit (g)	0.540				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.604	0.700	0.855	0.466	0.855
	0.272	0.272	0.466	0.894	0.311
	0.894	0.117	1.244	0.855	1.866
	3.420	0.117	2.060	0.466	2.021
Friability Initial Mass (g)	6.711				
Friability Final Mass (g)	6.704				
Friability Lost (%)	0.104				
Tablet hardness data (N)	72.000	77.000	58.000	71.000	72.000
	84.000	81.000	69.000	82.000	84.000
Average Tablet Hardness (N)	75.000				

Table C-30: Emcompress®: Pyridoxine (25:75) tablet test data and results for determination of dilution potential.

25:75					
API Ratio	75	Theoretical Total Mass (g)			100.00
Filler Ratio	25.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			75
Mass Modifier	1.00	Theoretical Filler Mass (g)			25
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.499	0.499	0.503	0.501	0.502
	0.497	0.497	0.503	0.492	0.490
	0.490	0.503	0.503	0.504	0.500
	0.505	0.501	0.511	0.503	0.504
Average tablet mass (g)	0.500				
Lower Limit (g)	0.475				
Upper Limit (g)	0.525				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.270	0.270	0.530	0.130	0.330
	0.670	0.670	0.530	1.669	2.069
	2.069	0.530	0.530	0.729	0.070
	0.929	0.130	2.129	0.530	0.729
Friability Initial Mass (g)	6.499				
Friability Final Mass (g)	2.991				
Friability Lost (%)	53.978				
Tablet hardness data (N)	35.000	34.000	34.000	29.000	28.000
	30.000	29.000	32.000	103.000	29.000
Average Tablet Hardness (N)	38.300				

Table C-31: Emcompress®: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	5.00			Result #	0.83333333
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.497	0.504	0.501	0.486	0.502
	0.503	0.489	0.497	0.493	0.500
	0.502	0.499	0.480	0.500	0.484
	0.505	0.500	0.491	0.500	0.499
Average tablet mass (g)	0.497				
Lower Limit (g)	0.472				
Upper Limit (g)	0.521				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.081	1.490	0.886	2.135	1.087
	1.289	1.530	0.081	0.725	0.685
	1.087	0.483	3.343	0.685	2.537
	1.692	0.685	1.128	0.685	0.483
Friability Initial Mass (g)	6.475				
Friability Final Mass (g)	5.975				
Friability Lost (%)	7.722				
Tablet hardness data (N)	36.000	42.000	46.000	48.000	40.000
	49.000	52.000	46.000	51.000	48.000
Average Tablet Hardness (N)	45.800				

Table C-32: FlowLac®: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	40.00			Result Time	0.04
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.467	0.463	0.461	0.465	0.466
	0.458	0.466	0.458	0.454	0.454
	0.465	0.457	0.441	0.459	0.456
	0.449	0.459	0.441	0.468	0.444
Average tablet mass (g)	0.458				
Lower Limit (g)	0.435				
Upper Limit (g)	0.480				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.065	1.191	0.754	1.628	1.847
	0.098	1.847	0.098	0.776	0.776
	1.628	0.120	3.617	0.317	0.339
	1.869	0.317	3.617	2.284	2.961
Friability Initial Mass (g)	6.41				
Friability Final Mass (g)	3.417				
Friability Lost (%)	46.693				
Tablet hardness data (N)	37.000	30.000	42.000	55.000	48.000
	34.000	28.000	22.000	47.000	43.000
Average Tablet Hardness (N)	38.600				

Table C-33: FlowLac®: Pyridoxine (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.499	0.499	0.497	0.499	0.498
	0.499	0.498	0.499	0.502	0.499
	0.498	0.502	0.498	0.505	0.500
	0.499	0.498	0.500	0.497	0.497
Average tablet mass (g)	0.499				
Lower Limit (g)	0.474				
Upper Limit (g)	0.524				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.030	0.030	0.431	0.030	0.230
	0.030	0.230	0.030	0.571	0.030
	0.230	0.571	0.230	1.172	0.170
	0.030	0.230	0.170	0.431	0.431
Friability Initial Mass (g)	6.494				
Friability Final Mass (g)	6.449				
Friability Lost (%)	0.693				
Tablet hardness data (N)	136.000	213.000	203.000	192.000	152.000
	123.000	162.000	151.000	130.000	158.000
Average Tablet Hardness (N)	162.000				

Table C-34: FlowLac®: Pyridoxine (60:40) tablet test data and results for determination of dilution potential.

60:40					
API Ratio	40	Theoretical Total Mass (g)			100.00
Filler Ratio	60.00	Actual Total Mass (g)			50.00
Actual API Mass	20.00				
Actual Filler Mass	30.00	Theoretical API Mass (g)			40
Mass Modifier	1.00	Theoretical Filler Mass (g)			60
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.512	0.517	0.512	0.516	0.513
	0.514	0.514	0.515	0.514	0.516
	0.511	0.513	0.515	0.514	0.514
	0.514	0.514	0.515	0.513	0.516
Average tablet mass (g)	0.514				
Lower Limit (g)	0.488				
Upper Limit (g)	0.540				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.408	0.564	0.408	0.370	0.214
	0.019	0.019	0.175	0.019	0.370
	0.603	0.214	0.175	0.019	0.019
	0.019	0.019	0.175	0.214	0.370
Friability Initial Mass (g)	6.693				
Friability Final Mass (g)	6.671				
Friability Lost (%)	0.329				
Tablet hardness data (N)	95.000	96.000	101.000	83.000	75.000
	74.000	84.000	97.000	75.000	70.000
Average Tablet Hardness (N)	85.000				

Table C-35: FlowLac®: Pyridoxine (40:60) tablet test data and results for determination of dilution potential.

40:60					
API Ratio	60	Theoretical Total Mass (g)			100.00
Filler Ratio	40.00	Actual Total Mass (g)			50.00
Actual API Mass	30.00				
Actual Filler Mass	20.00	Theoretical API Mass (g)			60
Mass Modifier	1.00	Theoretical Filler Mass (g)			40
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.500	0.513	0.490	0.503	0.505
	0.504	0.503	0.516	0.505	0.501
	0.499	0.494	0.492	0.502	0.504
	0.503	0.485	0.513	0.478	0.502
Average tablet mass (g)	0.501				
Lower Limit (g)	0.476				
Upper Limit (g)	0.526				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.120	2.477	2.117	0.479	0.879
	0.679	0.479	3.076	0.879	0.080
	0.320	1.318	1.718	0.280	0.679
	0.479	3.116	2.477	4.515	0.280
Friability Initial Mass (g)	6.519				
Friability Final Mass (g)	6.518				
Friability Lost (%)	0.015				
Tablet hardness data (N)	81.000	71.000	94.000	71.000	81.000
	82.000	83.000	85.000	78.000	80.000
Average Tablet Hardness (N)	80.600				

Table C-36: FlowLac®: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.513	0.504	0.506	0.499	0.507
	0.508	0.490	0.505	0.505	0.500
	0.501	0.475	0.505	0.514	0.497
	0.507	0.504	0.508	0.506	0.508
Average tablet mass (g)	0.503				
Lower Limit (g)	0.478				
Upper Limit (g)	0.528				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.968	0.179	0.576	0.815	0.775
	0.974	2.604	0.378	0.378	0.616
	0.417	5.585	0.378	2.167	1.212
	0.775	0.179	0.974	0.576	0.974
Friability Initial Mass (g)	6.52				
Friability Final Mass (g)	6.488				
Friability Lost (%)	0.491				
Tablet hardness data (N)	36.000	44.000	41.000	39.000	42.000
	43.000	42.000	40.000	43.000	45.000
Average Tablet Hardness (N)	41.500				

Table C-37: FlowLac®: Pyridoxine (10:90) tablet test data and results for determination of dilution potential.

10:90					
API Ratio	90	Theoretical Total Mass (g)			100.00
Filler Ratio	10.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			90
Mass Modifier	1.00	Theoretical Filler Mass (g)			10
Disintegration Time (s)	180.00			Result Time	0.20
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.502	0.501	0.497	0.501	0.507
	0.498	0.495	0.503	0.506	0.513
	0.512	0.500	0.503	0.498	0.498
	0.503	0.493	0.504	0.498	0.503
Average tablet mass (g)	0.502				
Lower Limit (g)	0.477				
Upper Limit (g)	0.527				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.050	0.149	0.947	0.149	1.046
	0.747	1.345	0.249	0.847	2.242
	2.043	0.349	0.249	0.747	0.747
	0.249	1.744	0.448	0.747	0.249
Friability Initial Mass (g)	6.493				
Friability Final Mass (g)	2.382				
Friability Lost (%)	63.314				
Tablet hardness data (N)	17.000	15.000	18.000	20.000	21.000
	24.000	21.000	23.000	21.000	22.000
Average Tablet Hardness (N)	20.200				

Table C-38: MicroceLac®: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.499	0.502	0.495	0.501	0.498
	0.504	0.498	0.498	0.502	0.503
	0.499	0.499	0.499	0.501	0.514
	0.518	0.501	0.508	0.500	0.505
Average tablet mass (g)	0.502				
Lower Limit (g)	0.477				
Upper Limit (g)	0.527				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.637	0.040	1.434	0.239	0.836
	0.358	0.836	0.836	0.040	0.159
	0.637	0.637	0.637	0.239	2.350
	3.146	0.239	1.155	0.438	0.558
Friability Initial Mass (g)	6.519				
Friability Final Mass (g)	6.506				
Friability Lost (%)	0.199				
Tablet hardness data (N)	134.000	173.000	168.000	145.000	136.000
	175.000	177.000	159.000	172.000	169.000
Average Tablet Hardness (N)	160.800				

Table C-39: MicroceLac®: Furosemide (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.511	0.498	0.497	0.506	0.505
	0.510	0.536	0.494	0.502	0.479
	0.484	0.497	0.504	0.498	0.510
	0.490	0.501	0.502	0.500	0.504
Average tablet mass (g)	0.501				
Lower Limit (g)	0.476				
Upper Limit (g)	0.526				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.915	0.678	0.878	0.917	0.718
	1.715	6.901	1.476	0.120	4.467
	3.470	0.878	0.519	0.678	1.715
	2.274	0.080	0.120	0.279	0.519
Friability Initial Mass (g)	6.466				
Friability Final Mass (g)	6.434				
Friability Lost (%)	0.495				
Tablet hardness data (N)	110.000	89.000	64.000	91.000	82.000
	98.000	70.000	85.000	66.000	63.000
Average Tablet Hardness (N)	81.800				

Table C-40: MicroceLac®: Furosemide (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.475	0.481	0.476	0.478	0.501
	0.480	0.499	0.483	0.488	0.475
	0.467	0.501	0.496	0.486	0.469
	0.483	0.481	0.470	0.487	0.478
Average tablet mass (g)	0.483				
Lower Limit (g)	0.459				
Upper Limit (g)	0.507				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.595	0.352	1.388	0.974	3.791
	0.559	3.377	0.062	1.098	1.595
	3.253	3.791	2.755	0.684	2.838
	0.062	0.352	2.631	0.891	0.974
Friability Initial Mass (g)	6.744				
Friability Final Mass (g)	0.707				
Friability Lost (%)	89.517				
Tablet hardness data (N)	71.000	55.000	74.000	93.000	78.000
	49.000	60.000	57.000	123.000	81.000
Average Tablet Hardness (N)	74.100				

Table C-41: MicroceLac®: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	720.00			Result Time	0.80
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.516	0.512	0.525	0.510	0.507
	0.506	0.506	0.487	0.509	0.507
	0.510	0.501	0.504	0.510	0.507
	0.507	0.508	0.502	0.501	0.509
Average tablet mass (g)	0.507				
Lower Limit (g)	0.482				
Upper Limit (g)	0.533				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.735	0.946	3.509	0.552	0.039
	0.237	0.237	3.983	0.355	0.039
	0.552	1.222	0.631	0.552	0.039
	0.039	0.158	1.025	1.222	0.355
Friability Initial Mass (g)	6.611				
Friability Final Mass (g)	6.605				
Friability Lost (%)	0.091				
Tablet hardness data (N)	340.000	246.000	223.000	247.000	252.000
	246.000	250.000	236.000	300.000	364.000
Average Tablet Hardness (N)	270.400				

Table C-42: MicroceLac®: Paracetamol (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.486	0.502	0.490	0.490	0.489
	0.484	0.477	0.496	0.485	0.496
	0.498	0.495	0.482	0.478	0.491
	0.481	0.479	0.480	0.486	0.471
Average tablet mass (g)	0.487				
Lower Limit (g)	0.462				
Upper Limit (g)	0.511				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.164	3.122	0.657	0.657	0.452
	0.575	2.013	1.890	0.370	1.890
	2.301	1.684	0.986	1.808	0.863
	1.191	1.602	1.397	0.164	3.246
Friability Initial Mass (g)	6.384				
Friability Final Mass (g)	6.372				
Friability Lost (%)	0.188				
Tablet hardness data (N)	121.000	135.000	121.000	114.000	117.000
	113.000	121.000	121.000	113.000	116.000
Average Tablet Hardness (N)	119.200				

Table C-43: MicroceLac®: Paracetamol (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	60.00			Result Time	0.07
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.476	0.463	0.443	0.415	0.462
	0.417	0.442	0.448	0.434	0.437
	0.395	0.452	0.441	0.452	0.401
	0.440	0.455	0.456	0.450	0.378
Average tablet mass (g)	0.438				
Lower Limit (g)	0.416				
Upper Limit (g)	0.460				
Allowed Deviation (%)	5				
Mass Deviations (%)	8.713	5.744	1.176	5.219	5.516
	4.762	0.948	2.318	0.879	0.194
	9.786	3.232	0.719	3.232	8.416
	0.491	3.917	4.145	2.775	13.669
Friability Initial Mass (g)	6.491				
Friability Final Mass (g)	3.355				
Friability Lost (%)	48.313				
Tablet hardness data (N)	13.000	11.000	49.000	68.000	51.000
	41.000	51.000	72.000	47.000	N/A
Average Tablet Hardness (N)	44.778				

Table C-44: MicroceLac®: Pyridoxine (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	3.00			Result #	0.5
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.498	0.503	0.498	0.508	0.492
	0.501	0.495	0.500	0.494	0.499
	0.503	0.485	0.496	0.504	0.501
	0.491	0.502	0.495	0.503	0.495
Average tablet mass (g)	0.498				
Lower Limit (g)	0.473				
Upper Limit (g)	0.523				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.030	0.974	0.030	1.977	1.235
	0.572	0.632	0.371	0.833	0.171
	0.974	2.640	0.432	1.174	0.572
	1.435	0.773	0.632	0.974	0.632
Friability Initial Mass (g)	6.45				
Friability Final Mass (g)	6.444				
Friability Lost (%)	0.093				
Tablet hardness data (N)	283.000	259.000	291.000	274.000	284.000
	335.000	266.000	286.000	270.000	251.000
Average Tablet Hardness (N)	279.900				

Table C-45: MicroceLac®: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	4.00			Result #	0.66666667
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.533	0.529	0.524	0.506	0.510
	0.519	0.524	0.522	0.533	0.527
	0.528	0.530	0.527	0.525	0.502
	0.523	0.532	0.514	0.524	0.526
Average tablet mass (g)	0.523				
Lower Limit (g)	0.497				
Upper Limit (g)	0.549				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.932	1.167	0.210	3.232	2.467
	0.746	0.210	0.172	1.932	0.784
	0.975	1.358	0.784	0.402	3.997
	0.019	1.740	1.702	0.210	0.593
Friability Initial Mass (g)	6.794				
Friability Final Mass (g)	6.78				
Friability Lost (%)	0.206				
Tablet hardness data (N)	60.000	61.000	61.000	64.000	62.000
	61.000	63.000	60.000	60.000	63.000
Average Tablet Hardness (N)	61.500				

Table C-46: MicroceLac®: Pyridoxine (10:90) tablet test data and results for determination of dilution potential.

10:90					
API Ratio	90	Theoretical Total Mass (g)			100.00
Filler Ratio	10.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			90
Mass Modifier	1.00	Theoretical Filler Mass (g)			10
Disintegration Time (s)	780.00			Result Time	0.87
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.516	0.516	0.526	0.521	0.514
	0.504	0.520	0.518	0.507	0.526
	0.500	0.516	0.519	0.520	0.504
	0.520	0.511	0.526	0.518	0.523
Average tablet mass (g)	0.516				
Lower Limit (g)	0.490				
Upper Limit (g)	0.542				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.048	0.048	1.889	0.920	0.436
	2.373	0.726	0.339	1.792	1.889
	3.148	0.048	0.533	0.726	2.373
	0.726	1.017	1.889	0.339	1.308
Friability Initial Mass (g)	6.719				
Friability Final Mass (g)	5.664				
Friability Lost (%)	15.702				
Tablet hardness data (N)	67.000	66.000	65.000	55.000	69.000
	60.000	63.000	67.000	66.000	69.000
Average Tablet Hardness (N)	64.700				

Table C-47: Tablettose®: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.474	0.437	0.507	0.482	0.470
	0.464	0.457	0.453	0.484	0.443
	0.480	0.512	0.446	0.488	0.433
	0.454	0.472	0.444	0.474	0.474
Average tablet mass (g)	0.467				
Lower Limit (g)	0.444				
Upper Limit (g)	0.491				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.412	6.504	8.472	3.124	0.556
	0.727	2.225	3.081	3.552	5.220
	2.696	9.542	4.579	4.407	7.360
	2.867	0.984	5.006	1.412	1.412
Friability Initial Mass (g)	6.706				
Friability Final Mass (g)	5.61				
Friability Lost (%)	16.344				
Tablet hardness data (N)	25.000	58.000	18.000	64.000	52.000
	109.000	12.000	31.000	31.000	44.000
Average Tablet Hardness (N)	44.400				

Table C-48: Tablettose®: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	360.00			Result Time	0.40
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.481	0.438	0.491	0.498	0.469
	0.511	0.525	0.485	0.521	0.515
	0.479	0.501	0.482	0.481	0.499
	0.495	0.483	0.501	0.499	0.498
Average tablet mass (g)	0.493				
Lower Limit (g)	0.468				
Upper Limit (g)	0.517				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.355	11.084	0.325	1.096	4.791
	3.735	6.577	1.543	5.765	4.547
	2.761	1.705	2.152	2.355	1.299
	0.487	1.949	1.705	1.299	1.096
Friability Initial Mass (g)	6.298				
Friability Final Mass (g)	6.099				
Friability Lost (%)	3.160				
Tablet hardness data (N)	110.000	128.000	107.000	85.000	41.000
	77.000	82.000	23.000	80.000	49.000
Average Tablet Hardness (N)	78.200				

Table C-49: Tablettose®: Pyridoxine (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	600.00			Result Time	0.67
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.502	0.496	0.494	0.501	0.523
	0.498	0.501	0.497	0.498	0.503
	0.504	0.501	0.496	0.520	0.501
	0.502	0.500	0.500	0.499	0.492
Average tablet mass (g)	0.501				
Lower Limit (g)	0.476				
Upper Limit (g)	0.526				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.120	1.077	1.476	0.080	4.308
	0.678	0.080	0.878	0.678	0.319
	0.519	0.080	1.077	3.710	0.080
	0.120	0.279	0.279	0.479	1.875
Friability Initial Mass (g)	6.495				
Friability Final Mass (g)	6.472				
Friability Lost (%)	0.354				
Tablet hardness data (N)	131.000	123.000	107.000	102.000	105.000
	59.000	128.000	72.000	160.000	131.000
Average Tablet Hardness (N)	111.800				

Table C-50: Tablettose®: Pyridoxine (40:60) tablet test data and results for determination of dilution potential.

40:60					
API Ratio	60	Theoretical Total Mass (g)			100.00
Filler Ratio	40.00	Actual Total Mass (g)			50.00
Actual API Mass	30.00				
Actual Filler Mass	20.00	Theoretical API Mass (g)			60
Mass Modifier	1.00	Theoretical Filler Mass (g)			40
Disintegration Time (s)	600.00			Result Time	0.67
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.486	0.486	0.510	0.510	0.508
	0.513	0.501	0.501	0.500	0.502
	0.501	0.505	0.511	0.512	0.507
	0.504	0.496	0.500	0.510	0.506
Average tablet mass (g)	0.503				
Lower Limit (g)	0.478				
Upper Limit (g)	0.529				
Allowed Deviation (%)	5				
Mass Deviations (%)	3.466	3.466	1.301	1.301	0.904
	1.897	0.487	0.487	0.685	0.288
	0.487	0.308	1.500	1.698	0.705
	0.109	1.480	0.685	1.301	0.507
Friability Initial Mass (g)	6.553				
Friability Final Mass (g)	6.534				
Friability Lost (%)	0.290				
Tablet hardness data (N)	41.000	39.000	35.000	44.000	45.000
	37.000	47.000	43.000	48.000	48.000
Average Tablet Hardness (N)	42.700				

Table C-51: Tablettose®: Pyridoxine (30:70) tablet test data and results for determination of dilution potential.

30:70					
API Ratio	70	Theoretical Total Mass (g)			100.00
Filler Ratio	30.00	Actual Total Mass (g)			50.00
Actual API Mass	35.00				
Actual Filler Mass	15.00	Theoretical API Mass (g)			70
Mass Modifier	1.00	Theoretical Filler Mass (g)			30
Disintegration Time (s)	600.00			Result Time	0.67
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.524	0.517	0.500	0.519	0.521
	0.517	0.526	0.524	0.521	0.519
	0.528	0.519	0.521	0.525	0.524
	0.530	0.521	0.520	0.496	0.514
Average tablet mass (g)	0.519				
Lower Limit (g)	0.493				
Upper Limit (g)	0.545				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.905	0.443	3.717	0.058	0.327
	0.443	1.290	0.905	0.327	0.058
	1.675	0.058	0.327	1.098	0.905
	2.060	0.327	0.135	4.487	1.021
Friability Initial Mass (g)	6.739				
Friability Final Mass (g)	6.675				
Friability Lost (%)	0.950				
Tablet hardness data (N)	29.000	28.000	32.000	32.000	24.000
	32.000	28.000	32.000	27.000	34.000
Average Tablet Hardness (N)	29.800				

Table C-52: Tablettose®: Pyridoxine (25:75) tablet test data and results for determination of dilution potential.

25:75					
API Ratio	75	Theoretical Total Mass (g)			100.00
Filler Ratio	25.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			75
Mass Modifier	1.00	Theoretical Filler Mass (g)			25
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.476	0.480	0.477	0.483	0.483
	0.477	0.474	0.481	0.471	0.479
	0.480	0.487	0.483	0.486	0.487
	0.480	0.476	0.481	0.481	0.475
Average tablet mass (g)	0.480				
Lower Limit (g)	0.456				
Upper Limit (g)	0.504				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.802	0.031	0.594	0.656	0.656
	0.594	1.219	0.240	1.844	0.177
	0.031	1.490	0.656	1.282	1.490
	0.031	0.802	0.240	0.240	1.011
Friability Initial Mass (g)	6.714				
Friability Final Mass (g)	6.537				
Friability Lost (%)	2.636				
Tablet hardness data (N)	24.000	23.000	24.000	23.000	25.000
	27.000	26.000	27.000	25.000	25.000
Average Tablet Hardness (N)	24.900				

Table C-53: Tablettose®: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	300.00			Result Time	0.33
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.517	0.519	0.436	0.514	0.515
	0.521	0.471	0.518	0.496	0.520
	0.517	0.504	0.514	0.501	0.484
	0.518	0.514	0.393	0.512	0.498
Average tablet mass (g)	0.499				
Lower Limit (g)	0.474				
Upper Limit (g)	0.524				
Allowed Deviation (%)	5				
Mass Deviations (%)	3.586	3.987	12.643	2.985	3.186
	4.388	5.630	3.787	0.621	4.188
	3.586	0.982	2.985	0.381	3.025
	3.787	2.985	21.258	2.585	0.220
Friability Initial Mass (g)	6.559				
Friability Final Mass (g)	4.362				
Friability Lost (%)	33.496				
Tablet hardness data (N)	20.000	25.000	24.000	22.000	25.000
	26.000	28.000	28.000	28.000	28.000
Average Tablet Hardness (N)	25.400				

Table C-54: Tricalcium citrate: Furosemide (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.498	0.513	0.482	0.513	0.504
	0.499	0.492	0.489	0.503	0.497
	0.486	0.505	0.495	0.493	0.499
	0.495	0.498	0.507	0.487	0.482
Average tablet mass (g)	0.497				
Lower Limit (g)	0.472				
Upper Limit (g)	0.522				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.231	3.250	2.989	3.250	1.439
	0.433	0.976	1.580	1.238	0.030
	2.184	1.640	0.372	0.775	0.433
	0.372	0.231	2.043	1.982	2.989
Friability Initial Mass (g)	6.523				
Friability Final Mass (g)	6.522				
Friability Lost (%)	0.015				
Tablet hardness data (N)	388.000	365.000	396.000	387.000	423.000
	382.000	413.000	370.000	357.000	342.000
Average Tablet Hardness (N)	382.300				

Table C-55: Tricalcium citrate: Furosemide (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.501	0.493	0.488	0.497	0.485
	0.506	0.480	0.493	0.488	0.489
	0.487	0.491	0.498	0.491	0.488
	0.495	0.484	0.472	0.482	0.492
Average tablet mass (g)	0.490				
Lower Limit (g)	0.466				
Upper Limit (g)	0.515				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.245	0.612	0.408	1.429	1.020
	3.265	2.041	0.612	0.408	0.204
	0.612	0.204	1.633	0.204	0.408
	1.020	1.224	3.673	1.633	0.408
Friability Initial Mass (g)	6.422				
Friability Final Mass (g)	6.395				
Friability Lost (%)	0.420				
Tablet hardness data (N)	232.000	279.000	245.000	267.000	230.000
	226.000	266.000	252.000	275.000	283.000
Average Tablet Hardness (N)	255.500				

Table C-56: Tricalcium citrate: Furosemide (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.460	0.454	0.490	0.453	0.468
	0.442	0.447	0.487	0.468	0.488
	0.447	0.434	0.452	0.444	0.433
	0.458	0.450	0.444	0.425	0.445
Average tablet mass (g)	0.454				
Lower Limit (g)	0.432				
Upper Limit (g)	0.477				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.221	0.099	7.823	0.319	2.982
	2.740	1.639	7.163	2.982	7.383
	1.639	4.500	0.539	2.299	4.720
	0.781	0.979	2.299	6.480	2.079
Friability Initial Mass (g)	6.497				
Friability Final Mass (g)	6.478				
Friability Lost (%)	0.292				
Tablet hardness data (N)	172.000	119.000	130.000	96.000	109.000
	133.000	124.000	113.000	94.000	147.000
Average Tablet Hardness (N)	123.700				

Table C-57: Tricalcium citrate: Paracetamol (90:10) tablet test data and results for determination of dilution potential.

90:10					
API Ratio	10	Theoretical Total Mass (g)			100.00
Filler Ratio	90.00	Actual Total Mass (g)			50.00
Actual API Mass	5.00				
Actual Filler Mass	45.00	Theoretical API Mass (g)			10
Mass Modifier	1.00	Theoretical Filler Mass (g)			90
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.492	0.482	0.483	0.486	0.475
	0.481	0.490	0.493	0.493	0.495
	0.490	0.480	0.490	0.480	0.486
	0.484	0.486	0.488	0.493	0.481
Average tablet mass (g)	0.486				
Lower Limit (g)	0.462				
Upper Limit (g)	0.511				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.151	0.905	0.699	0.082	2.344
	1.110	0.740	1.357	1.357	1.768
	0.740	1.316	0.740	1.316	0.082
	0.493	0.082	0.329	1.357	1.110
Friability Initial Mass (g)	6.359				
Friability Final Mass (g)	6.35				
Friability Lost (%)	0.142				
Tablet hardness data (N)	415.000	447.000	431.000	476.000	390.000
	475.000	440.000	400.000	435.000	498.000
Average Tablet Hardness (N)	440.700				

Table C-58: Tricalcium citrate: Paracetamol (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.511	0.498	0.509	0.502	0.490
	0.498	0.492	0.507	0.509	0.508
	0.508	0.501	0.497	0.500	0.512
	0.503	0.510	0.501	0.486	0.495
Average tablet mass (g)	0.502				
Lower Limit (g)	0.477				
Upper Limit (g)	0.527				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.823	0.767	1.425	0.030	2.361
	0.767	1.963	1.026	1.425	1.225
	1.225	0.169	0.966	0.369	2.023
	0.229	1.624	0.169	3.158	1.365
Friability Initial Mass (g)	6.509				
Friability Final Mass (g)	6.501				
Friability Lost (%)	0.123				
Tablet hardness data (N)	382.000	366.000	362.000	365.000	339.000
	400.000	373.000	304.000	273.000	239.000
Average Tablet Hardness (N)	340.300				

Table C-59: Tricalcium citrate: Paracetamol (75:25) tablet test data and results for determination of dilution potential.

75:25					
API Ratio		Theoretical Total Mass (g)			0.00
Filler Ratio		Actual Total Mass (g)			0.00
Actual API Mass					
Actual Filler Mass		Theoretical API Mass (g)			0
Mass Modifier	1.00	Theoretical Filler Mass (g)			0
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.527	0.529	0.476	0.506	0.533
	0.516	0.484	0.503	0.592	0.513
	0.486	0.505	0.506	0.514	0.487
	0.517	0.489	0.486	0.503	0.521
Average tablet mass (g)	0.510				
Lower Limit (g)	0.484				
Upper Limit (g)	0.535				
Allowed Deviation (%)	5				
Mass Deviations (%)	3.404	3.797	6.603	0.716	4.582
	1.246	5.033	1.305	16.158	0.657
	4.640	0.912	0.716	0.854	4.444
	1.442	4.052	4.640	1.305	2.227
Friability Initial Mass (g)	6.617				
Friability Final Mass (g)	6.472				
Friability Lost (%)	2.191				
Tablet hardness data (N)	31.000	52.000	75.000	38.000	21.000
	42.000	35.000	44.000	47.000	38.000
Average Tablet Hardness (N)	42.300				

Table C-60: Tricalcium citrate: Paracetamol (70:30) tablet test data and results for determination of dilution potential.

70:30					
API Ratio	30	Theoretical Total Mass (g)			100.00
Filler Ratio	70.00	Actual Total Mass (g)			50.00
Actual API Mass	15.00				
Actual Filler Mass	35.00	Theoretical API Mass (g)			30
Mass Modifier	1.00	Theoretical Filler Mass (g)			70
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.520	0.501	0.505	0.510	0.519
	0.499	0.513	0.498	0.505	0.511
	0.503	0.499	0.506	0.507	0.516
	0.500	0.513	0.518	0.502	0.519
Average tablet mass (g)	0.508				
Lower Limit (g)	0.483				
Upper Limit (g)	0.534				
Allowed Deviation (%)	5				
Mass Deviations (%)	2.322	1.417	0.630	0.354	2.125
	1.810	0.945	2.007	0.630	0.551
	1.023	1.810	0.433	0.236	1.535
	1.614	0.945	1.928	1.220	2.125
Friability Initial Mass (g)	6.619				
Friability Final Mass (g)	6.418				
Friability Lost (%)	3.037				
Tablet hardness data (N)	222.000	227.000	259.000	205.000	225.000
	238.000	226.000	238.000	238.000	126.000
Average Tablet Hardness (N)	220.400				

Table C-61: Tricalcium citrate: Paracetamol (60:40) tablet test data and results for determination of dilution potential.

60:40					
API Ratio	40	Theoretical Total Mass (g)			100.00
Filler Ratio	60.00	Actual Total Mass (g)			50.00
Actual API Mass	20.00				
Actual Filler Mass	30.00	Theoretical API Mass (g)			40
Mass Modifier	1.00	Theoretical Filler Mass (g)			60
Disintegration Time (s)	900.00			Result Time	1.00
Tablets Disintegrated	0.00			Result #	0
Tablets Tested	6.00				
Disintegration Result	0.00				
Mass Data (g)	0.495	0.482	0.498	0.497	0.472
	0.511	0.504	0.489	0.485	0.500
	0.483	0.508	0.496	0.496	0.488
	0.506	0.495	0.479	0.495	0.477
Average tablet mass (g)	0.493				
Lower Limit (g)	0.468				
Upper Limit (g)	0.517				
Allowed Deviation (%)	5				
Mass Deviations (%)	0.446	2.192	1.055	0.852	4.221
	3.693	2.273	0.771	1.583	1.461
	1.989	3.084	0.649	0.649	0.974
	2.679	0.446	2.800	0.446	3.206
Friability Initial Mass (g)	6.335				
Friability Final Mass (g)	5.016				
Friability Lost (%)	20.821				
Tablet hardness data (N)	64.000	83.000	86.000	77.000	98.000
	88.000	72.000	75.000	85.000	92.000
Average Tablet Hardness (N)	82.000				

Table C-62: Tricalcium citrate: Pyridoxine (80:20) tablet test data and results for determination of dilution potential.

80:20					
API Ratio	20	Theoretical Total Mass (g)			100.00
Filler Ratio	80.00	Actual Total Mass (g)			50.00
Actual API Mass	10.00				
Actual Filler Mass	40.00	Theoretical API Mass (g)			20
Mass Modifier	1.00	Theoretical Filler Mass (g)			80
Disintegration Time (s)	720.00			Result Time	0.80
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.536	0.546	0.542	0.544	0.544
	0.545	0.543	0.546	0.542	0.544
	0.540	0.544	0.533	0.545	0.544
	0.545	0.538	0.544	0.530	0.545
Average tablet mass (g)	0.542				
Lower Limit (g)	0.515				
Upper Limit (g)	0.569				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.107	0.738	0.000	0.369	0.369
	0.554	0.185	0.738	0.000	0.369
	0.369	0.369	1.661	0.554	0.369
	0.554	0.738	0.369	2.214	0.554
Friability Initial Mass (g)	6.484				
Friability Final Mass (g)	6.471				
Friability Lost (%)	0.200				
Tablet hardness data (N)	378.000	374.000	336.000	91.000	351.000
	382.000	337.000	361.000	332.000	373.000
Average Tablet Hardness (N)	331.500				

Table C-63: Tricalcium citrate: Pyridoxine (30:70) tablet test data and results for determination of dilution potential.

30 : 70					
API Ratio	70	Theoretical Total Mass (g)			100.00
Filler Ratio	30.00	Actual Total Mass (g)			50.00
Actual API Mass	35.00				
Actual Filler Mass	15.00	Theoretical API Mass (g)			70
Mass Modifier	1.00	Theoretical Filler Mass (g)			30
Disintegration Time (s)	540.00			Result Time	0.60
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.490	0.502	0.504	0.503	0.505
	0.498	0.497	0.502	0.499	0.495
	0.501	0.504	0.501	0.503	0.504
	0.486	0.492	0.505	0.501	0.503
Average tablet mass (g)	0.500				
Lower Limit (g)	0.475				
Upper Limit (g)	0.525				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.951	0.450	0.850	0.650	1.051
	0.350	0.550	0.450	0.150	0.950
	0.250	0.850	0.250	0.650	0.850
	2.751	1.551	1.051	0.250	0.650
Friability Initial Mass (g)	6.489				
Friability Final Mass (g)	6.481				
Friability Lost (%)	0.123				
Tablet hardness data (N)	97.000	83.000	93.000	105.000	102.000
	102.000	102.000	106.000	104.000	101.000
Average Tablet Hardness (N)	99.500				

Table C-64: Tricalcium citrate: Pyridoxine (25:75) tablet test data and results for determination of dilution potential.

25:75					
API Ratio	75	Theoretical Total Mass (g)			100.00
Filler Ratio	25.00	Actual Total Mass (g)			50.00
Actual API Mass	45.00				
Actual Filler Mass	5.00	Theoretical API Mass (g)			75
Mass Modifier	1.00	Theoretical Filler Mass (g)			25
Disintegration Time (s)	540.00			Result Time	0.60
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.507	0.504	0.499	0.510	0.507
	0.503	0.511	0.500	0.501	0.500
	0.511	0.502	0.501	0.506	0.503
	0.503	0.497	0.472	0.498	0.503
Average tablet mass (g)	0.502				
Lower Limit (g)	0.477				
Upper Limit (g)	0.527				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.016	0.418	0.578	1.614	1.016
	0.219	1.813	0.379	0.179	0.379
	1.813	0.020	0.179	0.817	0.219
	0.219	0.976	5.957	0.777	0.219
Friability Initial Mass (g)	6.489				
Friability Final Mass (g)	4.998				
Friability Lost (%)	22.977				
Tablet hardness data (N)	14.000	37.000	27.000	36.000	26.000
	33.000	32.000	33.000	38.000	25.000
Average Tablet Hardness (N)	30.100				

Table C-65: Tricalcium citrate: Pyridoxine (20:80) tablet test data and results for determination of dilution potential.

20:80					
API Ratio	80	Theoretical Total Mass (g)			100.00
Filler Ratio	20.00	Actual Total Mass (g)			50.00
Actual API Mass	40.00				
Actual Filler Mass	10.00	Theoretical API Mass (g)			80
Mass Modifier	1.00	Theoretical Filler Mass (g)			20
Disintegration Time (s)	540.00			Result Time	0.60
Tablets Disintegrated	6.00			Result #	1
Tablets Tested	6.00				
Disintegration Result	1.00				
Mass Data (g)	0.505	0.500	0.500	0.486	0.501
	0.532	0.495	0.499	0.492	0.508
	0.510	0.498	0.496	0.468	0.499
	0.499	0.494	0.501	0.500	0.481
Average tablet mass (g)	0.498				
Lower Limit (g)	0.473				
Upper Limit (g)	0.523				
Allowed Deviation (%)	5				
Mass Deviations (%)	1.365	0.361	0.361	2.449	0.562
	6.784	0.642	0.161	1.244	1.967
	2.369	0.040	0.442	6.062	0.161
	0.161	0.843	0.562	0.361	3.452
Friability Initial Mass (g)	6.469				
Friability Final Mass (g)	5.513				
Friability Lost (%)	14.778				
Tablet hardness data (N)	48.000	37.000	40.000	45.000	38.000
	42.000	51.000	41.000	53.000	62.000
Average Tablet Hardness (N)	45.700				