DEVELOPMENT OF A FILLER-BINDER DISINTEGRANT FOR DIRECT COMPRESSION TABLETING BY CO-PROCESSING MICROCRYSTALLINE CELLULOSE AND CROSPOVIDONE

BY

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APRIL 2021

DECLARATION

I declare that the work in this Dissertation entitled**, "Development of aFiller-Binder Disintegrant for Direct Compression Tableting by Co-Processing Microcrystalline Cellulose and Crospovidone"** was carried out by me under the supervision of Prof. A. R. Oyi and Dr. Y. E. Apeji in the Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University, Zaria.

The information derived from the literature have been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at this or any other Institution.

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Name of student	Signature	Date

CERTIFICATION

This Dissertation entitled **"Development of a Filler-Binder Disintegrant for Direct Compression Tableting by Co-Processing Microcrystalline Cellulose and Crospovidone**"by Fatima Haruna meets the requirements for the award of the degreeof Masterof Science in Pharmaceutics of the Ahmadu Bello University and was approved by the committee for its contribution to knowledge and literary presentation.

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DEDICATION

This work is dedicated to my late grandfather Pa Peter Omar Ishaku who inspired me to become a Pharmacist, my husband, John James for his encouragement and to our children: Winnie and Joseph.

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ABSTRACT

The aim of the study was to improve the disintegration functionality of microcrystalline cellulose (MCC) as a direct compression excipient in tablet formulation by co-processing MCCwith crospovidone (CPV), a superdisintegrant. Design of Experiment (DoE) approach was adopted to optimize the composition of the co-processed excipient (CPE). The optimized CPE containing MCC (99 %) and CPV (1 %) was prepared using wet massing technique. Solid-state properties of CPE were characterized in comparison to MCC and CPV using optical and scanning electron microscopy (SEM), Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-red spectroscopy (FT-IR). Powder properties such as flowability, compressibility, moisture sorption capacity, moisture content, dilution potential and lubricant sensitivity ratio (LSR) were also evaluated using standard techniques. Compaction studies were carried out using Heckel and Kawakita equations as well as compressibility-tabletability-compactibility (CTC) profiling. Tablets were formulated by direct compression incorporating metronidazole as the model drug and properties of tablets evaluated.

The study revealed an increase in particle size which enhanced the flowability of MCC as a co-processed excipient. Solid state properties of CPE revealed a material consisting of irregular shaped fibrous particles characterized by a rough texture. PXRD and DSC scans presented a material that is semi-crystalline in nature. Moisture content and moisture sorption capacity of MCC was found to decrease as a result of co-processing. The extent of plastic deformation was reduced in MCC when co-processed with CPV and this translated to a reduction in the tabletability of MCC. Tablets formulated with CPE disintegrated at 11.48mins as compared to MCC tablets that disintegrated at 26.88 mins and this was reflected in the *in vitro* drug release profile with CPE tablets

attaining maximum drug release at 20mins compared to MCC tablets that attained maximum drug release at 60mins. Thus, the functionality of MCC as a disintegrating filler binder for direct compression tableting was improved by co-processing with crospovidone.

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ABBREVIATIONS

ABU	Ahmadu Bello University
API	Active pharmaceutical ingredients
ANOVA	Analysis of variance
BCS	Biopharmaceutics Classification System
BD	Bulk density
BP	British Pharmacopoeia
CI	Carr's Index
CSD	Colloidal silicon dioxide
CPE	Co-processed excipient
CPP	Critical Process Parameter
CPV	Crospovidone
CQA	Critical Quality Attribute
D	Relative Density
DC	Direct Compression
DCE	Directly compressible excipients
DNA	Deoxyribonucleic Acid
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
FBSG	Fluidized Bed Spray Granulation
FDA	Food and Drug Administration
FMC	Federal Manufacturing Corporation
FIN	Finasteride
FTIR	Fourier Transform Infrared
GSH	Granisetron HCl

HCL	Hydrochloric acid
HPMC	Hydroxypropyl methylcellulose
HR	Hausner's Ratio
ICH	International Conference on Harmonization
IPEC	International Pharmaceutical Excipient Council
IID	Inactive Ingredient Database
IR	Infra-red
KN	Kilo Newton
LSR	Lubricant Sensitivity Ratio
MCC	Microcrystalline cellulose
M-CPVP	Micronized crospovidone
NMR	Nuclear Magnetic Resonance
NAOH	Sodium Hydroxide
OVAT	One variable at a time
PME	Physical mixture of constituent excipients
PS	Plantain starch
PH	Pharmaceutical use
PXRD	Powder X-Ray Diffraction
PVP	Polyvinylpyrrolidone
QbD	Quality by Design
RSM	Response surface methodology
SEM	Scanning Electron Microscopy
SMCC	Silicified microcrystalline cellulose
SD	Standard deviation
TD	Tapped density

TPQP	Target Product Quality Profile
TS	Tensile Strength
WHO	World Health Organization

CHAPTER ONE

1.0 INTRODUCTION

1.1 Solid Dosage Forms

Tablets are the most preferred solid dosage forms by virtue of their ease of administration, patient acceptability, availability, low price, and accuracy in dosing and reduction in the toxicity associated with parenteral administration. Furthermore, it offers better stability to heat and moisture with greater resistance to alteration compared to other dosage forms, hence more than 80% of marketed dosage forms are tablets(Camargo, 2011; Mangal *et al.,* 2015;Franc *et al*., 2018).

1.2 Excipients

These are substances other than active pharmaceutical ingredients (APIs) which have been appropriately evaluated for safety andare added intentionally into a finished pharmaceutical dosage form such as tablet(IPEC, 1994).The role of excipients inpharmaceutical preparations is to improve powder physical properties, bulking up formulations and handling of poorly compressible APIs(Grobelny*et al.,* 2015).The chemical nature of excipients used in solid dosage formulations determines itsclassification as either natural (such as cellulose, starch, chitosan,etc.), inorganic (such as dicalcium phosphate), synthetic (such as polyvinylpyrrolidone) or semi synthetic (such as hydroxypropyl cellulose).Some of the frequently employed excipients in tableting include microcrystalline cellulose, starch, lactose, mannitol, sorbitol, and dicalcium phosphate.Solid dosage forms are prepared either by direct compression, wet granulation,extrusion/spheronisation and dry granulationtechniques(Camargo, 2011).

1.3 Direct Compression (DC)

DCis the process by which tablets are compressed directly from the powder blends of activepharmaceutical ingredients (APIs) and suitable excipients, without prior granulation or agglomeration process. Theoverall simplicity of DC in terms of equipment, personnel, speed of production and economic nature makes it the method of choice for tableting. DC requires good flow and compactibilityand is largely dependent on excipients to achieve desirable optimized formulations (Mangal*et al.*, 2015). It is therefore highly influenced by material characteristics such as flowability, compressibility and dilution potential(Camargo, 2011;Adeoye and Alebiowu, 2014). Consequently, directly compressible excipients (DCE)have been developed to meet the needs of DC.

1.3.1 Advantages of direct compression

1. DC is economical because it requires fewer operational units and steps than wet and dry granulation leading to an overall cost effectiveness.
2. There is improved stability of APIs: DC is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps by reducing detrimental effects of moisture and heat.
3. Tablets prepared by DC disintegrate into API particles instead of granules that encounter dissolution fluid.It exhibits comparatively faster dissolution than wet granulation.Therefore, changes in dissolution profiles are less likely to occur in tablets made by DC on storage than in those made from granulations. This is extremely important because the official compendium such as British Pharmacopoeia (BP) or United State Pharmacopoeia (USP-NF) or European Pharmacopoeia (Ph.Eur) or Japanese Pharmacopoeia (JP) now requires dissolution specifications in most solid dosage forms.

4. The high compaction pressure involved in the production of tablets by slugging or roller compaction is avoided by employing direct compression for tableting.
5. Lesser wear and tear of punches during production which is minimized due to the shorter production time interval.
6. Reduced validation and documentation requirements due to fewer unit operations.
7. Reduced microbial growth in DCdue to the absence of water.
8. Less contamination or cross contamination due to the shorter in-process time for materials, making it easier to meet the requirement of current good manufacturing practices(Gohel and Jogani, 2005).

1.3.2 Limitations of direct compression

1. Segregation: DC is more prone to segregation due to the differences in density of the API and excipients. The dry state of the material during mixing may induce static charges leadingto segregationthat may lead to problems in weight variation and content uniformity.Furthermore,poorly flowable APIs may segregate or agglomerate during DC(Camargo, 2011).
2. Low dilution potential: Most commercially available DCE are employed as filler-binders, exhibiting low dilution potential that results in weight variation and content uniformity problems especially with high dose APIs.Most APIs are poorly compressible and only about 30% can be added to a formulation due to the low compressibility of these APIs that influences dilution potential of added excipients. Most of the directly compressible excipients can accommodate only 30-40 % of the poorly compressible active ingredientsespecially in the formulation of high dose APIs. These APIs mostly depend on the addition of a much higher concentration of DCE which results in the formulation of large-sized tablets, since a tablet size should at least be greater than 3mm and the

corresponding weight be more than 50mg to obtain a uniform content uniformity (Waterman and Fergione, 2003). It therefore means that the final weight ofacetaminophen tablet for example to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing(Shangraw and Demarest, 1993;Allen*et al.,* 1999).

3. Poor reworkability especially with all the spray-dried directly compressible excipients since on preparation of tablets, the original spherical nature of the excipient particles is lost.
4. Poorly compressible APIs which amounts to about 70% of all APIs, may not form compact during DC, since directly compressible excipients are demanded to compact APIs even at levels lower than 50 %. Hence these APIs will require higher concentration of excipients up to 80% during tableting (Jacob*et al.,* 2007;Camargo, 2011).
5. Lubricant sensitivity: Fillers are adversely affected by lubricants due to their hydrophobic nature (Gohel and Jogani, 2005).

These drawbacks associated with the use ofDCE necessitated the need to develop newer excipients with direct compression functionality. Excipient functionality is defined as a desirable property that aids and/or improves the manufacture, quality or performance of the drug product (Thoorens*et al.,* 2014). DCE with improved functionality can be obtained either as a new chemical entity or by physical/chemical modification ofan existing excipient or by co-processed mixture of existing excipients. Newer grades of existing excipients can be achieved by modifying the powder's fundamental properties leading to improved derived (functional) properties. Fundamental characteristics, such as morphology, particle size, shape, surface area, porosity and densitydetermine excipient functional properties such as flowability,

compressibility, compactibility, dilution potential, disintegration time and lubricant sensitivity(Rojas*et al.,* 2012). Functionality of a mixture of excipients is improved by co-processing. Co-processing is based on the concept of excipient interaction at the sub particlelevel. It provides substantial benefits of the incorporated excipients hence minimizing their drawbacks(Saha and Shahiwala, 2009).

1.4 Statement of Research Problem

Microcrystalline cellulose (MCC) is an excellent filler-binder exhibiting great binding capacity due to the presence and proximity of a large number of hydroxyl groups (OH) on adjacent cellulose molecules that enables the formation of numerous hydrogen bonds resulting in the strength and cohesiveness of compacts even under low compression forces. Furthermore, MCC plastically deforms enhancing its compressibility properties commonly employed in direct compression (Thoorens*et al.,* 2014).It is also employed as a disintegrant in concentrations not exceeding 15% in tablets formulated by wet granulation(Vandana and Priyanka, 2012).

However, disintegrating effect is lost when MCC is used as a sole excipient due to poor flow and low bulk density in the formulation of tablets by direct compression (Apeji*et al.,* 2011; Olorunsola*et al.,* 2017).To address this limitation, MCC will be co-processed with an existing superdisintegrant: example crospovidone, croscarmellose sodium and sodium starch glycolate, to improve itsdisintegrating ability in direct compression formulations.

1.5 Justification for the Study

The method of co-processing is a proven strategy that has generated excipients with improved functionalities. It is a simple and cost effective process that does not go through the regulatory hurdle of developing a new chemical entity as an excipient.

Furthermore, because of the high demand placed on excipients by the direct compression process, there is a need to develop more versatile excipients that will accommodate these demands.

1.6 Aim

The aim of this study isto improve the disintegration functionality of MCC in tablets formulated by direct compression by co-processing with CPV.

1.6.1 Specific objectives include

1. To optimise the composition of the co-processed excipient (CPE) using design of experiment (DOE) approach.
2. To prepare the co-processed excipient containing the optimized proportions of MCC and CPV by wet massing technique.
3. To characterize the solid state, powder and compaction properties of the co-processed excipient.
4. To formulate tablets by direct compression and evaluate their properties in comparison to Prosolv ®.

1.7 Hypothesis

1.7.1 Null hypothesis

Co-processing of MCC with CPV will not significantly improve its disintegration property in tablets formulated by direct compression.

1.7.2 Alternate hypothesis

Co-processing of MCC with CPV will significantly improve its disintegration property in tablet formulated by direct compression.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Oral Solid Dosage Forms

Oral soliddosage forms are the most utilized amongst all pharmaceutical dosage forms, owing to their stability, easy dosage control and patient acceptability. The emerging trends in tablet production about two decades ago were prompted bytechnological advancesin order to meet the growing demand for tablets. The introduction of direct compression tableting conveniently met the demand, because it was faster ensuring better time management at alower production cost(Nachaegari and Bansal, 2004). Direct compression involves fewer steps compared to dry and wet granulation; it involves blending of the dry powders (APIs and excipients) followed by compression into compacts making it the preferred method of choice for tablet production. It is apparent that direct compression is highly influenced by powder characteristics from the tableting process; therefore, powder properties must be enhanced to improve their performance during direct compression. The desire to enhance powder properties led to the search for high functionality excipient to accommodate the demands of direct compression, consequently co-processing evolved as one of the means by which high functionality excipients are developed(Marwaha*et al.*, 2010).

2.2 Excipients

The International Pharmaceutical Excipient Council (IPEC) defines excipients as substances other than active pharmaceutical ingredients (APIs) which have been appropriately evaluated for safety and are intentionally included in a drug delivery system (IPEC, 1994). Reasons for the addition of excipients into a drug delivery system include:

1) They provide bulk to the APIs in formulation ensuring accurate dosage forms are obtained especially those with low dose potent APIs.
2) They enhance the stability of formulations by protecting them from degradation, as most APIs in their pure form do not retain their stability for long but denature with time or stick to the container wall thus making it unstable for consumption. Excipients are added to maintain the stability of products by ensuring that APIs retain their stability thus improving the shelf life of the product.
3) They enhance bioavailability especially of poorly soluble APIs that must be dissolved in or mixed with an excipient that may either act as solvent or aid in absorption of the drug in human body.
4) They enhance patient acceptability and compliance in terms of elegance in size, shape and colour.
5) They aidin product identification and other attributes relating to the overall safety.
6) They assist in the effectiveness and/or delivery of the drug.
7) They assist in maintaining the integrity of the drug product during storage and use (Kumar and Nirmala, 2012).

2.2.1 Ideal properties of an excipient

Excipients even though considered as inert substances, have the tendency to react with drug components, other excipients, and the packaging system. Excipients may also contain various impurities which may result in decomposition of the active pharmaceutical ingredients. Therefore they are expected to be:

i. Non-toxic
ii. Non - reactive
iii. Pharmacologically inert

iv. Physically and chemically stable

v. Acceptable to the regulatory agencies

vi. Commercially available

vii. Have pleasing organoleptic properties

viii. They must be compatible with the APIbe readily available and cheap.

The success of every tablet is determined to a large extent by the excipientsperformance. It is necessary therefore to keep developing novel excipients that will meet up with the demand of tableting process.

2.2.2 Types of excipients

2.2.2.1 Single entity excipients

These are compendial or non-compendial substances that are neither mixed excipients'nor co-processed excipients. They may contain other components including concomitant components, residual processing aids and/or additivee.g. lactose.

2.2.2.2 Mixtures or blends of multiple excipients

These are simple physical mixtures or blends of two compendial or non-compendial excipients produced by means of low to medium shear processes, where the individual components are mixed together without significant chemical change either for solid or liquid mixtures or blends, the individual excipients remain physically separate at a particulate level i.e. the nature of the components is not chemically changed e.g. Eudragit.

2.2.2.3 Novel excipients or new chemical entities

These are excipients which are chemically modified to form new/novel excipients. They are generally not listed in FDA Inactive Ingredient Database (IID). IID is not an

approval but the excipient is “likely deemed to be safe for use in other products that involve use under similar circumstances, but the agency may ask that the database be brought up to current standards in relation to even that “similar” use”. In this guidance, the phrase new excipients means any inactive ingredients that are intentionally added to therapeutic and diagnostic products but that:

i. are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery e.g., enhance absorption or modify the release of the drug substance
ii. and arenot licenced by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration e.g. Hydroxypropylmethylcellulose (HPMC).

2.2.2.4 Co-processed excipients (CPE)

These area combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing without significant chemical change(Saha and Shahiwala, 2009). Many different co-processing methods may be used, including standard unit operations such as granulation, spray drying, melt extrusion, milling etc. The choice for a specific application will depend on the materials used, their form (e.g. whether dry powders or liquid) and the specific physical properties desired. Likewise the ratios of the components may vary depending on the desired performancee.g. Cellactose(International Pharmaceutical Excipients Council, 1994).

Classes ofexcipients commonly used in co-processing include fillers, binders, disintegrants and lubricants(Franc *et al*., 2018). Co-processingis a particle engineering technique that involves the combination of two or more excipients at the sub-particle

level, to produce a single composite excipient with improved properties compared to the individual excipients or their physical mixtures.The resulting particles are commonly known as “co-processed”, “high functionality”,or “multifunctional” excipients (Nachaegari and Bansal, 2004; Priyanka *et al*., 2016).

It is a novel conceptintroduced to improve excipientfunctionality. This is achieved bymaintainingfavorable attributes, supplementing with newer ones, and byprocessing the parent excipient with another excipient. The high functionality excipients so formed improve processability such as flow properties, compressibility, and improved disintegrationand dissolution profiles. In addition, they provides better dilution potential, fewer fill weight variation and reduced lubricant sensitivity without a chemical change, hence reducing the number of excipients required in a formulation. They may also enhance organoleptic properties especially where microcrystalline cellulose is used (Saha and Shahiwala, 2009; Sreekanth*et al.*, 2013).

2.3 The Need for Co-processed Excipients

It has been found that less than 20 per cent of active pharmaceutical ingredients can be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directlycompressible excipients during tableting (Mirani *et al*., 2011). Theneed for CPEs includes:

1) Tomaximize theuse of existing excipients

To identify new applications for the existing excipientsthis is relatively less expensive and a less time-consuming process as compared to entirely new development e.g. cellulose an existing excipient is co-processed with silicon dioxide into silicified microcrystalline cellulose (SMCC) a new direct compression excipient with improved flow, compressibility and compactibility(Nachaegari and Bansal, 2004).Chitosan is

another existing excipient co-precipitated with silicon dioxide to developed a new excipient which can be used as a superdisintegrant with improved flow and compaction properties(Rashid *et al.*,2008). It is also employed as a filler(El-Barghouthi *et al*., 2008).

2) Developing excipients with desirable properties

Someof the existing excipients lack desirable properties required in carrying out some formulations, therefore such must be improved upon to achieve the desirable properties e.g. spray dried lactose loses its compressibility on initial compaction.Furthermore, it possesses low dilution potential. Co-processing it with povidone and crospovidone resulted into Ludipress®,a direct compression filler(Saha and Shahiwala, 2009).

3) Emergence of drugs developed by genetic engineering

As new drugs are being developed e.g. enzymes, hormones e. t. c, their compatibility with the existing excipients sometimes poses a big question. Hence, the development of new excipients will be necessary to overcome these challenge for e.g.5α-reductase, an enzyme that converts testosterone to dihydrotestosteronewas co-processed with crospovidone, MCC, Aerosil® and mannitol to formulate orodispersible tablets of Finasteride (FIN) to improve the patient compliance (Ashoor*et al.*, 2018).

4) Advances in production process and equipment

The developments or improvements in pharmaceutical processesby the introduction of direct compression and high-speedequipment particularly to increase production rates at lower cost stimulated the need for new excipients.The newer developed tableting machines require materials with better compressibility because they operate with shorter dwell and contact times(Ogunjimi and Alebiowu, 2013).

5) Improving patient compliance

Some excipients currently in use are unsuitable for some patients due to the safety and comfort considerations e.g. lactose intolerance occurs in persons who are deficient in the enzyme lactase, leading to abdominal cramps, diarrhoea, distension and flatulence, hence the need for suitable excipient to overcome the challenge(Viscasillas*et al.*, 2013).

6) Introduction of specialized drug delivery systems

The development of novel or specialized drug delivery systems requires the use of special excipients. Metered dose inhalation devices require excipients of a particular size grade and development of mucoadhesive preparations necessitated the utilization of new bioadhesive polymers and development of oral strip preparations(Sweetman, 2002; Gohel *et al.*, 2007; Buckton, 2008)

2.4 Factors tobe considered when selecting Excipients for Co-Processing

1.The choice of excipients

Co-processing of excipientsdepends onmaterial characteristics and the functional requirement.Materials, by virtue of their response to applied forces can be classified as ***elastic***,***plastic***, or ***brittle***. In reality, materials such as pharmaceuticalsexhibit all the three types of behaviour with one type becoming the predominant response.Co-processing is generally conducted with one excipient that is plastic and another that is brittle. A combination of plastic and brittle materials is necessary for optimum tableting performance. Hence, co-processing these two kinds of materials produces a synergistic effect, in terms ofcompressibility, by selectively overcoming their drawbacks. This combination can improve functionalities such as compaction performance, flow properties, strain-rate sensitivity of material is related to the plastic flow of some materials which are sensitive to strain rate (It is an important parameter for measuring the deformation mechanism of materials, based on the incremental changes in strain rate during tests performed at a fixed temperature and fixed microstructure, to

determine corresponding changes in flow stress),lubricantsensitivity, sensitivity to moisture and reducedquasi-hornification (when an excipientloses compressibility upon the addition of water) (Allen, 1996; Wang *et al*., 2015).

2.The choice of the selected excipientsand their proportions

This is achieved by identifying the group of excipients to be co-processed and carefully studying their functional requirements and material characteristics.

3. Assessing and estimating the particle size requirement

This is especially important when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.

4. Selecting a suitable process of drying

Drying is an intermediate step that is encountered during co-processing. The choice of a suitable drying method is critical, because the presence of moisture influences functionality in terms of flow, compaction and stabilitythat controls particle characteristicswhich may result in batch to batch variations such as spray drying.

5.Optimizing the selected process

The production of optimum functional excipient depends on a fixed ratio of the mixture of excipientsand is based on the desired functionality for developing the new formulation. The selected process if not optimized can contribute to functionality variations, henceby developing controlled production parameters batch to batch variationscan be avoided. Various optimization techniques and experimental designs with sound statistical analysis have been employed to obtain a final product with desired functionalities(Nachaegari and Bansal, 2004; Saha and Shahiwala, 2009;Liew *et al.*,2019).Fig 2.1 is a schematic diagram representing how the factors are interrelated.

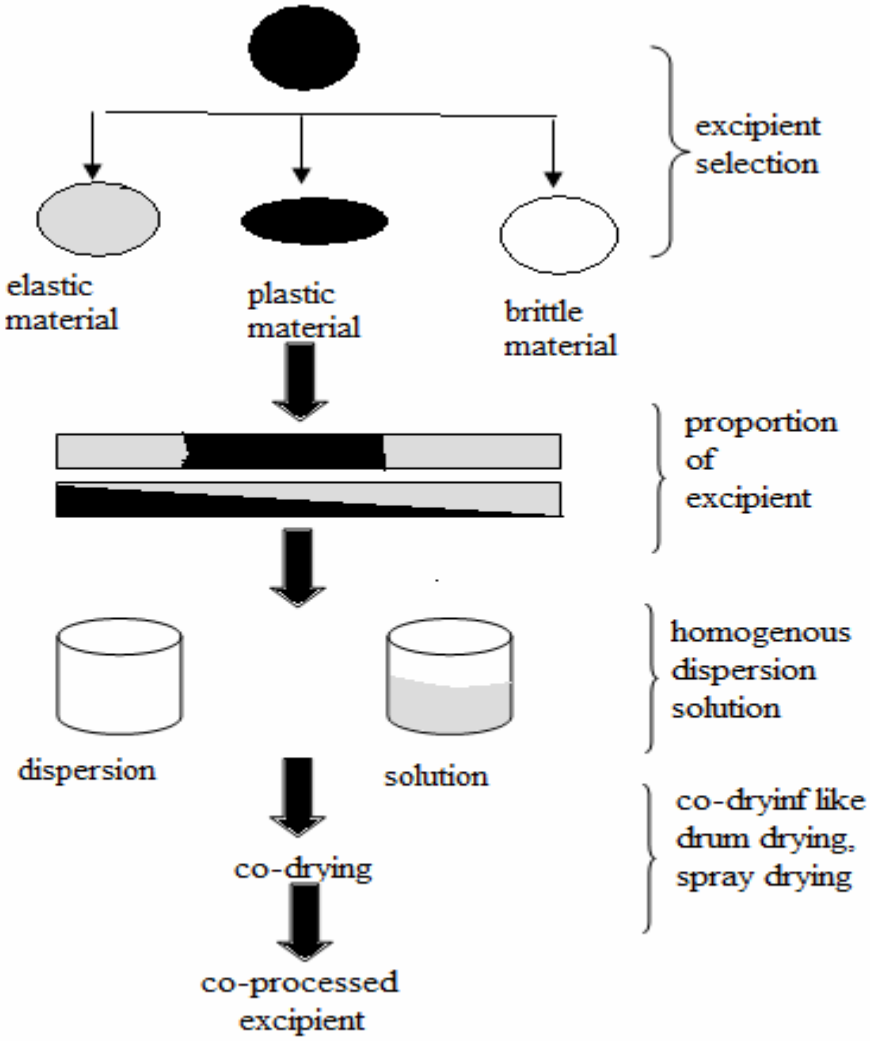


Figure2.1: The sequence of co-processing (Priyanka *et al*., 2016)

2.4.1 Advantagesof co-processed excipient

1. The absence of chemical change

The major significance of co-processed excipients is the absence of a chemical change which has been proven by many detailed studies of excipientschemical properties after co-processing indicatingno chemical change. A detailed study of Silicified microcrystalline celluloses (SMCC) with X-ray diffraction analysis, solid-state nuclear

magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and ^{13}C NMR spectroscopy detected no chemical changes indicating a similarity to the physicochemical properties of MCC.The absence of a chemical change helps reduce company's regulatory concerns during the development phase(Toby*et al.*,1998).

2.Enhancement in flow properties

Flow is enhanced due to the controlled optimal particle size and particle-size distribution ensuring the superior flow properties of co-processed excipients without the need to add glidants. This was observedwhen the volumetric flow properties of SMCC(silicified microcrystalline cellulose) were studied in comparisonwith MCC and the particle-size range of these excipientswere found to be similar to those of the parent excipients, but theflow of co-processed excipients was better than the flow ofsimple physical mixtures(York, 1992). The flow properties of Cellactose and lactose were also compared. Cellactose was found to have better flow characteristics than lactose or a mixture of cellulose and lactose and thespray-dried product had a spherical shape and even surfaces, which also improved the flow properties(Belda and Mielck, 1996).

3.Better dilution potential

Dilution potential is the ability of an excipient to retain its compressibility even when diluted with another material.Most active drug substances are poorly compressible, and as a result excipient must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients(Sherwood and Becker, 1988).

4.Lower fill weight variation

Materials for direct compression tend to show high fill-weight variations as a result of poor flow properties, but co-processed excipients as compared with simple mixtures or parent materials, have been shown to have fewer fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into thematrix of another, which reduces the rough particle surfaces and creates a near-optimal size distribution, causing better flow properties. Fill-weight variation was studied with various machine speeds for SMCC and MCC, and SMCC showed less fill-weight variation than MCC(Maarschalk and Bolhuis, 1999).

5.Reduced Lubricant Sensitivity

Most co-processed excipients consist of relatively large amount of brittle materials such as lactose monohydrate and a smaller amount of plastic materials such as cellulose fixed between or distributed on the particle surface of the brittle material. The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network(Joshi and Duriez, 2004).

6.Improved Compressibility

Co-processed excipients like SMCC and Cellactose have been used mainly in direct-compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a **filler–binder**. The pressure–hardness relation of co-processed excipients, when plotted and compared with simple physical mixtures showed a marked improvement in the compressibility profile. The compressibility performance of excipients such as Cellactose, SMCC and

Ludipress® have been reported to be superior to the simple physical mixtures of their constituent excipients(Schmidt and Rubensdorfer, 1994; Joshi, 2002). SMCC retained its compaction properties even at high compression forces, yielding tablets of good hardness(Flores *et al*., 2000). MCC however, lost its compaction properties. Excipients such as MCC lose compressibility upon the addition of water, a phenomenon called quasi-hornification. This property is improved however, when it is co-processed into SMCC(Liew*et al.*, 2019).

7. Ease of production

Co-processed excipient simplifies the tablet formulation and development steps. Tablet formulation normally consists of weighing of active ingredients and various excipients followed by mixing, granulation, drying, sieving, and compression. Weighing of each ingredient might be time-consuming, and it may incur error in the process. Use of co-processed excipients might simplify the production process and reduces the probability of error (Smewing, 2002).

8. Rapid disintegration

Fast disintegration is a compendial and formulation requirement for immediate release and orally disintegrating dosage forms. Co-processed adjuvants, by virtue of their high solubility, swelling and wicking property, provide rapid disintegration for the developed formulatione.g. sodium starch glycolate, crospovidone (Pateland Bhavsar, 2009).

9. Economic gains

The manufacturer uses a single excipient with multiple functional properties, thereby reducing the number of excipients in the inventory and labour cost involved in their processing other than direct compression method. The use of co-processed adjuvants simplifies manufacturing process and reduces the overall product cost because of

improved functionality and fewer test requirements compared with individual excipients(Liew *et al*., 2019).

10. Reducing Limitations

Co-processingof excipients help in designing tailor-made excipients whichcan retain functional attributes and selectively reduce limitations, thus reducing the time required for development and process validation efforts(Sujatha *et al*., 2013).

2.4.2 Limitations of Co-Processed Excipients

1) The fixed ratio of co-processed excipient mixture

The ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the API and the dose per tablet under development(Mamatha *et al*., 2017).

2) High cost

Multifunctional directly compressible co-processed excipients are specialized products that have been utilized to improve the compressibility of poorly compressible drugs. They are produced by patented processes such as spray drying, fluidized bed drying, roller drying etc. Hence, these products are relatively more costly than their respective raw materials from which they are made e.g.silicified microcrystalline cellulose (SMCC) from cellulose(Chauhan *et al*., 2016).

3) Dilution potential up to 40%

Most directly compressible co-processed excipients have a capacity to accommodate up to 40% of the API, for e.g. acetaminophen, which indicates that the weight of the final tablet to administer 500 mg of drug would be more than 1.3 grams making the tablet size large and may create difficulty in swallowing(Kathpalia and Jogi, 2014).

4) Lack of reworkability

Spraydried co-processed particleslosetheir original spherical nature of the excipient particles when reworked,hence its intrinsic property is lost with a corresponding increase in the disintegration and dissolution profiles (Nawaj*et al.*, 2017)

5) Lack of Pharmacopoeia acceptance

Co-processed adjuvant lacks the official acceptance in Pharmacopoeia(Kumar and Nirmala, 2012).

2.5 Methods of Co-processing

2.5.1 Spray drying

This technique involves atomizing the solution, suspension, emulsion or homogenous dispersion of the excipients to be co-processed into fine droplets. Fine droplets are then thrown radially into a moving stream of hot gas. The increased droplet surface area and high temperature causes the formation of spherical particles, which makes them suited for the direct compression process. It is a continuous particle processing drying operation. Precise control of various spray drying process parameters like inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in the feed and disc speed can help in designing particles with desired characteristics. Spray drying by virtue of precise control over particle characteristics and easy scale up has been extensively used to produce co-processed excipients. The dried product obtained can be in the form of powders, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer designand final powder properties desired(Sujatha *et al*., 2013).

2.5.2 Co-spraydrying

This involves the incorporation of other ingredients under dry or solid form during drying, by atomizing active compounds in solution or under the form of emulsion. It assists in ensuring the mixing of non-miscible products in a continuous operation. Blending and simultaneously drying soluble and insoluble products can be achieved with the possibility of fixing and protecting sensitive active compounds on neutral carrier.

This method was described byChauhan *et al*. (2016) todevelop and characterize a multifunctional co-processed excipient for improving the compressibility of poorly compressible drugs (Etodolac). Microcrystalline cellulose (MCC), lactose monohydrate (lactose), and StarCap 1500 (StarCap) were selected as components of the co-processedexcipient. It yielded a product with excellent flow andimproved compressibility.Rojas and Kumar (2011)also developed novel silicified microcrystalline cellulose II (SMCCII) prepared by co-processing cellulose II and silicon dioxide (SiO_2) at a95:5ratio. The product exhibited higher bulk and tapped densities, better powder packing ability, reduced porosity, increased surface area, and increased flowability.

2.5.3 Crystallization

Crystallization is the process (natural or artificial) of formation of solid crystals precipitating from a solution, melts or more rarely deposited directly from a gas. Crystallization is also a chemical solid/liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs(Gohel and Jogani, 2005).

For crystallization to occur from a solution, it must be supersaturated. This means that the solution must contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution). This can be achieved by various methods including (1) solution cooling, (2) addition of a second solvent to reduce the solubility of the solute (technique known as anti-solvent or drown-out), (3) chemical reaction and (4) change in pH, being the most common methods used in industrial practice(Kumar and Nirmala, 2012).

Patel and Patel(2009) described this method for the co-processing of mannitol and cellulose for dispersible tablets using freeze-thawing technique. The resulting product was less sensitive to lubricant with improved flowability, compactibility, and dissolution rate.Rosenbaum *et al*. (2018)developed a novel process for generating agglomerates of active pharmaceutical ingredient (API) and polymer by swelling the polymer in a water/organic solvent mixture.The API is dissolved in water and then hydroxypropyl methylcellulose (HPMC) is added into the mixture which imbibes into the HPMC matrix. On addition of acetone and isopropyl acetate (anti-solvents) into the mixture the API crystallizes inside and on the surface of HPMC agglomerates.These agglomerates exhibited better flow, improved bulk density, acceptable chemical stability, and high compressibility.

2.5.4 Melt extrusion

It is a process of formation of small beads, pellets from the molten mass which is extruded through an extruder.No solvent or wateris required during the process. It has fewer processing steps resulting in shorter time and less energy required compared with high shear methods. It is a better alternative for poorly soluble drugs exhibiting a more uniform dispersion because of intense mixing and agitation. Complicated and intricate

shapes can be produced using this method; however thermal degradation may arise due to use of high temperature (Gohel and Jogani, 2003).

This method was described in detail by Goyanes*et al.*,(2011) for the co-processing of microcrystalline cellulose and Eudragit® E (as excipients) and sorbitol (as soluble filler-disintegrant) that resulted in pellets with enhanced flow and mechanical properties.

2.5.5 Wet granulation

Co-processing of excipients using wet granulation technique simply involves wet massing of the blend of the excipients to be co-processed with a granulating liquid, wet sizing, drying and finally screening of dry granules. Wet granulation is a cost-effective method of co-processing as it can be adopted for conventional equipment like a planetary mixer/high shear mixer and requires validation of fewer process variables(Gohel *et al.*,2003).Daraghmeh*et al*. (2010) developed a co-processed excipientobtained from crystalline mannitol and α-chitin using this technique which produced a product with optimal physicochemical properties for tableting.Goyanes and Martínez-Pacheco(2015)developed a novel excipient by co-processingmicrocrystalline cellulose (MCC), sorbitol, chitosan and Eudragit® E that resulted in a product with improved flow, mechanical properties and increased dissolution rate.This method was adopted by Apeji *et al.*,(2017) for the co-processing of maize starch (90%), acacia gum (7.5%) and colloidal silicon dioxide (2.5%) that yielded a product with better properties in terms of flow, compressibility, dilution potential, deformation, disintegration, crushing strength and friability

2.5.6 Dry granulation

In this technique a uniform powder blend of the excipients to be co-processed is compressed between counter rotating rollers to form a ribbon of compacted material

that is then milled into granules. Roller compaction is suitable for co-processing of moisture or heat sensitiveexcipients because there is no drying. Bauer and Kleeli (2002)described co-processed excipient derived from a polysaccharide product and an insoluble disintegrating agent. The polysaccharide based co-processed excipient was used as a tablet disintegrant and as dispersion or suspension stabilizer in the manufacture of liquid and semisolid preparation.Daraghmeh*et al.*,(2015)co-processedchitin and mannitol with this technique which resulted in a product with excellent physicochemical properties, exceptional binding, fast wetting and superdisintegrating properties.

2.5.7 Melt granulation

This involves mixing the blend of excipients to be co-processedwith a corresponding amount of meltable binder (binder is in solid state at room temperature but melts in the temperature range of 50 – 80ºC). The mixture is then heated with continuous blending in order to break the mass into agglomerates. The agglomerates are then cooled to room temperature and finally screened to obtain the granules of desired size. Melt granulation technique eliminates the use of water or any other solvent, requires only a short processing time and can be adopted for conventional equipment. Cucula *et al*.(2006)described melt granulation technique for co-processingcalcium phosphate with fatty acid wax. The fatty acid wax used ispreferably glyceryl behenate or glyceryl palmitostearate.Co-processing of calcium phosphate with fatty acid wax overcomes the abrasiveness and capping issues normally associated with calcium phosphate. Co-processed calcium phosphate and fatty acid wax was used in the preparation of venlafaxine HCl modified release tablet and venlafaxine besylate extended release tablet.Gohel*et al*(2012)developed a novel multifunctional co-processed diluent consisting of microcrystalline cellulose (Avicel PH 102), crospovidone (Polyplasdone

XL) and polyethylene glycol 4000 that exhibited better flow. Eraga *et al*. (2015) developed a novel multifunctional excipient by co-processing gelatinized maize starch with sodium carboxymethylcellulose and microcrystalline cellulose in a ratio of 2:1:1 that resulted in a product with excellent flow properties and good swelling index.Garg *et al*. (2015) described melt granulation for co-processing dibasic calcium phosphate anhydrous, polyethylene glycol 4000(PEG4000) and crospovidone.The yielded product exhibited better hardness, disintegration time and dissolution.

2.5.8 Fluid bed spray granulation (FBSG)

It involves spraying a solution of one excipient onto a fluid bed of other excipient, drying and optionally screening to obtain the granules of co-processedexcipients. Menon*et al*., (1996)described FBSG for co-processingof corn starch and polyvinyl pyrrolidone. The developed co-processed excipient is free flowing and exhibitsgood compressibility.Davar *et al*(2010) described co-processingof sodium carbonate with polyethylene glycol using FBSG technique. Co-processing of sodium carbonate with polyethylene glycol protectsit from moisture, thus, prevent caking of sodium carbonate. The developed co-processedexcipient was used as pH modifying agent in non-effervescentpharmaceutical composition of zolpidem orscopolamine. Al Omari *et al*.(2011) developed co-processedexcipient containing α-chitin and mannitol. Co-processedα-chitin and mannitol was used in the preparation of orally disintegrating tablets. Tablets made with this improved composite exhibited low friability, low ejection force and hardness sufficient to be processed in high speed tableting machines, while retaining rapid disintegration or dissolution properties.

2.5.9 Roller drying

It involves preparing a homogenous solution or dispersion of the excipients to be co-processed and then drying of the resultant solution or dispersion on a roller dryer. This technique was adopted by Meggelaars *et al.* (1996) for co-processinglactose with sugar alcohol. The sugar alcohol is preferably sorbitol or lactitol. In this case, the rolling temperature should be sufficiently high, toobtain a product that consists principally of α-lactose in crystalline form. Novel co-processedα-lactose and sugar alcohol was used as pharmaceutical excipient in the preparation of direct compression tablets with improved hardness.

2.5.10 Milling

Milling or dry grinding to produceco-processed excipients may be carried out in a roller mill, a ball mill, a bead mill, a millstone mill, a jet mill, and a hammer mill. Ball milling has been adopted by Rao *et al*. (2012)forco-processing cross-linked polyvinylpyrrolidone andcalcium silicate. In this case, ball mill wasoperated for hours at a speed of 200 revolutions per minutes(rpm) using 25 stainless steel balls. The co-processed binary mixture of cross-linked polyvinylpyrrolidone and calcium silicate enhanced the rate and extent of dissolution of a poorly soluble drug.

2.5.11 Co-grinding (physical mixtures)

It involves the use of equal amount each of the dry excipients required, which are triturated together using a porcelain mortar and pestle for 10 min to ensure a uniform size reduction and mixing of the two powders. The resulting product is passed through a selected sieve and stored.Adeoye and Alebiowu (2014)utilized this method for the co-processing of tapioca starch with mannitol that resulted in a product with enhanced flow, packing and compaction properties. Adetunji and Odeniyi (2016)co-processed

plantain starch (PS) and microcrystalline cellulose (MCC) with this method that yielded a product with significant increase in compressibility.Katsuno *et al*. (2013)co-processeda mixture of sugar alcohol (mannitol) and micronized crospovidone (M-CPVP)that resulted in a product with good stability profile, rapid disintegration and increased hardness of the tablets.

2.5.12 Co-precipitation

Co-processing of excipients by means of co-precipitation may incorporate any modern method referred to, for example, as wet or dry granulation, pHchanges co-precipitation, spray drying, freeze drying or basic solution mixing. Co-precipitation by pH change has been adopted byBadwan *et al.*(2006) for co-processingstarch (corn starch) with silica (colloidal silica). The method involves preparation of an alkaline solution of colloidal silicon dioxide to which corn starch was slowlyadded with vigorous stirring. The pH of the mixture was adjusted with hydrochloric acid to pH 7.0. The solid particulates of silicate starch were then filtered out and dried up in the oven. The novel silicate starch was used as filler and disintegrant in immediate release solid dosage forms.Kittipongpatana and Kittipongpatana (2011) developed a co-precipitated powder composed of rice starch and colloidal silicon dioxide (CSD).The ratio of Starch:CSD were 8:1, 4:1, 2:1, 4:3 and 1:1, with three different concentrations of sodium hydroxide NaOH (0.5, 1.0and 2.0M) usedin the dispersion of CSD.The co-precipitated powders exhibited improved flowability, compactibility, superior bulk and tapped densities compared to that of native starch and physical mixtures.

2.5.13 Co-fusion

It involves the dispersion of excipient prepared in distilled water and then mixed with another excipient before thermal treatment at a temperature of 54± 2ºC for 15mins in a

water bath. The product is subsequently dehydrated with ethanol and tray dried in a hot air oven at 40ºC for 2hours.This method was employed byMsheli*a et al.* (2015)in the co-processing of cassava starch and colloidal silicon dioxide (silicification of cassava starch) that generated a product with improved flow and compaction properties.Apeji*et al.*(2017)developed a co-processed excipient consisting of maize starch (90%), acacia gum (7.5%) and colloidal silicon dioxide (2.5%)that yielded a product with improved flow and tableting properties.

2.5.14 Crystal coating

This method involves the introduction of solid, dry particles into an atomized spray during spraydrying in order to coat and agglomerate individual particles. This method was adopted by Vanhoorne *et al.* (2014) for the co-processingof amorphous lactose and polyvinylpyrrolidone (PVP), which yielded a product withexcellent compression properties.

2.6 Microcrystalline cellulose (MCC) as a tableting excipient

Microcrystalline cellulose (Figure 2.2) is a purified, partially depolymerised cellulose prepared by treating α - cellulose, obtained as a pulp from fibrous plant material with mineral acids. MCC occurs as a white, insoluble, neutral, non-reactive, odourless, tasteless, and crystalline powder composed of porous particles. Microcrystalline cellulose was discovered in 1955 by Battista and Smith and was commercialized under the brand name Avicel®(Thoorens *et al*., 2014)

In 1964, FMC Corporation introduced Avicel® PH to the pharmaceutical industry as an ingredient for direct compression tableting; the “PH” designation indicates that the product is suitable for pharmaceutical use (Alber*set al.*, 2006). In 1966, it was first registered in the supplementary document to the National Formulary (12th ed.), (Suzuki

and Nakagami, 1999)and is currently manufactured globally by more than 10 suppliers (Thoorens*et al.,* 2014). The moisture content of less than 7 % in MCC enhances compression to avoid capping tendency. It has good compactibility and compressibility (Jivraj *et al.,* 2000).

Limitations of MCC include that tablet compactibility is adversely affected when processed by wet granulation,it also exhibits poor flow (Sherwood and Becker, 1998;Gustafsson, 2000).Magnesium stearate may lead to compact capping and lamination. It also requires disintegrants to aid faster disintegration(Moreton, 2008).

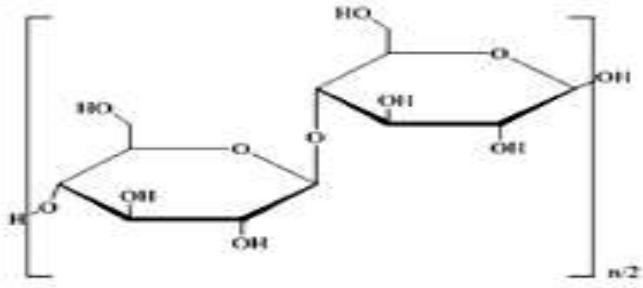


Figure2.2.Chemical structure of Microcrystalline cellulose (MCC) (Desai*et al.*, 2016)

Functional attributes of microcrystalline cellulose include possessing excellent compressibility and hardness (compaction), with excellent binding capacity. It is odourless, tasteless, showing low absorption (water insoluble), with the highest dilution potential, low friability, and inherent lubricant property. Other properties include its broad compatibility with active pharmaceutical ingredients, physiological inertness (non-reactive), ease of handling and security of continuous supply (Krawczyk*et al.,* 2009;Thoorens*et al.,* 2014), low bulk density, high lubricant sensitivity, and poor flow characteristic (El-Sakhawy and Hassan, 2007). It is consequently employed as diluent,

disintegrant or filler/binder in tablet production for wet granulation, dry granulation and direct compression processes (Ali*et al.,* 2009).

2.6.1 Microcrystalline cellulose based co-processed excipients

Co-processedMCC and calcium carbonatewas the first co-processed excipient in the pharmaceutical industry anddates back to 1980s, composed in a weight ratio from about 75:25 to 35:65 that resulted in Vitacel® with improved lubricant sensitivity. The product exhibited low lubricant sensitivity; its compression profile (tablet hardness versus tablet compression force) remained relatively unchanged when various lubricants were employed. This lubricant insensitivity extends both to lubricant level (amount) and lubricant type (magnesiumstearate, stearic acid, etc.)(Mehra *et al*., 1986; Nachaegari and Bansal, 2004; Saha and Shahiwala, 2009)

Co-processing of98 % MCC and 2 % colloidal silicon dioxide into SMCC (Prosolv®) has been reported to improveflow, disintegration properties, strength of tablet compacts, reducedfriability, improved compressibility and reduced sensitivity to wet granulation(Sherwood *et al*., 1996; Nachaegari and Bansal, 2004). Fraser*et al*. (1998)reported that there is no discernible chemical or polymorphic difference among the SMCC, MCC and dry mixes of MCC and silicon dioxide, indicating that the material produced by 'silicification' process is chemically and physically very similar to standard MCC.Co-processing of 85% MCC and 15%guar gum, mainly used in chewable tablets, offers improved palatability, creamier mouth feel with less grittiness and reduced tooth packing(Ratnaraj and Reilly,1997 ;Marwaha*et al*., 2010).

Co-processing of 90% MCC and 10% mannitol resulted in a product with better flow properties, improved compactibility profile and less sensitive to lubrication(Li *et al.,* 2008) while co-processingmannitol and MCC in the ratio 1.2:1 was found to optimize

the powder compressibility characteristics and fast disintegrating property (Jacob *et al.*, 2007).Co-processing MCC and sodium carboxymethylcellulose by co-drying process resulted in an excipient with improved high stability profile over a wide range of pH (Marwaha*et al.*, 2010).Co-processing of 75% α-lactose monohydrate and 25% microcrystalline cellulose resulted in a product with superior flowability and binding properties compared to the physical mixtures of microcrystalline cellulose with different lactose grades e.g. α-lactose monohydrate (lactose 100 M), anhydrous β-lactose (Pharmatose DCL21), and spray dried lactose (Pharmatose DCL11)(Kumar and Nirmala, 2012).

Co-processing of microcrystalline cellulose, silica and sodium starch glycolate resulted in a co-processed superdisintegrant with improved flowability(Jyoti*et al.*,2017).Co-processing of microcrystalline cellulose, hydroxypropylmethylcellulose and crospovidone yielded a superdisintegrant with improved flowability(Jyoti*et al.*, 2017). Augello *et al*. (1999)developed aco-processed excipient by wet granulating MCC and methylcellulose. The end product served as a coating polymer which provided complete taste masking of a bitter drug such as ibuprofen while having no adverse impact on the bioavailability of the drug.Thoorens *et al*.(2011)co-processed calcium phosphate and MCC by mixing the aqueous slurries of microcrystalline cellulose and calcium phosphate, followed by drying the slurries to produce particulate products which yielded a product with improved compactibility.Deorkar *et al*. (2011) prepared a co-processed excipient by spray dry granulating aqueous slurry comprised of themicrocrystalline cellulose and HPMC; the product exhibited enhanced flowability, high compactibility, and increased API loading and blending ability as compared to the individual components.

2.7 Disintegrants

Disintegrating agents are substances routinely included in the tablet formulations to modulate the break-up of the compacted mass into the primary particles to facilitate its dissolution when the dosage form encounters an aqueous environmentthereby increasing the available surface area and a more rapid release of the drug substance. The major function of disintegrants is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet (Konapure*et al.,* 2011).The stronger the binder, the more effective the disintegrating agents must be for proper dissolution. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared. Disintegrants,though hydrophilic in nature, are insoluble in water or gastrointestinal juices.They absorb significant amounts of water or aqueous fluidswithin the tablet matrix, which results in rapid swellingand physical dispersion of the drug due to moisture penetration (Pahwa and Gupta, 2011). Disintegrants have been classified into the conventional disintegrants and superdisintegrants.

2.7.1 Superdisintegrants

They are super-absorbing materials with tailor-made swelling properties. These materials are not designed to absorb significant amounts of water or aqueous fluids butdesigned to swell very fast. Superdisintegrants are used as structural breakers for the disintegrable solid dosage forms as a result of physical dispersion within the matrix of the dosage form which expand when exposed to wet environment.Theyare more effective at lower concentrations,typically 1 - 10 % by weight relative to the total weight of the dosage unitwith greater disintegrating efficiency and mechanical strength. Their particles are generally small and porous, which allow for rapid tablet

disintegration in the mouth without an objectionable mouth feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability. Effective superdisintegrants provide improved compressibility, compactibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.The synthetic superdisintegrant are obtained by chemical modification of starch, cellulose, and povidone with greater disintegrating efficiency and mechanical strength in the tablet formulation(Omidian and Park, 2008;Desai*et al.*, 2016).

2.7.1.1 Crospovidone (CPV)

It is a water insoluble synthetic superdisintegrant, cross-linked from polyvinyl pyrrolidone. This polymer is known as a “popcorn” polymer as it possesses a “popped” structure as shown in Figure 2.3.

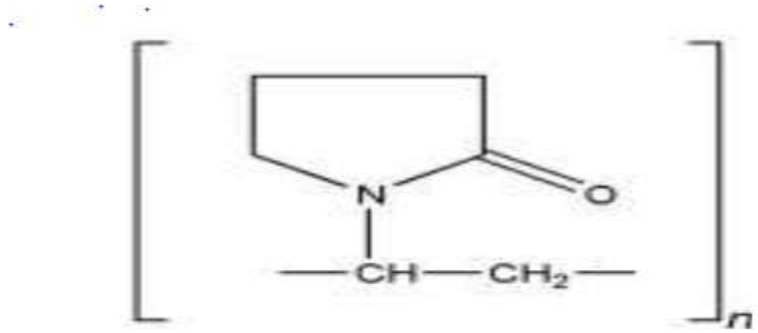


Figure 2.3: Chemical Structure of Crospovidone (CPV) (Vandana and Priyanka, 2012)

Two methods to manufacture crospovidone include the action of the crosslinking agent formed *in situ* while it is added in the other method. The coarse crospovidone grades disintegrate tablets faster. Generally, crospovidone is used in the range of 2-5 % in tablets prepared by direct compression and wet granulation methods (Desai*et al.*, 2016). Crospovidone particles are found to be granular and highly porous which

facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Crospovidone disintegrants are highly compressible materials as a result of their unique particle morphology. It is available in two particle sizes in the form of Polyplasdone XL and Polyplasdone XL-10. Compared to other disintegrants, it has the greatest rate of swelling and greater surface area to volume ratio, due to its high crosslink density (Pahwa and Gupta, 2011). Crospovidone uses a combination of swelling, wicking and deformation mechanism for rapid disintegration of tablets, swells rapidly in water without forming gel, is highly compressible and unaffected by pH media (Kumar and Nirmala, 2012).

2.7.2 Co-processed excipients incorporated with superdisintegrants

Co-processing93.4% α-lactose monohydrate, 3.2% polyvinyl pyrrolidone(Kollidon 30) and 3.4% crospovidone (Kollidon CL) yielded Ludipress®(Lang, 1991). It was used in chewable tabletsandlozenges,foreffervescenttabletsand as a bulking agent formodifiedrelease formulations. It possessesgood flowability,lowhygroscopicity and hardness(Nachaegari and Bansal, 2004;Gohel and Jogani, 2005; Kumar and Nirmala, 2012)

Co-processing of lactose and polyvinyl pyrrolidone (PVP)yielded Ludipress® LCE that was developed to improve dissolution in the oral cavity. Its predecessor Ludipress®does notcontain crospovidone that is insoluble in water(Mistry, 2009;Franc*et al.*, 2018).

Co-processing of Mannitol (90%), crospovidone (5%) and polyvinyl acetate (5%) resulted inLudiflash®. It disintegrates rapidly within seconds with soft, creamy consistency. It was specially designed for direct compression on standard high-speedTablet Press for hard tablet with very low friability. It gives extremely fast release rate(Block *et al*., 2009; Chaudhari *et al*., 2012).

Deorkar *et al*. (2011) developed a co-processed excipient consisting of microcrystalline cellulose (MCC),hydroxypropyl methylcellulose (HPMC) and crospovidone exhibiting enhanced flowability, excellent compactibility,high dilution potential and homogenous mix.

2.7.3 Co-processed superdisintegrants

Gohel*et al*.(2007)developed a co-processed superdisintegrant through wet granulation and tray drying technique. Blend of crospovidone and sodium starch glycolate was added to isopropyl alcohol for wet granulation. The wet mass was sieved and dried in a tray dryer. The product obtained exhibited good flow, compaction and disintegration properties. The co-processed excipient was applied as a superdisintegrant in the formulation of cefixime trihydrate and ibuprofen tablet characterized by quick disintegration and improved drug dissolution.

Nagendrakumar *et al*. (2010)developed a novel co-processed superdisintegrant consisting of crospovidone and sodium starch glycolate in different ratios (1:1, 1:2 and 1:3),exhibiting good flow and compression characteristics while the fast dissolving tablets of granisetron HCl (GSH) containing the co-processedsuperdisintegrants exhibited quick disintegration and improved drug dissolution.Nagendrakumar *et al*. (2010)blended croscarmellose sodium and crospovidone in ethanol. The mixtures were stirred until most of the ethanol evaporated. The wet coherent mass was sieved and dried in a hot air oven. The co-processed superdisintegrant was applied to formulate granisetron fast dissolving tablet. The product showed good flow and compressibility properties.Kumar*et al.* (2013)developed a co-processed superdisintegrant consisting of crospovidone and croscarmellose sodium whichexhibited good flow and compression characteristics.

2.8 Quality by design (QbD)

QbDis a systematic technique to improve pharmaceutical product quality based on scientific facts that is efficient, risk managed and cost effective. Quality by Design evolved from International Conference for Harmonization (ICH) Guidelines, based on ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management and Q10 for pharmaceutical quality systems. Pharmaceutical Quality by DesignICH Q8 defines quality as, "the suitability of either a drug substance or drug product for its intended use". It includes such attributes as the identity, strength, and purity of the product (Yu, 2008;Charoo and Ali, 2013).

Furthermore "ICH Q8 guidelines state that Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management".Important aspects of QbD include Target Product Quality Profile (TPQP), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Risk Assessment, Design Space, Control Strategy and Life Cycle Management(Patel*et al.,* 2013). Quality by design (QbD) approach provides a good understanding of the sources of variability either from the process or the excipient.

Current advances in oral drug formulations led to the emergence of oral drug delivery systems that require a more rational approach to optimizing formulation composition and manufacturing process. An optimal composition/process cannot be achieved using the traditional trial and error approach of OVAT (One Variable at a Time) due to the influence of one or more variables on others.

2.8.1 Design of experiments (DoE)

It is an essential quality tool of QbD that is intended to systematically apply statistics to the research design and analysis. It is an optimization technique that can evaluate all the potential variables/factors simultaneously for either the product or process hence it is cost effective, rational, systematic, and efficient. DoE is achieved using statistical experimental designs, generation of mathematical equations and graphic outcomes showing a complete picture of variation of the responses as a function of the factors (Singh*et al*., 2011).DoE is used to determine the relationship between inputs and outputs of a process by utilizing variables simultaneously which can be quantified and statistically analysed to optimize the composition of co-processed excipient (IPEC, 2008; Zhang and Mao, 2017).DoE mixture design based on simple lattice design experimental design having multiple mixture components was implemented in optimising the composition of the formulation (Khuri and Conlon, 1981; Politis*et al.*, 2017).

DoE methodology involves:

1. Defining the objective of the study and identifying all the input variables, process parameters and desired output responses according to the objectives.
2. Response variables and factors influencing the study are selected either by performing a screening process or by previous formulation experience.
3. A suitable experimental design is selected based on the objective of the study, number and type of input variables and outcome responses. A design matrix is generated according to the experimental design.
4. A suitable numeric model is proposed based on the experimental data and statistical significance. Response surface methodology (RSM) is used to relate a

response variable to the level of the input variables. Optimum formulation compositions are searched from the response surface, a graphical presentation of the mathematical relationship between the input variables and outcome responses.

5. The generated model is validated by confirmatory experimental runs. The model is used to predict the input–output responses, effect of process parameters and possible interactions(Singh *et al*., 2011).

DoE and RSM allow the collection of data with fewer experimental runs; in combination they can fit linear or quadratic equations while assessing response surfaces, thus providing mathematical models of output responses as a function of input variables(Dholariya*et al.*, 2014).

2.9 Metronidazole

It belong to the nitroimidazoles class of drugs; it acts by inhibiting nucleic acid synthesis by disrupting the DNA of microbial cells. Metronidazole is classified in the WHO Essential Medicines List as antiamoebic, antigiardiasis, and antibacterial.It is used in combination with other drugs such as bismuth compounds, proton pump inhibitors for treatment of peptic ulcer disease caused by *Helicobacterpylori.* Metronidazole has been employed in the treatment of periodontal diseasebecause of its activity against anaerobic bacteria.

Approved indications include treatment of trichomoniasis, vaginitis, and urethritis caused by *Gardnerella vaginalis*, giardiasis, amoebiasis, and infections caused by anaerobic bacteria,which comprise intra-abdominal infections, skin and skin structure infections, gynaecologic infections, bacterial septicaemia, bone and joint infections, central nervous system infections, lower respiratory tract infections, and endocarditis.

Based on the indication, the dosage regimen can vary from 250 mg three times daily for 7 days to 750 mg three times daily for 10 days. Single doses of 2 g can also be used. Daily doses can be as high as 2.5 g.Metronidazole is generally very well tolerated and has a wide therapeutic index.Available tablet strengths range from 200 to500 mg.Tablets of higher strengths are not known to be marketed. Metronidazole is Biopharmaceutics Classification System (BCS) Class I, being highly soluble and highly permeable and is soluble at a pH range of 1.0–7.0(Rediguieri*et al.*, 2011).

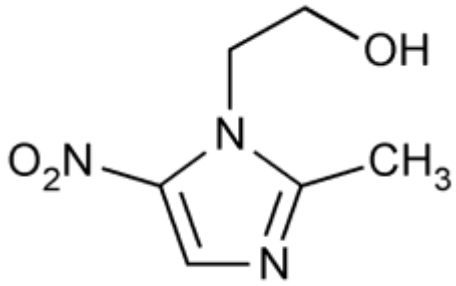


Figure 2.4. Chemical structure of Metronidazole (Diós, 2016)

CHAPTERTHREE

3.0 MATERIALS AND METHODS

3.1 Materials

3.1.1 Drugs

- Metronidazole powder(Central Drug House (P) Ltd CDH LaboratoryChemicalsNew Delhi, India).
- Paracetamol powder (Burgoyne Burbidge's and Co.Laboratory Chemical Mumbai, India)

3.1.2 Excipients

- Microcrystalline cellulose, PH. Eur. NF, JP (VIVAPUR® 102), Crospovidone (Viva Pharm® PVPP XL-10), Prosolv® and Sodium stearyl fumarate(JRS Pharma, GMBH and Co. KG73494 Rosenberg, Germany).
- Magnesium stearate British Drug Houses (BDH) Chemicals Ltd Poole, England.

3.1.3 Solvent

Xylene(Guangdong Guanghua Chemical Factory Co Ltd,China)

3.2 Methods

3.2.1 Experimental design for optimization of the composition of co-processed excipient

Design of Experiment (DoE) was carried out to optimize the relative proportions of microcrystalline cellulose (MCC) and Crospovidone (CPV) in the co-processed excipient (CPE)using the method of Zhang and Mao (Zhang and Mao, 2017). Multivariate experiments were generated using the Simplex Lattice Mixture Design

(Design-Expert ver. 11, Stat-Ease, Inc., Minneapolis, MN 55413, US) to investigate the effect of varying the relative proportions of MCC and CPV on the properties of tablets produced with CPE. The input variables of MCC and CPV ranged from 90 – 99 % and 1 – 10 % respectively.

Ten (10) experimental formulations of CPE were prepared based on the composition of the mixture design experiments given in Table 3.1 and each formulation of CPE was used to prepare tablets by direct compression containing 100 mg of Paracetamol per tablet. The tablet properties such as tensile strength and disintegration time were evaluated as response variables for the design and data obtained were fitted into regression models. Model fitting and analysis were done using ANOVA integrated in the Design Expert Software and mathematical equations were generated for each response to quantify the impact of each input variable on the response. Two component mixture plots were drawn for each response to determine the optimum level content for each component of the co-processed excipient.

Table 3.1. Compositions of the binary mixture design experiments showing the relative proportions of MCC and CPV in the co-processed excipient

Batch	MCC (%)	CPV (%)
1	96.00	4.00
2	93.00	7.00
3	99.00	1.00
4	92.25	7.75
5	96.75	3.25
6	90.00	10.00
7	99.00	1.00
8	90.00	10.00
9	99.00	1.00
10	94.50	5.50

3.2.2 Preparation of the co-processed excipient (CPE)

Wet massing technique as described by Goyanes *et al*.(2011) with modifications was adopted to prepare the co-processed excipient. The corresponding percentages of MCC and CPV as shown in Table 3.1 were weighed on a digital weighing balance (OhausCorporation, Pine Brook, NJ USA) premixed together in the mortar for 2min to achieve a homogenous mix, and thenmassed with 2mL of water. The wet mass wasscreened through a 0.5mm sieve to achieveuniform distribution, air dried for 24h and finally dried in an oven (Hot air oven BS by Gallenkamp, England) at 40^0 C for 1h.

3.2.3 Powder characterization

3.2.3.1 Angle of repose

The flow properties of MCC, CPV and CPE were assessed by measuring the angle of repose formed by 20g powderplaced in a plugged glass funnel suspended from a height of 8 cm above the flat surface. The material was poured through the funnel and the height and diameter of the resulting heap were recorded. The mean of three recordings of height and diameterto determination the angle of repose were obtained using equation (Chaheen*et al.*, 2018).

$$Tan\ \theta\ =\ \frac{2h}{d} \ldots\ldots\ldots\ldots\ldots Eq.1$$

Where*h*is height of heap of powder cone(cm), d is diameter of the cone base(cm), and$\boldsymbol{\theta}$ is the angle of repose.

3.2.3.2 Flow rate

A 30g sample of the powder was passed through the flowability tester (Erweka Flow apparatus). The time taken for the powder to flow out of the orifice,in

seconds,wasrecorded. The mean of three determinations in grams per seconds (flow rate) was calculated using equation 2 (Oyeniyi and Itiola, 2012).

$$Flowrate = \frac{Weightofmaterial\ (g)}{Timeofflowinseconds} \ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{Eq. } 2$$

3.2.3.3 Bulk and Tapped densities

Bulk density of powder samples was determined by pouring 30g of each sample into a 100mL measuring cylinder and the volume occupied (V_B) without tapping was noted. Bulk density was calculated using equation 3and the mean of three replicates was recorded(Bhimte and Tayade, 2007).

$$BulkDensity(BD) = \frac{Mass}{Volume\ (V_B)} \ldots\ldots\ldots\ldots\ldots \text{ Eq. } 3$$

The powder was tapped to constant volume (V_T) and tapped density calculated using equation 4

$$Tappeddensity(TD) = \frac{Mass}{Volume\ (V_T)} \ldots\ldots\ldots\ldots \text{Eq. } 4$$

3.2.3.4 Carr's index (CI) and Hausner's ratio (HR)

These parameters were calculated using equations 5 and 6 respectively.

$$CI = \frac{Tappeddensity - Bulkdensity}{Tappeddensity} \times 100\ \% \ldots\ldots\ldots \text{Eq. } 5$$

$$HR = \frac{Tappeddensity}{Bulkdensity} \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq. } 6$$

3.2.3.5 True density (ρ_T)

True density was calculated for MCC, CPV and CPE using liquid displacement method. The empty weight of a pycnometer bottle wasobtained, after which it was filled with xylene and its weight determined. A sample of the powder weighing 2 g was transferred into the bottle and the excess liquid wiped off. The new weight was determined, and the equation below was used to calculate true density having obtained the weight of xylene displaced by the sample(Ohwoavworhua and Adelakun, 2005).

$$\rho_T = \frac{weight\ of\ sample \times \rho\ of\ xylene\ (0.864)}{weight\ of\ xylene\ displaced\ by\ sample} \ldots\ldots\ldots\ldots\ldots Eq.7$$

3.2.3.6 Powder Porosity(Ɛ)

The porosities of MCC,CPV and CPE were determined by fitting the true and bulk densities into equation 8(Ohwoavworhua and Adelakun, 2010).

$$Ɛ = 1 - \frac{BD}{\rho_T} x\ 100 \ldots\ldots\ldots \text{Eq. } 8$$

Where*BD*is the bulk density,ρ_T is the true density and $\mathcal{E}$ is the porosity.

3.2.3.7 Swelling Capacity (S)

Swelling capacities of MCC, CPV and CPE were measured using 1g of powder sample. The volume(V_1) occupied by the powder in an empty 100mLmeasuring cylinder was noted. Distilled water 85mls was added to disperse the powder which was made up to 100mL. The volume of the sediment (V_2) was noted after 24h and the swelling capacity calculated using equation 9(Assaf*et al.*, 2019).

$$S = \frac{V_2 - V_1}{V_1} \times 100 \ldots\ldots\ldots\ldots \text{Eq. } 9$$

3.2.3.8 Moisture sorption capacity

The percentage of moisture adsorbed by 1g each of MCC, CPV and CPE wasmeasured under the conditions of 75% RH and 25 ± 2^0C using a desiccator containing saturated solution of NaCl in its reservoir. The weight gained by the exposed samples over a five-day period was taken and the amount of water sorbed calculated from the weight difference and expressed in percentage(Assaf*et al.,* 2019).

3.2.3.9 Moisture content

The amount of moisture retained by MCC, CPV and CPE was measured using 1 g powder samples dried to constant weight at 105^0C.The % moisture content was expressed as the ratio of weight loss to weight of sample prior to drying(Mshelia*et al.,* 2015).

$$\frac{Initialweight - Finalweight}{Initialweigt} \times 100 \ldots\ldots\ldots \text{Eq. } 10$$

3.2.3.10 pH Determination

A 2.5 g quantity eachof MCC, CPV and CPE were dispersed in 50mL of distilled water while stirring vigorously and allowed to stand. The pH of the supernatant liquid was read off using a pH meter (pH 55 with replaceable electrode)(Ohwoavworhua*et al.,* 2009).

3.2.3.11 Particle size analysis

Particle size analysis was carried out by mounting a small quantity of the sample in glycerol and viewing under an optical microscope (Fisher Scientific Company, Kent, UK). A minimum of 100 particles were counted for each sample using a calibrated eyepiece micrometre for measurement(Apeji *et al.,* 2017).

3.2.3.12 *Scanning electron microscopy* (SEM)

Particle morphology of MCC, CPV and CPE were characterized using the scanning electron microscope (Phenom ProX by Phenom world Eindhoven, The Netherlands) The samples were placed on a double adhesive which was placed on a sample stub and then sputter-coated with gold under vacuum in an argon atmosphere prior to observation. The SEM images of the samples were taken at an acceleration voltage of 20 kV at 300 × magnification.

3.2.3.13 Powder X-ray diffraction

X-ray diffraction analysis was carried out on MCC, CPV and CPE using a Rigaku Miniflex 300 II Benchtop X-Ray diffractometer (Rigaku Corporation, Japan). The samples were positioned in the holding tray of the machine and scanned from 5 to 90 º on a 2θ scale, measuring the angle between the emitted ray and the reflected ray. The raw data obtained was analysed with DIFFRAC plus EVA, version 9.0 (Bruker, AXS, Karlsruhe, Germany) diffraction software.

3.2.3.14 Differential scanning calorimetry(DSC)

DSC thermograms of MCC, CPV, and CPE were obtained using a DSC Q2000 (TA Instruments, Delware, USA). A 5mg samples were deposited in standard aluminium pans with perforated lid, heated at a rate of 10ºC/min from 25ºC to 200ºC. Data acquisition was performed under an inert atmosphere of nitrogen at a flow rate of 50mL/min. The DSC cell was previously calibrated with high purity indiumas metallic standard. Analysis of scan was carried out using the Universal Analysis software, version 4.5A (TA Instruments, New Castle, DE, USA).

3.2.3.15 Fourier transform Infra-red spectroscopy (FT-IR)

FT-IR scans of MCC, CPV, CPE, MTZ, and MTZ+CPE were collectedover a range (4000 – 650cm^{-1}) using aCary 630 FT-IR Spectrometer (Agilent Technologies, USA). Each sample was subjected to an average of 32 scans at a nominal resolution of 8 cm^{-1}, employing background spectrum of gold. The Cary 630 Micro Lab PC software was used for data collection and Agilent Resolution Pro software was used to analyse the data

3.2.3.16 Lubricant sensitivity ratio (LSR)

The effect of lubricant on the tensile strength of tablets prepared from MCC and CPE was investigated by preparing tablets with or without magnesium stearate/sodium stearate fumarate using a Single Punch Tablet Press. Lubricant sensitivity ratio was computed using equation(Camargo, 2011).

$$LSR = \frac{T_o - T_L}{T_o} \times 100\% \ldots\ldots\ldots\ldots \text{Eq. } 11$$

Where T_0 =tensile strength without lubricant, T_L=tensile strength with lubricant.

3.2.3.17 Compaction Studies

Compaction profilesof MCC, CPV and CPE were generated using the Powder Compaction Analyser(PCA-028-1208, London, UK).Powder samples weighing 80 mg were filled manually into the die cavity measuring 5 mm and compressed at a speed of 120 mm/min at compression loads ranging from 100 – 500 kg (50 - 250 MPa).The parameters of weight, thickness and hardness of tablets were measured using a balance (UWE serial no 136271/05), Micrometre (Mitutoyo Tokyo, Japan) and Tablet Tensile

Analyser (TTA 331-1750, London, UK) respectively and used to compute the volume, apparent density and relative density (D) of the tablets from the equations below:

$$Volume\ (V) = \pi r^2 h \ldots\ldots\ldots\ldots Eq.12$$

$$Apparent\ density\ (\rho_A) = \frac{Weight\ of\ tablet\ (W)}{\pi r^2 h} \ldots\ldots\ldots\ldots\ldots Eq.13$$

$$Rel.density\ (D) = \frac{\rho_A}{\rho_T} \ldots\ldots\ldots\ldots\ldots Eq.14$$

Where *r* is the radius of the tablet and *h* is the thickness of the tablet

ρ_T is the true density.

The compaction data obtained were used to generate Heckel(Heckel, 1961), Kawakita(Kawakita and Lüdde, 1971), compressibility, compactibility and tabletability plots for each material(Egart*et al.*, 2014).

$$Heckel\ equation, ln\left(\frac{1}{1-D}\right) = KP + A \ldots\ldots\ldots\ldots\ldots\ldots Eq.15$$

Where *D* is the relative density of the compact, *P* isthe applied pressure, *K* is the slope of the linear portion of the plot and *A* is the intercept on the y axis.

$$Kawakita\ equation, \frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.16$$

Where C is degree of volume reduction of a powder compact at pressure P, *a*and *b* are constants,' where *a* is the total reduction for the powder bed (compressibility) and *b* is inverse measure of the amount of plastic deformation occurring in the material.

3.2.3.18 Dilution Capacity

Dilution capacity of CPE and MCC were evaluated by preparing tablets containing increasing concentration of the active pharmaceutical ingredient (metronidazole/paracetamol) in the following ratios; 20:80, 40:60, 50:50, 60:40, and 80:20.Tablets were prepared for each compression blend by direct compression on a Single Punch Tablet Press (Type EKO, Erweka Apparatebau-G.m.b.H Heusenstamm, Germany)and tensile strength of tablets determined after 24 h of elastic recovery. A graph of % proportion of the excipient against tensile strength was plotted and the dilution capacity of each material extrapolated from the plot(Camargo, 2011).

3.2.4 Tablet formulation

Four (4) formulations of tablets containing metronidazole as the model drug were prepared by direct compression according to the formula given in Table 3.2. Tablets weighing ~ 500 mg were compressed on a Single Punch Tablet Press (Type EKO, Erweka Apparatebau-G.m.b.H Heusenstamm, Germany) using 12 mm flat-faced punches compressed at a load of 7 KN. The processed tablets were kept for 24h and evaluated for their physical properties.

Table 3.2. Formula for preparing tablets containing metronidazole as model drug using MCC, CPE, PME and Prosolv® as directly compressible excipients

Ingredients	Formulations			
	I	**II**	**III**	**IV**
Metronidazole (40 %)	200	200	200	200
*MCC (59 %)	295	-	-	-
CPE (59 %)	-	295	-	-
CPE PM (59 %)	-	-	295	-
Prosolv® (59 %)	-	-	-	295
Sodiumstearyl fumarate (1 %)	5	5	5	5
Tablet weight	500	500	500	500

*****MCC – microcrystalline cellulose, CPE – co-processed excipient, PME – physical mixture of constituent excipients

3.2.5 Evaluation of physical properties of tablets

The physical properties of tablets were evaluated for all the formulations after 24 h of production according to the method described by BP (2013).

3.2.5.1 Weight variation test

Twenty (20) tablets of each tablet formulation selected randomly, were weighed individually using (Mettler Analytical Balance, (PhilipHarris Ltd., England) and their mean and standard deviations calculated(B P, 2013).

3.2.5.2 Content uniformity test

The weight of five tablets was obtained and the tablets powdered in a mortar. The mean weight of the five tablets powdered was weighed out and dissolved in 100 mL of 0.1 N HCl. The mixture was filtered and sufficiently diluted with 0.1 N HCl before the absorbance value was read off at 277 nm using the UV Spectrophotometer. This was carried out for the four formulations. The % drug content was computed using the straight-line equation, $y = 0.0395x + 0.1314$, derived from the calibration curve of metronidazole where y is the absorbance and x is drug concentration (µg/mL)(BP, 2013).

3.2.5.3 Tablet Thickness

The thickness of ten (10) tablets selected at random was measured for eachformulation of tabletsusing digital calliper. Their mean and standard deviations were calculated (Assaf*et al.*, 2019).

3.2.5.4 Crushing strength

Ten (10) tablets per formulation were assessed for crushing strength using a Monsanto Hardness Tester. The force required to break a tablet around its diameter was obtained and tensile strength was calculated using the following equation(Assaf*et al.,* 2019):

$$Ts = \frac{2F}{\pi dt} \ldots\ldots\ldots\ldots Eq.17$$

Where TS is the tensile strength, *F* is the breaking force, *d* and *t* are the diameter and thickness respectively.

3.2.5.5 Friability test

Tablet friability was determined for each formulation of tablets using a Digital Friability Test Apparatus 903 (Environmental & Scientific Instruments CO., India). The initial weight (W_i) of ten (10) tablets was taken, placed in the friabilator and allowed to rotate at 25 rpm for 4 min(B P, 2013). The final weight (W_f) of tablets was taken after removal of dust and friability calculated as follows:

$$Friability = \frac{W_i - W_f}{W_i} \times 100 \ldots\ldots\ldots Eq.18$$

3.2.5.6 Disintegration test

The time taken for six tablets from each formulation of tablets to disintegrate was determined using the disintegration apparatus. The entire experiment was set to run at 37 ºC in distilled water as the medium for disintegration. The mean and standard deviation of six replicates were computed and recorded for each formulation(BP, 2013).

3.2.5.7 Dissolution test

In-vitro dissolution studies were carried out on the four formulations using 0.1 N HCl as dissolution medium. A single tablet was placed in atablet dissolution test apparatus containing 900mL of 0.1 N HCl set at 37 ºC and allowed to rotate at 50 rpm. Five millilitre (5ml) samples were withdrawn at 1, 2, 5, 10, 15 and 30 mins respectively and replaced with equal volume of 0.1 N HCl after each withdrawal. The samples collected were filtered and sufficiently diluted with 0.1 N HCl before taking the absorbance readings at 277 nm using the UV-Visible spectrophotometer (UV – 1800 Spectrophotometer, Shimadzu Corporation, USA). The amount of drug released (%) was calculated based on the equation, $y = 0.0395x + 0.1314$, derived from the calibration curve of metronidazole and a plot against time was generated for the four formulations(BP, 2013).

3.2.6 Statistical analysis

Data analysis was carried out in Microsoft Excel using the analytical tool, ANOVA: Single factor to evaluate the differences in tableting properties across the batches. Differences in tableting properties were considered significant at $p \leq 0.05$.

CHAPTER FOUR

4.0 RESULTS

4.1 Preliminary results of experimental design

A summary of the tablet responses obtained for each experimental formulation is presented in Table 4.1. Tensile strength values ranged from 0.24 – 1.1 MPa and was found to be higher in formulations containing higher concentrations of MCC. Tablets also disintegrated in less than a minute across all the investigated formulations with rapid disintegration times recorded with formulations containing higher concentrations of CPV.

Table 4.1:Compositions of the mixture design experiments showing the relative proportions of microcrystalline cellulose (MCC) and crospovidone (CPV) for each formulation and the resultant tablet properties of tensile strength (TS) and disintegration time (DT) (automated process)

Batch	MCC (%)	CPV (%)	TS (MPa)	DT (min)
1	96.00	4.00	0.63±0.08	0.23±0.02
2	93.00	7.00	0.46±0.06	0.10±0.04
3	99.00	1.00	1.09±0.13	0.84±0.3
4	92.25	7.75	0.40±0.04	0.11±0.01
5	96.75	3.25	0.69±0.25	0.28±0.17
6	90.00	10.00	0.24±0.05	0.13±0.01
7	99.00	1.00	1.10±0.14	0.78±0.38
8	90.00	10.00	0.27±0.07	0.13±0.03
9	99.00	1.00	1.09±0.27	0.93±0.7
10	94.50	5.50	0.51±0.08	0.20±0.09

4.2 Model Fitting and Statistical analysis

The results of the statistical analysis carried out by ANOVA to determine the significance of the model selected for each study are presented in Table 4.2. F-values, *p*-values, R^2 values, adj R^2, Pred R^2, SD and CV were used to evaluate model fitness and adequacy. Summary statistics show that *p-values* for both models were less than 0.05 implying the significance of the model. F-values were relatively high for both models implying that the models selected for each response best fits the data set. R^2 values approached 1 for both models indicating a good correlation between the observed experimental and predicted response. For both responses, adj R^2 did not differ from Pred R^2 by more than 0.2 implying the reliability of the model.Adeq. Precision is defined as the signal-to-noise ratio and a value greater than 4 is statistically significant. Both responses recorded Adeq. Precision greater than 4 implying that there was adequate model discrimination.

Table 4.2: ANOVA data generated for Simple Lattice Mixture Design studies

Response	R^2	Adj R^2	Pred R^2	Adeq. Precision	CV %	F-value	P-value	SD
TS	0.9990	0.9985	0.9965	100.1978	2.0400	1943.77	< 0.0001	0.0132
DT	0.9824	0.9736	0.9592	20.9606	14.6400	111.48	< 0.0001	0.0546

Model Equations

TS = + 1.09*MCC + 0.2543*CPV – 0.6319*MCC*CPV – 0.7089*MCC*CPV (MCC - CPV) (cubic)……Eq.1

DT = + 0.8469*MCC + 0.1261*CPV – 1.40*MCC*CPV – 0.9112*MCC*CPV (MCC - CPV) (cubic)……Eq. 2

The mathematical equations given above for each model was used to express the relationship between the input factors investigated (MCC & CPV) and the corresponding tablet responses obtained. The polynomial equation above quantifies the relative contribution of each factor to the response.

The model equation for tensile strength (TS) shows that MCC had a greater effect on TS compared to CPV because of its higher coefficient (+1.09) compared to that of CPV (+0.2543). The interaction between MCC and CPV exerted a negative effect on TS (-0.6319). Similarly, model equation for DT shows that MCC also exerted a greater impact on DT (+0.8469)compared to CPV (+0.1261). The interaction between MCC and CPV produced a negative effect on DT (-1.40).

Figure 4.1 is a two-component mix plot illustrating the effect of each factor variable on tensile strength (TS). The plot shows that TS increases with increase in the proportion of MCC and decreases with increase in the concentration of CPV.

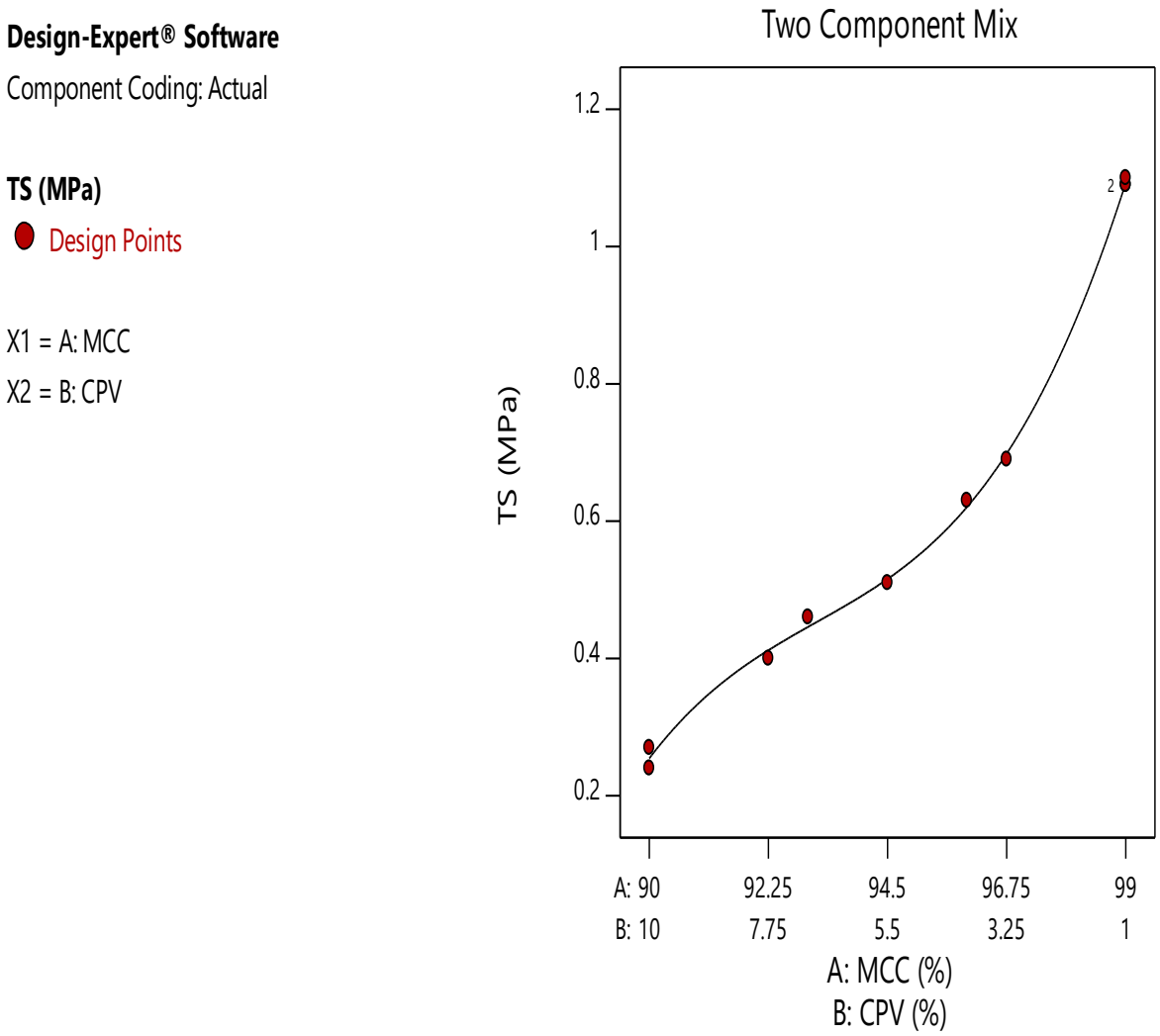


Figure 4.1. Two component mix plot showing the effect of changing proportions of MCC and CPV on TS

Figure 4.2 is a two-component mix plot illustrating the effect of each factor variable on disintegration time (DT). The plot shows that DT increases with increase in the proportion of MCC and decreases with increase in the concentration of CPV.

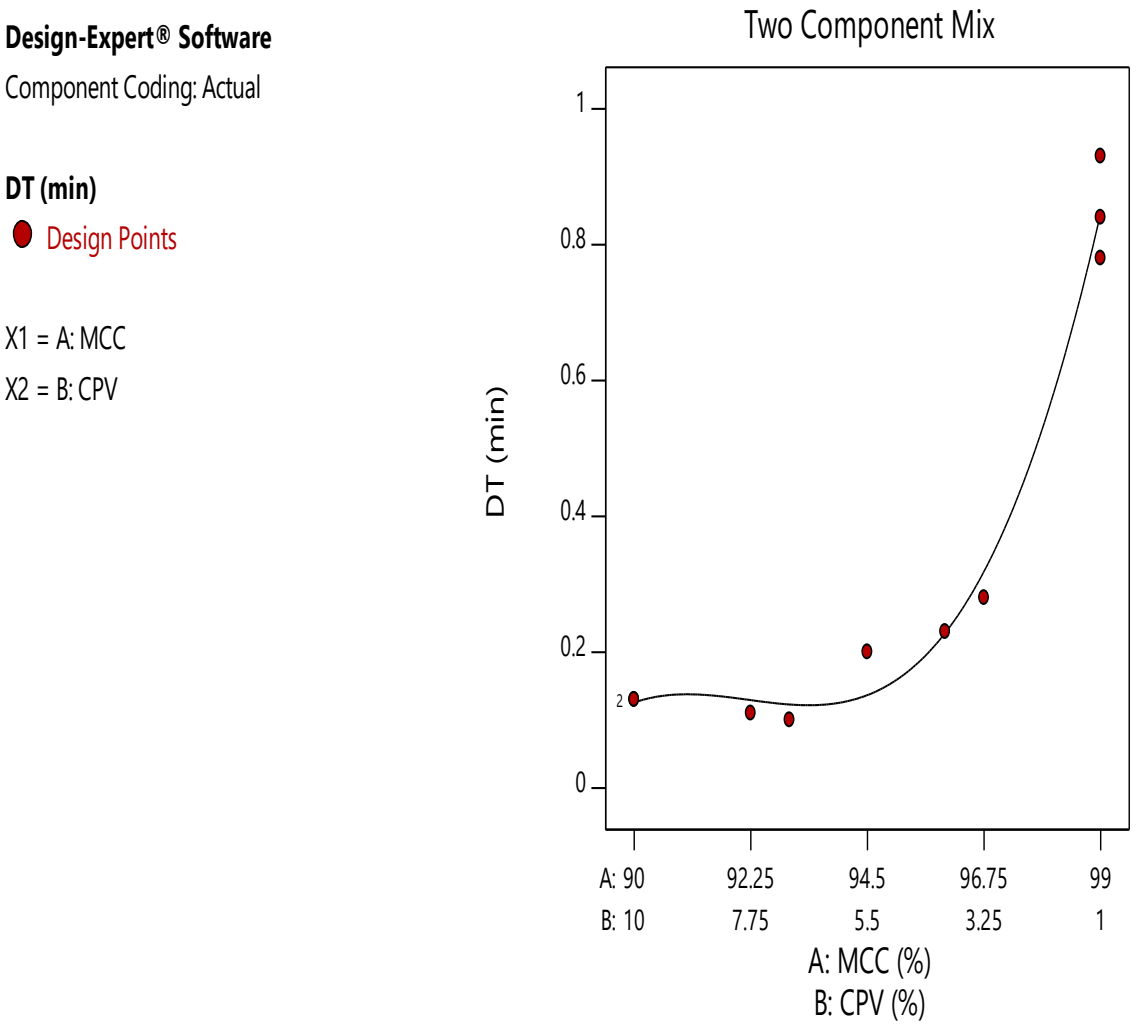


Figure 4.2. Two component mix plot showing the effect of changing proportions of MCC and CPV on DT

4.3 Solid State Characterization

4.3.1 Particle size analysis

Result of the particle size analysis of CPE, MCC and CPV is presented in Table 4.3. Based on the median diameter (d_{50}), CPE had the largest particle size while CPV had the smallest particle size. Particle size increased as a result of co-processing. The polydispersity index (PDI) values were ranked in the following order, MCC<CPE<CPV, implying that MCC had a more uniform particle size distribution.

Table 4.3: Particle size analysis of CPV, MCC and CPE

	Particle Size Parameters				
Materials	**d_{10} (µ)**	**d_{50} (µ)**	**d_{90} (µ)**	**Range(µ)**	**Polydispersity Index (PDI)**
CPV	20	40	70	10 - 120	1.25
MCC	70	100	170	40 - 250	1.00
CPE	90	180	280	50 - 500	1.06

4.3.2 Scanning electron microscopy (SEM)

The SEM images for CPV, MCC and CPE are presented in Plate 1. Particles of CPV are smaller, appearing in bunches or aggregates of primary particles. Particle morphology of MCC appears irregular and fibrouswith some degree of roughness of the surface. CPE particles appeared to have the same surface morphology and shape of MCC.

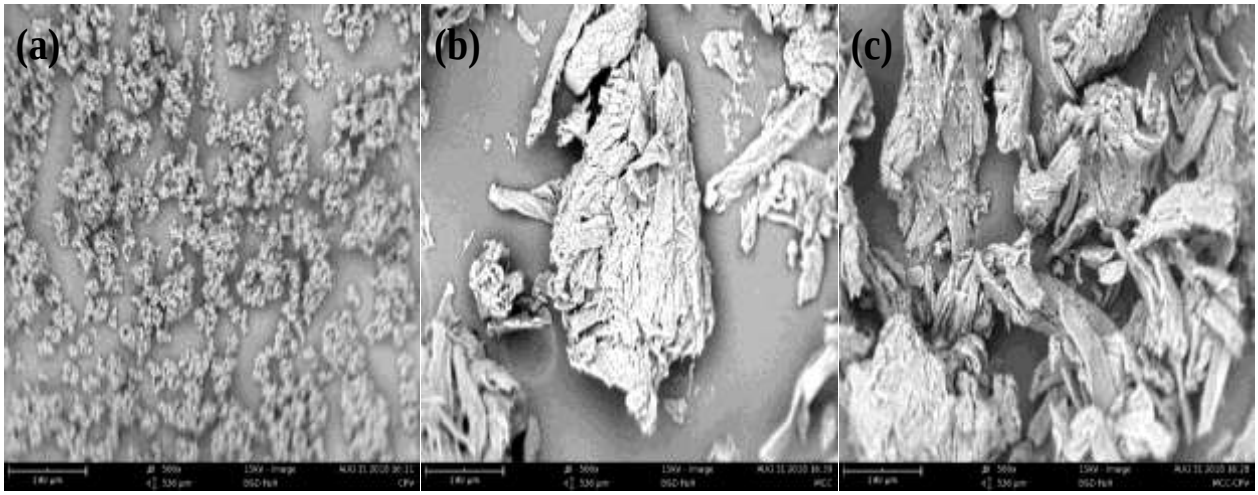


Plate I. SEM images of (a) CPV, (b) MCC, and (c) CPE (300 ×)

4.3.3 Powder x-ray diffraction (PXRD)

The diffraction curves of CPE, MCC and CPV are presented in Figure 4.3.The diffraction patterns of CPE and MCC are characterized by one major peak occurring at angle between 20 – 30 º on the 2 Theta scale. The absence of many peaks is an indication that both materials have a low degree of crystallinity and are semi-crystalline in nature. The diffraction curve of CPV displayed a halo pattern suggesting that the material is amorphous. The diffraction peaks identified in MCC were maintained in CPE suggesting that CPV and MCC are compatible.

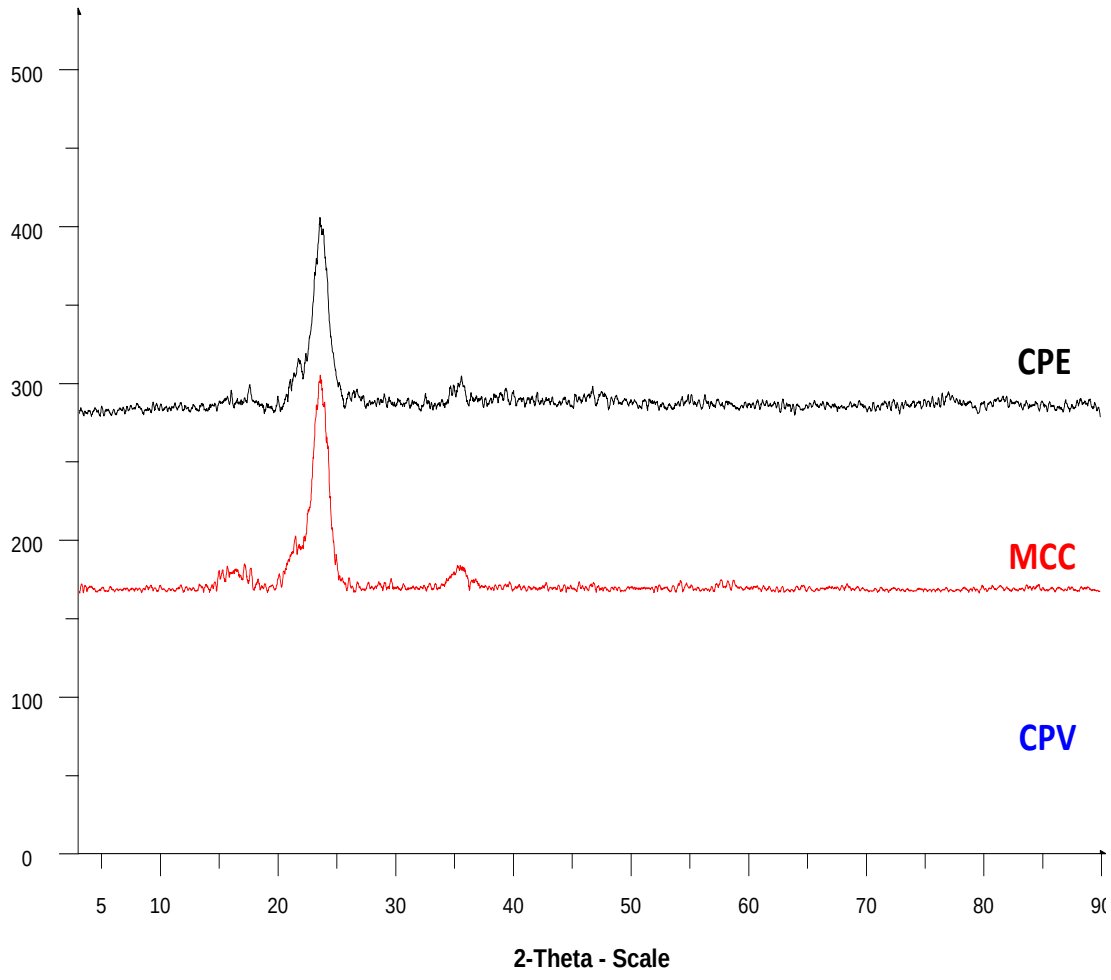


Figure 4.3: PXRD patterns of CPV, MCC, and CPE

4.3.4 Differential Scanning Calorimetry (DSC)

Overlay plots of the DSC scans of CPE, CPV, and MCC are presented in Figure 4.4. The three materials showed an endothermic transition corresponding to loss of moisture occurring between 50 – 100 º C. A greater degree of moisture loss was observed with MCC owing to its higher moisture content.

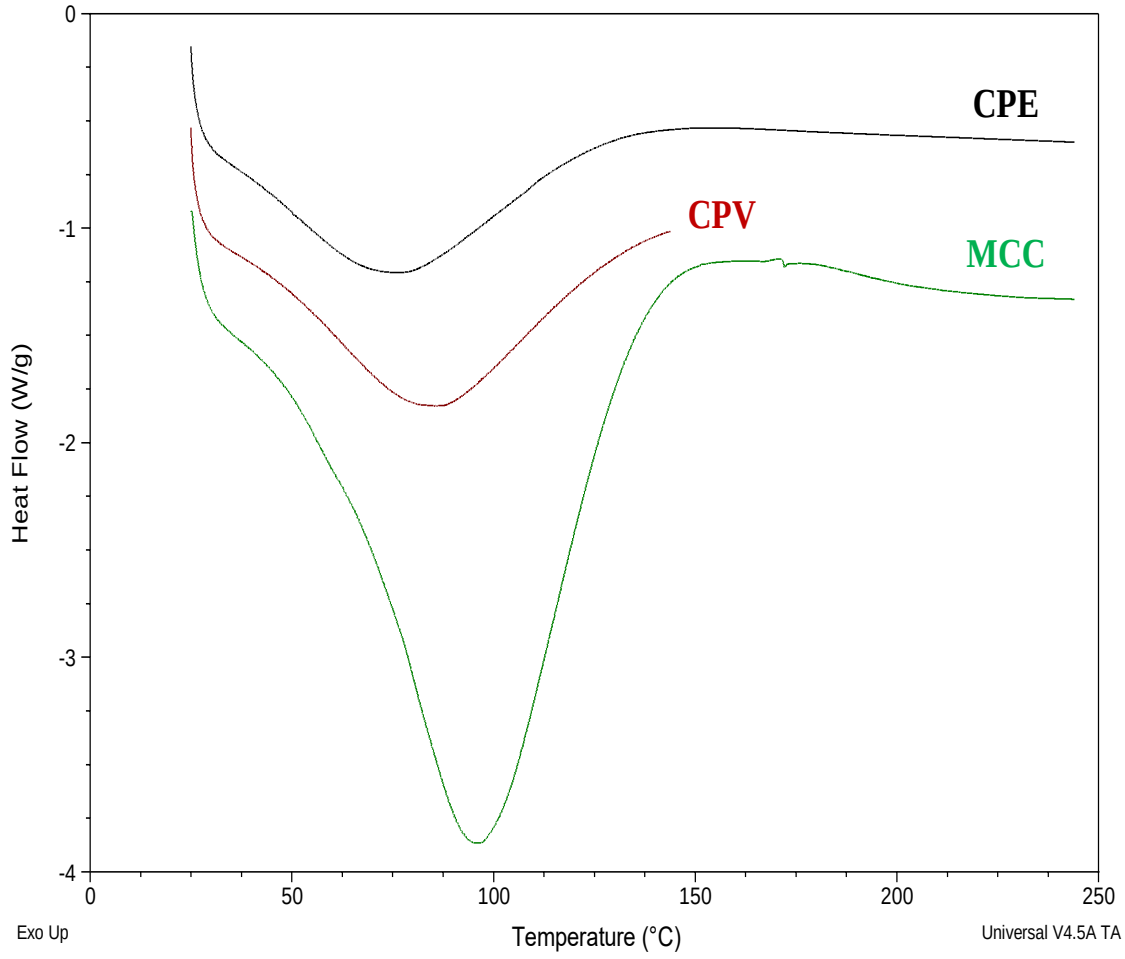


Figure 4.4:DSC overlay showing thermograms of CPE, CPV and MCC4.3.54

4.3.5 Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra for MCC, CPV and CPE are displayed as Figure 4.5. The IR spectrum of MCC showed absorption bands occurring at the following frequencies: 3331 cm^{-1} (O-H stretching), 2894 cm^{-1} (C-H stretching), 2322 cm^{-1} (O=C=O stretching), 1636 cm^{-1} (C=C stretching), and 1314 cm^{-1} (O-H bending). The IR spectrum of CPV was characterized by absorption bands appearing at the following frequencies: 3391 cm^{-1} (N-H stretching), 2324 cm^{-1} (O=C=O stretching), 1648 cm^{-1} (C=O stretching), 1423 cm^{-1} (C-H bending), 1283 cm^{-1} (C-N stretching), and 842.8 (C=C bending). These absorption bands were replicated in CPE implying that co-processing MCC and CPV did not result in any significant chemical reaction.

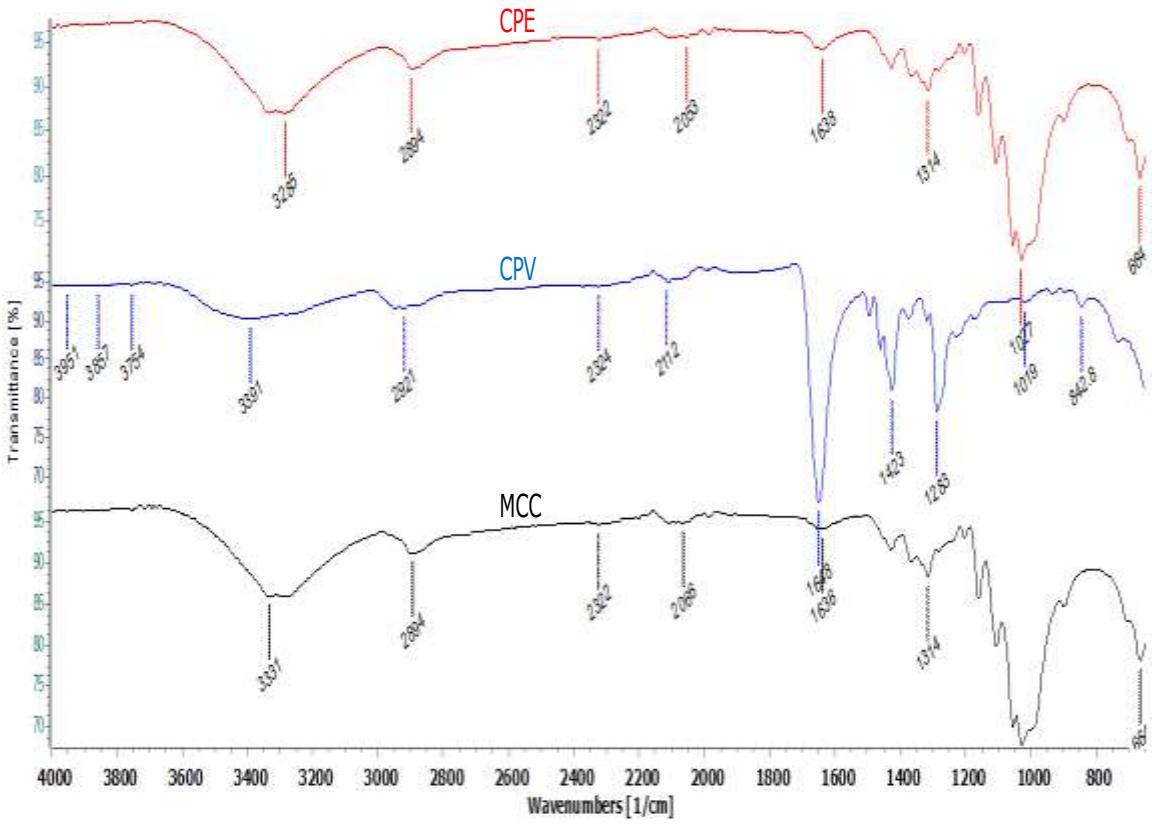


Figure 4.5: FT-IR spectra of CPE, CPV, and MCC

Figure 4.6 presents the FT-IR spectra of MTZ, CPE and MTZ+CPE. The IR bands of MTZ corresponding to O-H stretch, N-H stretch, C-H stretch, N=C=N stretch, and C-H bending appear at the following frequencies respectively: 3206 cm^{-1}, 3097 cm^{-1}, 2956 cm^{-1}, 2116 cm^{-1}, 1807 cm^{-1}, and 1366 cm^{-1}.

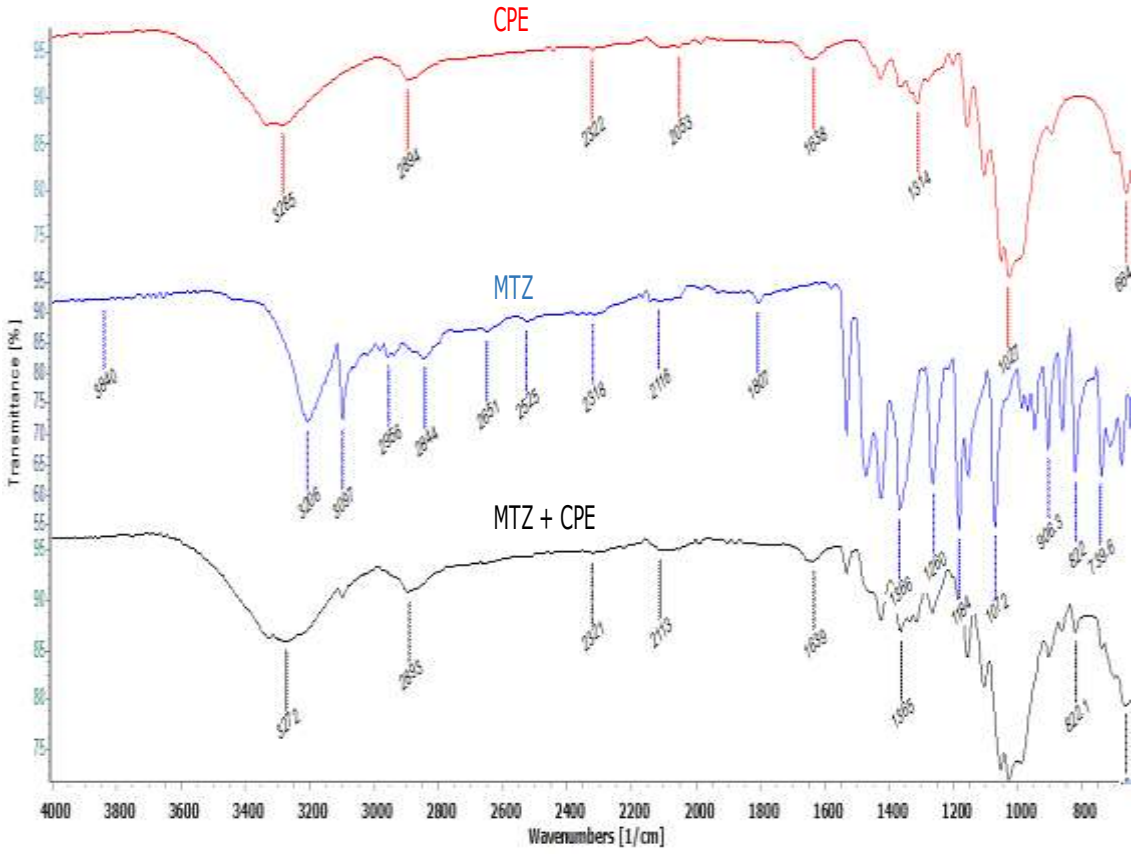


Figure 4.6: FT-IR spectra of CPE, MTZ, and MTZ+CPE

4.4 Powder Properties

Powder characteristics of MCC, CPV and CPE are presented in Table 4.4 showing the mean and standard deviation values in parenthesis. The angle of repose values were ranked in the following order, CPE<MCC<CPV, with CPE having a value of 18.23 º and CPV having a value of 43.90 º. Flow rate of all three materials ranged from 1.93 – 2.30 g/s with MCC having the highest value. Bulk and tapped density values of MCC and CPV were relatively smaller compared to that of CPV. Carr's index and Hausner's ratio parameters were relatively higher for CPV and CPE in comparison to MCC. A mean value of 1.48 g/mL was obtained as true density for both MCC and CPE in comparison to a lower value obtained for CPE (1.23 g/mL). Higher porosity values were obtained for MCC and CPE in comparison to a lower value obtained for CPV indicating that MCC and CPE had a greater degree of porosity compared to CPV. Swelling capacity of all three materials were ranked in the following order, CPV < CPE < MCC.Moisture content was found to be higher for MCC (14 %) when compared to that of CPV (8 %) and CPE (3 %). The pH of all three materials fell between 7.5 – 7.6 indicating that all three materials were neutral. The LSR shows that CPE was more sensitive to sodium stearylfumarate compared to the primary excipient, MCC. On the other hand, MCC was more sensitive to magnesium stearate compared to CPE. Overall, the degree of sensitivity to lubricants was higher with magnesium stearate compared to sodium stearyl fumarate.

Table 4.4: Powder Properties of MCC, CPV, and CPE (n = 3)

Parameters	**MCC**	**CPV**	**CPE**
Angle of Repose (º)	28.07 (2.30)	43.90 (4.65)	18.23 (1.70)
Flow Rate (g/s)	2.30 (0.01)	1.93 (0.26)	2.00 (0.06)
Bulk Density (g/mL)	0.32(0.004)	0.60 (0.01)	0.34 (0.01)
Tapped Density (g/mL)	0.40 (0.01)	0.78 (0.01)	0.45 (0.004)
Carr's Index (%)	19.42 (1.77)	23.83 (1.75)	23.65 (0.93)
Hausner's Ratio	1.24 (0.03)	1.31 (0.03)	1.31 (0.03)
True Density (g/mL)	1.48 (0.03)	1.23 (0.04)	1.48 (0.02)
Porosity (%)	78.25 (0.73)	51.88 (0.78)	76.78 (0.28)
Swelling capacity (%)	25.00	11.11	16.67
Moisture Content(%)	14.00	8.00	3.00
pH	7.50	7.60	7.50
LSR_{SSF} (%)	45.09	-	59.11
LSR_{MST} (%)	79.38	-	62.93

LSR—Lubricant Sensitivity Ratio.

The moisture sorption capacity for MCC and CPE was illustrated graphically in Figure 4.7. The plot shows that maximum weight gain for CPE did not exceed 3 % over a five-day period compared to about 10 % for MCC within the same time frame. This implies that MCC has a higher degree of hygroscopicity compared to CPE.

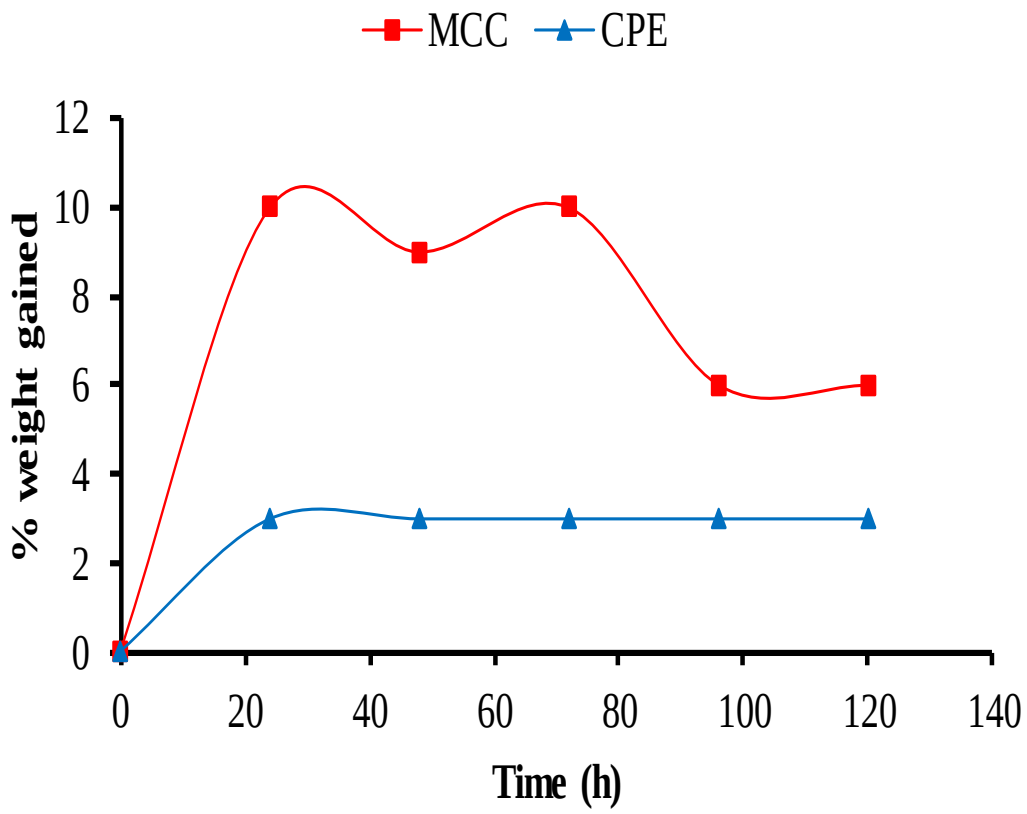


Figure 4.7. Percentage (%) weight gain due to moisture sorption with time

The outcome of dilution potential studies is represented graphically in Figure 4.8. The figure show that the tensile strength of PCM tablets formulated with either MCC or CPE as DC excipient increased as the proportion of the excipient in the formulation increased.

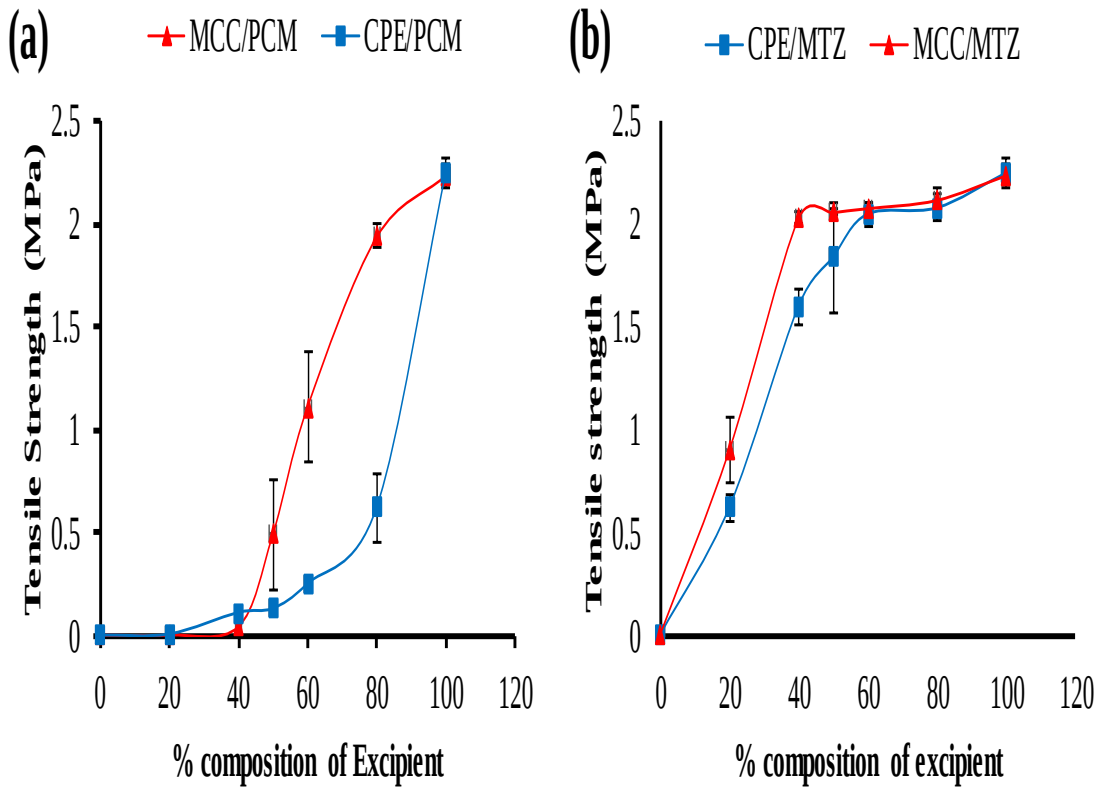


Figure 4.8. Therelationship between tensile strength and % composition of excipients in the formulation. (a) using PCM as model drug, (b) using MTZ as model drug

4.5 Compaction Studies

Heckel and Kawakita plots presenting the compaction profiles of MCC, CPV and CPE are displayed as Figure 4.10. The Heckel plot (Fig. 4.10a) shows that the degree of densification (1/Ɛ) increases as the compaction pressure increases, while the extent of volume reduction (P/C) increased with increase in compaction pressure as seen in the K

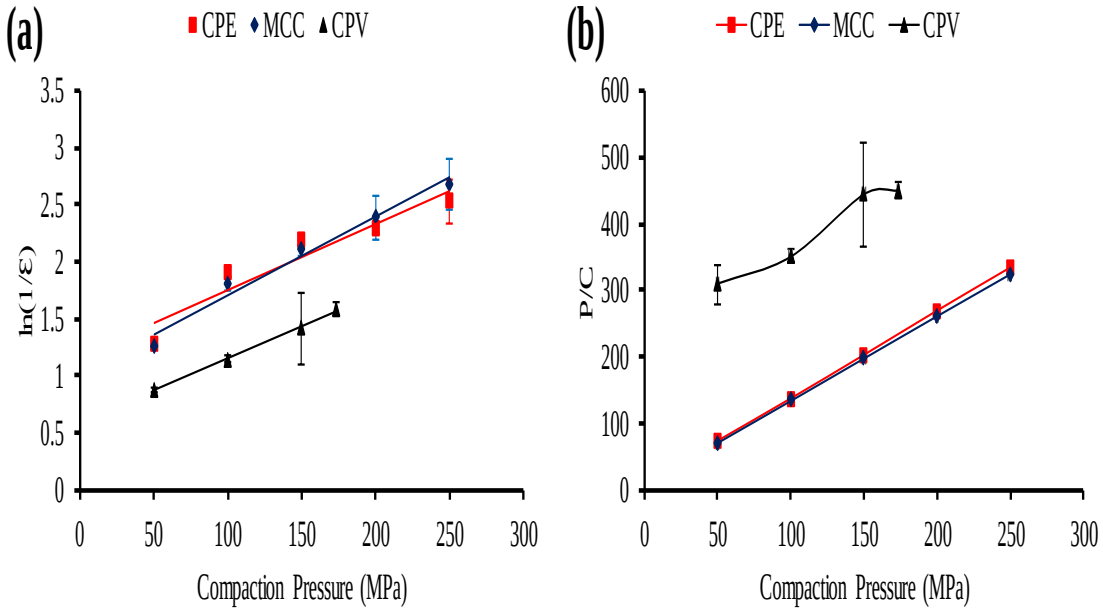


Figure 4.9. (a) Heckel Plot and (b) Kawakita Plot

The compaction parameters resolved from both plots are summarised in Table 4.5. Mean yield pressure, a Heckel parameter, which measures the degree of plasticity in a material was ranked in the following order, MCC<CPE<CPV implying that MCC had the least value of 144.93 MPa corresponding to a greater degree of plasticity. The D_A values representing the total degree of densification occurring at the initial stages of compression was relatively the same for MCC and CPE respectively(0.69, 0.64)but differed significantly from that of CPV (0.44).

Densification occurring as a result of particle slippage and rearrangement was quantified using D_0 parameter and the values obtained for MCC and CPE were similar compared to that of CPV which was relatively higher (0.49), implying that the extent of densification occurring as a result of particle slippage and rearrangement was higher with CPV compared to the other two materials. The D_B parameter representing the degree of densification occurring as a result of particle fragmentationwas relatively similar for MCC and CPE and higher when compared to CPV.

The Kawakita parameters show that the degree of compressibility for all three materials represented by '**a**' was found to be similar. However, the compression effort (P_K) required to achieve a 50 % reduction in the volume of the powder bed during compression was found to be much lower for both MCC and CPE in comparison to CPV implying a greater degree of plasticity for both MCC and CPE.

Table 4.5: Heckel and Kawakita Parameters for MCC, CPV and CPE

Materials	Heckel				Kawakita		
	P_Y (MPa)	D_A	D_0	D_B	*a*	*B*	P_K
CPE	172.41	0.69	0.23	0.46	0.77	0.17	5.74
MCC	144.93	0.64	0.22	0.42	0.79	0.16	6.28
CPV	178.57	0.44	0.49	-0.05	0.80	0.01	193.88

P_Y: Mean yield pressure,
D_A: Total degree of densification occurring at low pressures,
D_B: Degree of densification occurring due to particle fragmentation,
D_0: Degree of densification occurring due to slippage and particle rearrangement at the early stages of compression,
'**a':** Compressibility,
'**b':** Inverse measure of the amount of plastic deformation occurring in the material,
P_K: values obtained from the reciprocal of B.

The compresssibility, tabletability and compactibility (CTC) profile of MCC, CPV and CPE are presented in Figure 4.11. The compressibility plot denoted as Fig. 4.11 (a) shows the effect of compaction pressure on the porosity of compacts. There was a decline in porosity of compacts as the applied pressure increased for all three materials. The extent of reduction in porosity was higher in MCC and CPE compared to CPV. The plot shows that the level of porosity reduction seen in MCC and CPE compacts was relatively the same.

The compactibility plot displayed as Fig. 4.11 (b) illustrates the effect of porosity on tensile strength of compacts produced. The plot shows that the tensile strength of compacts increased with decreasing porosity. The compactibility profile of all three materials was ranked in the following order: MCC > CPE > CPV. At all levels of porosity, the compacts of MCC returned higher tensile strength values compared to those of CPE and CPV.

The tabletability plot presented as Fig. 4.11 (c) shows the effect of compaction pressure on tensile strength of compacts produced with all three materials. Tensile strength of compacts increased with increase in compaction pressure. At all pressures evaluated, the tensile strength of MCC compacts were consistently higher than those of CPE and CPV. The tabletability profile of the three materials were thus ranked in the following order: MCC > CPE > CPV.

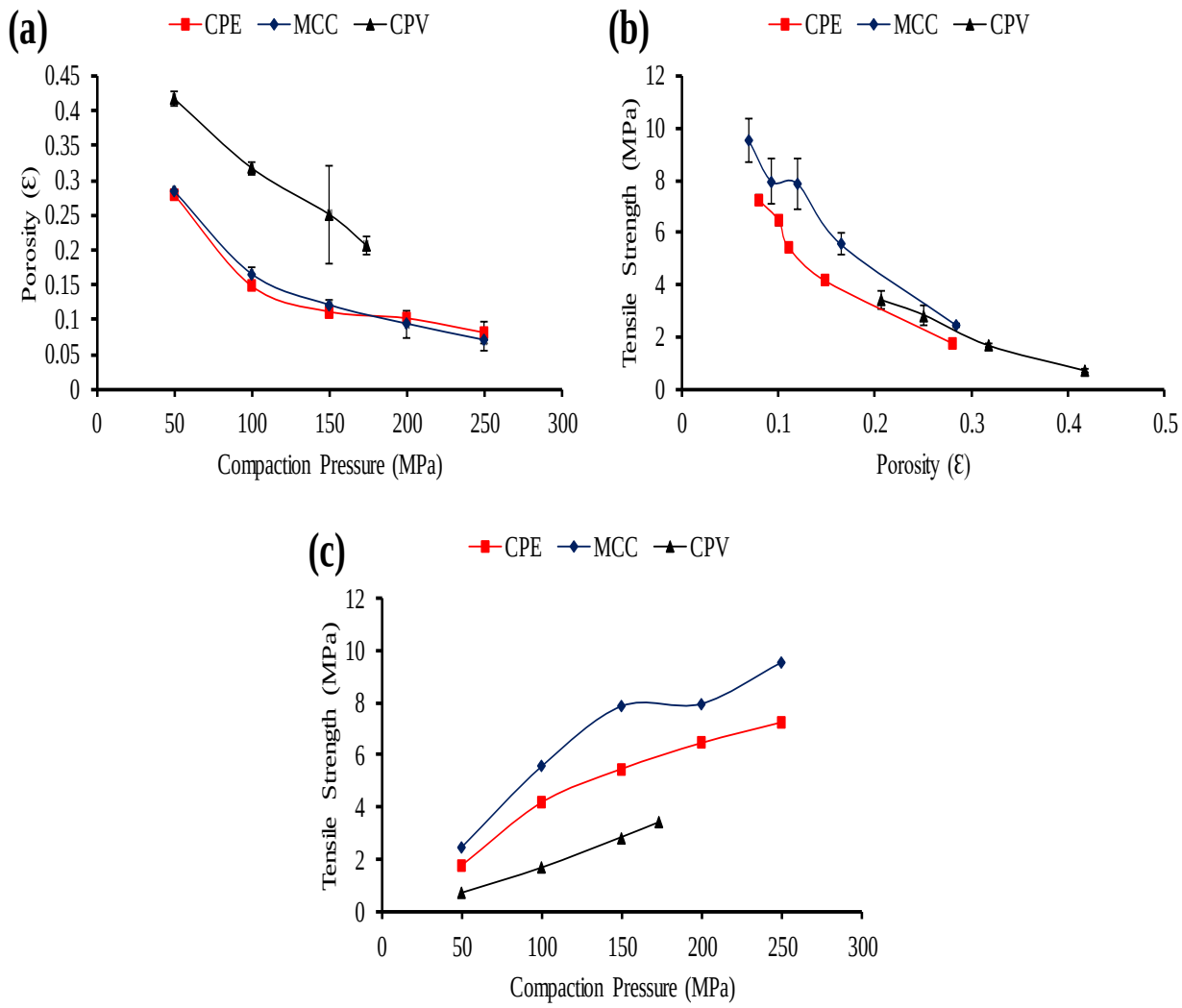


Figure 4-3. (a) Compressibility Plot, (b) Compactibility Plot, and (c) Tabletability Plot

4.6 Tablet Properties

The tablet properties of batches I – IV formulations are summarized in Table 4.6. The mean weight of tablets ranged from 491 – 497 mg with formulations I and IV having the least tablet mean weight. Drug content of metronidazole varied from 86.72 – 106.47 % with formulations III and I having minimum and maximum drug content respectively. Tablet thickness ranged from 3.83 – 3.90 mm. The tensile strengths obtained for the formulations were ranked in the following order: PME > CPE > MCC > Prosolv, where formulations containing PME and Prosolv® as DC excipient returned the highest and lowest mean tensile strength values respectively. The friability values obtained were consistent with the results obtained for tensile strength and all the formulations passed the friability test by not exceeding 1 % except for formulation IV (Prosolv®) that produced weak tablets having a friability > 1%. The time taken for disintegration of tablets across the formulations ranged from 1.33 – 26.88 mins, with Prosolv® and MCC yielding the maximum disintegration times. The amount of drug released (%) with time is represented by Fig. 4.12 as a dissolution plot. The time taken to release 80 % of metronidazole was ranked in the following order: Prosolv < CPE < PME < MCC. The extent of drug release was highest with CPE tablets, followed by Prosolv® and PME and then MCC tablets. All the formulations passed the dissolution test based on the USP requirement that 70 % of the drug should be released in 45 mins.

Table 4.6. Tablet properties of FormulationsI - IV

Parameters	I	II	III	IV
Mean weight (mg)	491.00±9.68	497.00±9.23	497.00±8.65	491.00±6.41
Drug content (%)	106.47±13.34	102.48±1.07	86.72±9.22	97.35±0.27
Thickness (mm)	3.83±0.62	3.90±0.08	3.90±0.05	3.85±0.03
Tensile strength (MPa)	1.38±0.11	1.45±0.08	1.62±0.08	0.82±0.04
Friability (%)	0.61±0.29	0.61±0.29	0.61±0.28	1.43±0.29
Disintegration time (min)	26.88±4.17	11.48±3.08	7.32±2.66	1.33±0.19
Dissolution time $T_{50\%}$ (min)	8.00	3.00	3.00	2.00
Dissolution time $T_{80\%}$ (min)	33.00	7.00	10.00	3.00

I – MCC as DC excipient, II – CPE as DC excipient, III – PME as DC excipient, IV – PROSOLV® as DC excipient

*Values are mean and standard deviation in bracket.

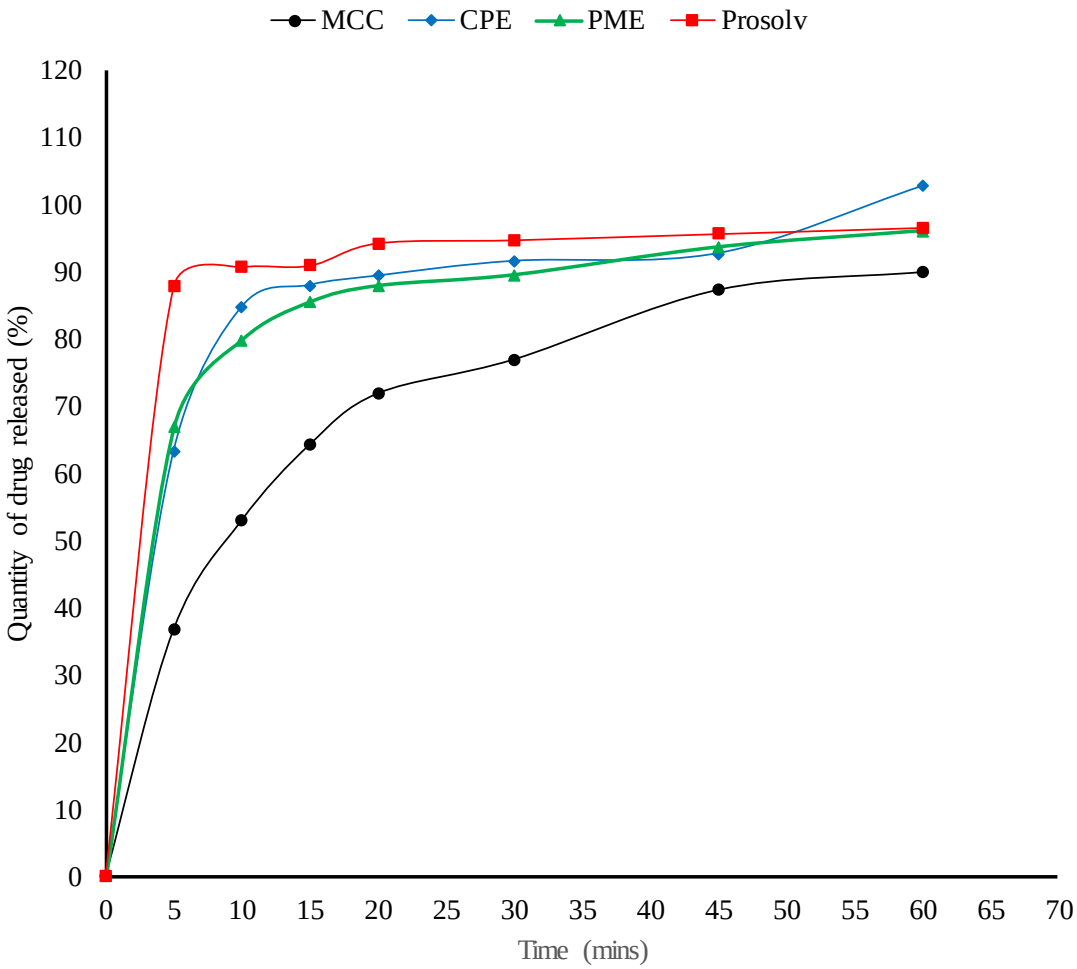


Figure 4.11. The Dissolution profile for metronidazole tablets formulated with either MCC, CPE, PME or Prosolv® as DC excipients

CHAPTER FIVE

5.0 DISCUSSION

Co-processed excipients are combinations of two or more excipients designed to improve functionality by particle engineering (Nachaegari and Bansal, 2004; Rojas *et al*., 2012). The development of a co-processed excipient requires optimizing the proportions of the parentexcipients that will be combined and is contingent on the desired functionality(Nachaegari and Bansal, 2004). In this study,the goal of optimization was to determine the proportion by weight of MCC and CPV that will be combined to yield a co-processed excipient with improved disintegration functionality when used in direct compression formulation. The Quality by Design (QbD) approach was employed using the Design of Experiment (DoE) platform to experimentally determine the optimum proportions of MCC and CPV. This is a systematic approach to pharmaceutical development recommended by International Conference on Harmonization (ICH) Q8 guidelines which state that quality should be built into product (Yu, 2008 ;Singh *et al*., 2011). This approach is currently being adopted by the pharmaceutical industry to optimize pharmaceutical processes and formulations.Many studies have been carried out employing the QbD approach (Gonnissen *et al*., 2008; Rodríguez-amado *et al*., 2015; Chauhan *et al*., 2016). The summary of this approach is that it provides a simple and efficient means of optimizing processes and formulations using multivariate analysis with minimum experiments rather than the one-variable-at-a-time (OVAT) approach which involves many experiments and is time consuming (Singh *et al*., 2011;Dahmash *et al*., 2018).

The outcome of the optimization studies revealed that combining MCC in varying proportions ranging from 90 – 99 % with CPV ranging from 1 – 9 % gave rise to co-

processed formulations with differing tensile strength and disintegration properties. Design of Experiment as a tool for implementing QbD was able to establish a relationship between the composition of CPE in terms of the proportions of the interacting excipients and the tableting properties of tensile strength and disintegration. Formulations of CPE containing higher concentrations of MCCgave rise to tablets with higher tensile strength and longer disintegration time as seen in Table 4.1. This has been attributed to the excellent binding characteristics of MCC as a direct compression excipient (Ohwoavworhua and Adelakun, 2005;Ali *et al*., 2009; Thoorens *et al*., 2014). The mechanical properties of MCC demonstrate a high degree of plasticity during compressiongiving rise to tablets with higher tensile strength that take a longer time to disintegrate (Edge *et al*., 2000; Khomane and Bansal, 2013). This has been attributed to extensive hydrogen bonding during plastic deformation leading to an increase in bonding surface area and bond strength (Thoorens *et al*., 2014). This agrees with the findings of Apeji *et al*.(2019) who studied the impact of several binders including MCC on the tableting properties of co-processed excipient developed using these binders. The co-processed excipient containing MCC performed better in terms of the tensile strength as a result of plastic deformation characterized by a lower yield pressure.

The overall effect of CPV on tensile strength and disintegration of CPE has been attributed to its superdisintegrating properties. Increasing the content of CPV in the formulations of CPE gave rise to tablets of lower tensile strength and corresponding shorter disintegration time.The effect on tensile strength may be due to the micronizedparticle size of CPV as observed during particle size analysis (Table 4.3), where the particle size ranged from 10 -120 μm. Due to its relatively small particle size, CPV may have been adsorbed onto the surface of MCC during co-processing thereby lowering the bonding surface area and bonding strength of MCC particles resulting in a

reduction in tensile strength of tablets(Sun, 2011). As observed during CTC profiling (Fig. 4.11), tabletability of MCC was found to decrease as a result of co-processing giving rise to tablets of lower tensile strength with CPE. The corresponding effect on disintegration time has been associated with a reduction in tensile strength of tablets. Tablets of lower tensile strength are expected to disintegrate faster due to the relatively weak interparticulate bonding matrix and increased porosity of the tablet. The rapid disintegration time observed with increasing concentrations of CPV may belinkedtoits cross-linked structure(Desai *et al*., 2016).CPV is a water insoluble synthetic cross-linked polyvinylpyrrolidone that exerts its disintegration effect primarily by strain recovery and to a lesser extent by wicking and secondary swelling(Komblum and Stoopak,1973;Chaudhari *et al*., 2012). It has been used at concentrations of 2 – 5 % in tablets prepared by direct compression and wet granulation to achieve rapid disintegration(Debotton and Dahan, 2017).Kaur *et al*. (2011) reported that when the concentration of a superdisintegrant is above a critical level of 5 %, the disintegration time remains almost constant.This explains why formulations of CPE containing higher concentrations of CPV exceeding 5 % maintained a constant disintegration time between 10 -20 s.Quantifying the optimal proportions of the two excipients, MCC and CPV, required for the development of a high functionality excipient with improved disintegration efficiency was made possible using the Design of Experiment approach.

Prior to formulation studies in pharmaceutical development, preformulation studies are carried out to characterize the properties of the drug and/or excipient in order to determine its suitability for a particular formulation. The design and manufacture of suitable dosage forms is predicated on the properties of the drug and/or excipients (Meehan, 2010; Moreton, 2004). Solid state properties of excipients play a critical role in defining the quality of formulations (Sun, 2009). Powder mixtures processed into

tablets by direct compression rely solely on the attributes of the directly compressible excipient to define the quality of the tablets (Rojas *et al*., 2013). The attributes of the DC excipient that promote the successful formulation of tablets by direct compression includes flowability, compressibility, dilution potential etc.(Saha and Shahiwala, 2009). Particle size and its distribution are fundamental properties of powders that influence their functional or derived properties e.g. flowability and compressibility(Ayenew *et al*., 2017).Increase in particle size was observed for CPE owing to the co-processing of MCC and CPV by wet massing technique. This is consistent with the findings of other studies carried out involving co-processing where the co-processed excipient developed had a larger particle size relative to the constituent excipients(Kittipongpatana and Kittipongpatana, 2011;Adeoye and Alebiowu, 2014; Apeji *et al*., 2018; Rosenbaum *et al*., 2018).Particle size enlargement of CPE translated to an improvement in the flow behaviour of CPE as shown in Table 4.4. This can be attributed to a reduction in interparticulate friction and cohesion between particles that normally hinders free flow of powders (Staniforth and Aulton, 2007). Many studies have reported a correlation between particle size and flow characteristics of the powder with an increase in particle sizeleading to enhanced flowability (Sun, 2010). Particle size distribution as characterized by polydispersity index (PI) corresponded to a uniform distribution of particle sizes implying that powder segregation will be minimized during processing and formulation of tablets.

Particle shape and surface morphology influence the mechanical behaviour of drugs and excipients during tablet formation (Sun, 2011). Materials characterized by irregular shape and rough surfaces tend to bind more firmly and form solid compacts owing to the effect of mechanical interlocking (Al-khattawi *et al*., 2014; Egart *et al*., 2014).Particle morphologies of MCCas examined by SEM showed that

MCC is primarily composed of irregularly shaped particles with intercalated microfibrillar structure (Plate I). This correlates well with the superior tabletability of MCC observed following compaction and agrees with the findings of Al-Khattawi *et al*.(2004) who attributed the hardness of MCC tablets to strong interparticulate bonding provided by mechanical interlocking and hydrogen bonding.Co-processing of MCC with CPV had little or no effect on the morphological appearance and shape of MCC which may be due to the relatively low proportion of CPV present in the co-processed excipient. However, there was remarkable improvement in particle size and flow behaviour of CPE implying that the presence of CPV (1 %) was sufficient to modify the physicomechanical properties of MCC.

Powder X-ray diffraction (PXRD) was carried out to evaluate the degree of crystallinity of the interacting excipients and note possible changes that may occur in the molecular structure of CPE as a result of co-processing. Crystalline materials are characterized by prominent, sharp diffraction peaks which correlate with the degree of crystallinity of the material and is typical of most active pharmaceutical ingredients (API) that occur as crystals. However, most excipients are classified as either semi-crystalline or amorphous in nature and therefore do not produce sharp diffraction peaks when exposed to X-ray (Apeji *et al*., 2019).The PXRD pattern obtained for MCC corresponds to that reported by Rojas *et al*. (2011) confirming the semi-crystalline nature of MCC due to the presence of broad diffraction peaks. This implies that MCC had a low degree of crystallinity which was maintained in CPE. Co-processing MCC with CPV did not alter significantly the crystallinity of MCC implying that there was no modification of the molecular structure of MCC as a result of co-processing. Although, CPV produced a diffraction halo pattern that

corresponds to amorphous materials(Chauhan and Chauhan, 2014; Sharma *et al*., 2015), it was not sufficient to cause a significant change in the crystallinity of MCC possibly because of the low proportion of CPV employed in co-processing. For tableting purposes, excipients that are largely amorphous are preferred because of their superior compressibility(Bryn *et al*., 2017).

Drug-excipient compatibility screening is usually conducted during preformulation studies to determine the suitability of combining drugs and excipients in a formulation(Bozdağ-Pehlivan *et al*., 2011). This screening also applies to excipient-excipient compatibility in the development of co-processed excipient. Though, excipients are regarded as inert materials, it was necessary to establish that there was no form of chemical modification occurring during co-processing. Functionality enhancements observed in co-processed excipients have been attributed to physical modification by particle engineering of the interacting excipients(Adetunji and Odeniyi, 2016; Li *et al*., 2017; Akin-Ajani *et al*., 2018; Chaheen *et al*., 2018).

The FT-IR spectrum obtained for MCC was consistent with that reported by Ciolacu *et al*. (2011). The appearance of the characteristic bands of MCC in the IR spectrum of CPE confirms the absence of a chemical change occurring during co-processing. This agrees with some findings in literature reporting the absence of chemical change during co-processing (Kittipongpatana and Kittipongpatana, 2011; Choudhari *et al*., 2018). The presence of the absorption bands of CPV in the IR spectrum of CPE was reduced in prominence and intensity possibly due to the low concentration of CPV (1 %) present in the co-processed excipient.There was no shift in position or the appearance/disappearance of peaks as observed in the FTIR

spectrum of CPE, revealing that there was no chemical interaction or modification of the interacting excipientduring co-processing.

For drug-excipient compatibility studies, metronidazole (MTZ) was found to be compatible with CPE as the absorption bands of MTZ were replicated in the IR spectrum of MTZ+CPE physical mixture establishing the absence of significant chemical reaction.The drug therefore chosen for this study was found to be compatible with CPE and was used to formulate tablets containing MTZ by direct compression.

The DSC thermograms of MCC and CPE confirmed their semi crystallinestatus as observed with PXRD. The three materials were characterized by broad endothermic peaks consistent with semi-crystalline or amorphous materials. The peaks obtained have been associated with loss of moisture occurring as a result of dehydration during heating of the sample(Bozdağ-Pehlivan *et al*., 2011).The intensity of the endothermic peak obtained for each material can be correlated with the degree of moisture loss as materials having a higher moisture content produced broader endothermic peaks. It was clearly seen that MCC having the highest moisture content of 14 % (Table 4.4) showed a greater degree of moisture loss corresponding to a much broader endothermic peak compared to the other materials. The absence of a melting peak for each material further confirms the predominant amorphous nature of all three materials.

The performance and functionality of a co-processed excipient has been linked to its particle and powder properties (Ogunjimi and Alebiowu, 2013; Lamešic *et al*., 2017; Li *et al*., 2017). Bulk powder properties like flowability have been assessed by measuring the angle of repose, Carr's index, Hausner's ratio etc. As a general rule, values of angle of repose < 30 º correspond to free flowing powders (Zhou *et*

al., 2010). The flow properties of MCC were improved as a result of co-processing giving rise to CPE with an angle of repose < 30 º (Table 4.4). Improvement in flow properties recorded with CPE has been associated with an increase in particle size that enhances flow and opposes particle cohesion (Hou and Sun, 2008; Majerová *et al*., 2016). Other factors that may have been responsible for modulating the powder flow of CPE include particle density, shape and surface area (Thoorens *et al*., 2014). The flow behaviour of a co-processed excipient designed for direct compression is a critical material attribute that is required for the robust formation of tablets by direct compression(Nachaegari and Bansal, 2004). The flow of the tableting mix influences uniformity in weight and drug content of tablet. Failure of the tableting mix to flow well during compression will result in uneven filling of the die cavity leading to tablets with wide variation in weight and drug content.An outstanding attribute of co-processed excipients is the improvement in flow properties relative to the constituent excipients as reported by several studies(Avachat and Ahire, 2007 ;Ogunjimi and Alebiowu, 2013; Adeoye and Alebiowu, 2014; Apeji *et al*., 2017). The improved flow of CPE will therefore impart flowability to the tableting mix giving rise to uniformly sized tablets with uniform weight and drug content.

True density of CPE and MCC were similar, suggesting that the degree of molecular packing was not affected by co-processing. True density of a material has been able to relate the tabletability profile of a material to the interparticulate bonding strength (Khomane *et al*., 2013). However,the tabletability profile of MCC differed significantlyfrom that of CPEowing to reduced interparticulate bonding caused by the presence of CPV in the particulate structure of MCC. Hence,

similarity in molecular packing behaviour (true density) does not necessarily translate to similar tabletability.

The ability of a material to swell in the presence of water is a function of its hydrophilicity, wetting and hydration potential (El-Barghouthi *et al*., 2008; Ohwoavworhua and Adelakun, 2010; Sharma *et al*., 2015; Yassin *et al*., 2015). Swelling has been generally accepted has an indication of tablet disintegration ability. Some disintegrants are known to exert their effect by swelling mechanism (Desai *et al*., 2016).Evaluation of the swelling capacity showed that MCC performed better relative to CPV and CPE. This implies thereforethat MCC ought to disintegrate faster than CPE in tablet formulation.However, it was observed from the disintegration results thattablets containing CPE disintegrated at 11.48min as compared to MCC tablets that disintegrated at 26.88 mins implying that swelling was not the sole mechanism of disintegration employed by CPE. Invariably, co-processing MCC with CPV had lowered the disintegration time significantly ($p < 0.05$).Scientific reports have shown that CPVeffects disintegration by a combination of wicking and swelling actions(Dhiraj *et al*., 2014; Desai *et al*., 2016). This explains the rapid disintegration of CPE compared to MCC.

Moisture content refers to the residual moisture retained in a material after drying (Callahan *et al*., 1982). Compared to MCC, CPE had a lower moisture content suggesting that co-processing MCC with CPV lowered its capacity to adsorb or retain moisture as evidenced by the moisture sorption capacity (Fig. 4.7). The improvement in flow property of CPE may also be attributed to its low moisture content considering the impact moisture content has on bulk powder properties like flowability and compressibility (Sun, 2016; Thapa *et al*., 2017). For the purpose of maintaining the stability of a formulation or product, it is necessary to use

excipients that are less hygroscopic or non-hygroscopic to guide against instability during development and storage. A similar study involving the co-processing of mannitol and crospovidone was carried out by Katsuno *et al*. (2013) and yielded a product with good stability profile, rapid disintegration and increased hardness of the tablets. Other studies have also reported that co-processing with crospovidone yielded a product with good flowability and low hygroscopicity (Gohel *et al*., 2007).

Lubrication is a tableting operation carried out prior to compression to lower interparticulate friction and prevent sticking of the tableting material to punch and die surfaces and to facilitate ejection of tablets after decompression (Wang *et al*., 2010; Paul and Sun, 2017). Lubricants exert their effect externally by coating the particle surfaces or forming a film layer at interparticulate surfaces(Jonat *et al*., 2005). This phenomenon interferes with interparticulate bonding and manifests as a reduction in tensile strength. Lubricant sensitivity testing is therefore carried out to quantify the degree of sensitivity of the tableting material to lubricant action. Depending on the mechanical properties, materials that are plastic deforming are more sensitive to lubricants compared to brittle materials (Patel *et al*., 2006).

Comparing the responses of MCC and CPE to lubricant action, both materials were generally more sensitive to magnesium stearate (MST) compared to sodium stearyl fumarate (SSF) possibly because MST has a greater degree of hydrophobicity(Perrault *et al*., 2011; Morin and Briens, 2013).CPE was found to be more sensitive to the action of SSF when compared with MCC. This has been attributed to flowability of CPE that generates high shear forces during mixing leading to more efficient particle coating by the lubricant resulting in higher lubricant sensitivity (Almaya and Aburub, 2008). However, MCC was found to be

more sensitive to the action of MST compared to the response of CPE. Due to the smaller particle size of MCC, a relatively larger surface area of the particles was made available for coating by the lubricant giving rise to tablets of lower tensile strength after lubrication due to a reduction in interparticulate bonding (Almaya and Aburub, 2008). This implies therefore that SSF will be a better candidate for lubrication compared to MST.

The ability of a DC excipient to incorporate a certain amount of active pharmaceutical ingredient (API) and form tablets of sufficient mechanical strength is described as the dilution potential of the excipient(Rojas*et al*., 2013). Dilution potential depends on the compaction behaviour of the excipient and varies with API(Rojas *et al*., 2013).Plastic deforming materials tend to have better dilution potential compared to materials that deform by brittle fracture (Almaya and Aburub, 2008). Dilution potential of MCC and CPE obtained with paracetamol (PCM) were found to be significantly lower when compared to the dilution potential of MCC and CPE obtained with metronidazole (MTZ).About 80 % of MCC was required to produce tablets having a tensile strength of 2 MPa in comparison to about 90 % of CPE that was required to produce tablets of the same tensile strength. This implies that MCC had a higher dilution potential compared to CPE with respect to PCM as model drug.This has been attributed to the brittleness and high elastic recovery exhibited by PCM upon compression (Roberts and Rowe, 1987; Joiris *et al*., 1998; Persson *et al*., 2018). On account of this, PCM, a high dose drug, could not be compressed into tablets of convenient size by direct compression because of its low dilution potential.

In the case of MTZ as model drug, the tensile strength of tablets also increased with increase in the proportion of DC excipient in the formulation. Comparing the two

excipients, 40 % of MCC was required to produce tablets of 2 MPa compared to 50 % with CPE. This implies that MCC has a higher dilution potential compared to CPE.

Hence, MTZ was selected as the drug of choice for the formulation of tablets by direct compression. Tablets designed to contain high dose poorly compressible drugs are best prepared by wet granulation (Tousey, 2002;Szumilo *et al*., 2017;Osamura *et al*., 2018). A better dilution potential was obtained with MCC compared to CPE with respect to MTZ as model drug possibly because of the plastic deforming ability of MCC (Ilić *et al*., 2013; Khomane and Bansal, 2013). The plastic deforming ability of MCC was lowered, however, when co-processed with CPV into CPE thereby reducing its capacity to take up more of the poorly compressible drug resulting in tablets of lower tensile strength due to a reduction in interparticulate bonding during compression. The dilution potential of MCC with respect to MTZ was therefore lowered as a result of co-processing to yield CPE.

As evidenced by Heckel analysis, compaction behaviour of CPE was characterized by a lower degree of plastic deformation compared to MCC. This may have been caused by the introduction of CPV, a brittle material, into the particle structure of MCC during co-processing thereby increasing its hardness and making it more resistant to plastic deformation. Hence, a higher yield pressure was required to initiate deformation in CPE as compared to MCC. Reduction in plastic deformation of MCC by co-processing, however, lowered the compressibility and compactibility as seen in CPE and by extension, the tabletability profile of CPE. Due to a reduction in compressibility and compactibility, tablets of lower tensile strength were obtained with CPE characterized by some degree of porosity relatively higher

than that of MCC. This led to a rapid disintegration of tablets prepared with CPE as opposed to those of MCC whose disintegration time exceeded the requirement for immediate release tablets. Hence, the disintegration functionality of MCC was modified by lowering its extent of plastic deformation which created a more porous structure that facilitated the rapid uptake of water due to the wicking properties of CPV leading to rapid disintegration of tablets. This agrees with the findings of Rojas and Kumar (2011), who co-processed MCC II with colloidal silicon dioxide to yield an excipient with rapid disintegrating effect.

The quality of tablets obtained correlated with the powder and compaction properties of the excipients used intablet formulation. Uniformity in weight and content of tablet were consistent with the flow properties of the excipients. Tablets of relatively higher tensile strength were obtained with MCC because of its excellent binding and tabletability profile associated with its tendency to undergo plastic deformation during compression (Thoorens *et al*., 2014). The hardness of MCC tablets was reflected in the disintegration time which exceeded 15 mins due to the inability of the disintegration medium to overcome the tightly bound tablet matrix created by extensive bonding area and strong interparticulate bonding occurring during tablet formation. The CPE tablets, however, disintegrated in less than 15 mins owing to the porous structure generated as a result of the lowered tabletability profile. This ensured the rapid uptake of water that facilitated the breakup of the tablets during disintegration. Drug-release profile was consistent with the disintegration as tablets of CPE attained maximum drug release in a short time compared to MCC tablets that released < 90 % of the drug after 60 mins.

P.M.E tablets exhibited a tensile strength of 1.62 MPa suggesting that the tablets will take a longer time to disintegrate. However, the tablets disintegrated at 7.32mins possibly because the component excipients did not interact at the sub-particle level to form a composite particle, but each component excipient existed as a separate entity with their different functionalities. Hence in contact with water they disintegrated easily because of the effect of CPV but reflected a high TS due to the high concentration of MCC and its plasticity. The tablets of Prosolv exhibited a tensile strength of 0.82 MPa reflecting fragile tablets that disintegrated at 1.33 mins, suggesting that Prosolv the reference standard will not be a suitable excipient for this formulation.

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary

1. Design of Experiment (DoE) was successfully applied to optimize the composition of co-processed excipient (CPE) using multivariate analysis todetermine the proportion by percentage weight of each of the ingredients used forco-processing. The optimized formula for preparing the co-processed excipient (CPE) was found to be microcrystalline cellulose (99 %), and crospovidone (1%).

2. Wet massing technique was adopted to prepare the co-processed excipient (CPE) containing optimized proportions of MCC and CPV obtained from DoE.

3. Solid-state characterization revealed that particle sizesof CPE were enlarged, and the particles appearedas fibrous or needle like shape particles with rough appearance. It was discovered that CPE is semi-crystalline in nature. No chemical change occurred during co-processingand it was found to be compatible with the model drugs.
4. Powder properties revealed that CPE possessed good flowability, low moisture content and low hygroscopicity.
5. Compaction studies revealed that CPE is a mixture of a brittle and plastic material with goodtabletability possessing suitable tensile strength and desired disintegration.
6. Tablets formulated with CPE showed rapid disintegration time compared to those formulated with MCC. In addition, the tablets with CPE passedthe non-compendial and compendial specifications for conventional tablets.

6.2 Conclusion

The aim of the study was to improve the disintegration functionality of MCC when used as a filler-binder in the formulation of tablets by direct compression. By co-processing MCC and CPV in a ratio of 99:1, a single composite excipient (CPE) with improved disintegrating property relative to MCC was obtained.

6.3 Recommendations

1. Several other methods of co-processing like spray drying can be employed to develop this excipient.
2. Further studies can be carried out to gain a mechanistic insight into the improvement of disintegration functionality as a result of co-processing.

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APPENDICES

Appendix I. Particle size analysis for CPE

Size (µm)	% Frequency	% Cumulative Frequency
0 – 99	10	10
100 - 199	42	52
200 - 299	40	92
300 - 399	7	99
500	1	100

Appendix II. Particle size analysis of MCC

Size (µm)	% Frequency	% Cumulative Frequency
0 – 49	1	1
50 - 99	36	37
100 - 149	43	80
150 - 199	14	94
200 - 249	5	99

Appendix III. Particle size analysis for CPV

Size (µm)	% Frequency	% Cumulative Frequency
0 – 39	30	30
40 – 79	61	91
80 – 119	8	99
120	1	100

Appendix IV. Dissolution data for MCC

Time	Absorbance 277nm	% drug released
0	0.0000	0.0000
5	0.4510	36.7779
10	0.5920	53.0035
15	0.6900	64.2808
20	0.7560	71.8757
30	0.8000	76.9390
45	0.8900	87.2957
60	0.9130	89.9425

Appendix V. Dissolution data for CPE

Time	Absorbance277nm	% drug released
0	0.0000	0.0000
5	0.6820	63.3602
10	0.8680	84.7641
15	0.8960	87.9862
20	0.9080	89.3671
30	0.9270	91.5535
45	0.9370	92.7043
60	1.0240	102.7160

Appendix VI. Dissolution data for PME

Time	Absorbance 277nm	% drug released
0	0.0000	0.0000
5	0.7130	66.9275
10	0.8250	79.8159
15	0.8740	85.4545
20	0.8950	87.8711
30	0.9090	89.4822
45	0.9450	93.6249
60	0.9660	96.0414

Appendix VII. Dissolution data for Prosolv® Tablets

Time	Absorbance 277nm	% drug released
0	0.0000	0.0000
5	0.8950	87.8711
10	0.9200	90.748
15	0.9220	90.9781
20	0.9510	94.3153
30	0.9550	94.7756
45	0.9630	95.6962
60	0.9710	96.6168

Appendix VIII. Compaction data for CPE

App. Press	TS	Sp. Vol	Porosity	ln(1/Ɛ)	P/C
49.94	1.720906	0.938874	0.280288	1.272379	73.35775
99.87	4.157819	0.793138	0.148077	1.91078	136.7463
149.81	5.457218	0.759874	0.110781	2.201491	201.9982
199.75	6.462622	0.751816	0.101242	2.292099	268.3444
249.68	7.260104	0.735006	0.080512	2.534892	332.8717

Appendix IX. Compaction data for MCC

App. Press	TS	Sp. Vol	Porosity	ln(1/Ɛ)	P/C
49.94	2.459842	0.943908	0.284166	1.258452	71.55256
99.87	5.5594	0.809276	0.164995	1.803525	134.7734
149.81	7.870321	0.768337	0.120536	2.118209	198.6537
199.75	7.96552	0.745546	0.093387	2.387063	262.3466
249.68	9.545603	0.726703	0.07001	2.678451	325.3418

Appendix X. Compaction data for CPV

App. Press	TS	Sp. Vol	Porosity	ln(1/Ɛ)	P/C
49.94	0.716906	1.396113	0.417515	0.873837	309.8002
99.87	1.671801	1.191317	0.317487	1.147756	350.3765
149.81	2.82849	1.092027	0.250616	1.418555	444.5469
173.39	3.40087	1.024711	0.206417	1.579755	450.4316