DESIGN AND DEVELOPMENT OF A STARCH-BASED MULTIFUNCTIONAL EXCIPIENT (*STARGELASIL*) FOR TABLET FORMULATION

BY

YONNI ESHOVO APEJI

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY
FACULTY OF PHARMACEUTICAL SCIENCES
AHMADU BELLO UNIVERSITY, ZARIA
NIGERIA

MARCH, 2016

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BY

YONNI ESHOVO APEJI, B.PHARM (ABU) 2004, M.SC (ABU) 2010
PHD/PHARM-SCI/1813/2010-11

A THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, AHMADU BELLO UNIVERSITY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DOCTOR OF PHILOSOPHY DEGREE IN PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY,
FACULTY OF PHARMACEUTICAL SCIENCES,
AHMADU BELLO UNIVERSITY, ZARIA

MARCH, 2016

DECLARATION

I declare that the work in this thesis entitled "Design and development of a starch-based multifunctional excipient (*StarGelaSil*) for tablet formulation" has been carried out by me in the Department of Pharmaceutics and Pharmaceutical Microbiology. The information derived from the literature has been duly acknowledged in the text and the list of references provided. No part of this dissertation was previously prevented for another degree or diploma at this or any other institution.

Yonni Eshovo Apeji

_____ _____ _____

Signature Date

CERTIFICATION

This thesis entitled DESIGN AND DEVELOPMENT OF A STARCH-BASED MULTIFUNCTIONAL EXCIPIENT (*STARGELASIL*) FOR TABLET FORMULATION by Yonni Eshovo APEJI meets the regulations governing the award of the degree of Doctor of Philosophy in Pharmaceutics of the Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

Prof. A. R. Oyi
_____ _____ Date_____
Chairman, Supervisory Committee

Prof. A. B. Isah
_____ _____ Date_____
Member, Supervisory Committee

Dr T. S. Allagh
_____ _____ Date_____
Member, Supervisory Committee

Prof. A. B. Isah
_____ _____ Date_____
Head of Department

Prof. Kabir Bala
_____ _____ Date_____
Dean, School of Postgraduate Studies

DEDICATION

This work is dedicated to everyone who has contributed significantly to the completion of this thesis.

ACKNOWLEDGEMENT

I will like to appreciate God Almighty for granting me the inspiration and grace to commence and complete this thesis. I ascribe all the glory to Him.

My sincere gratitude goes to my supervisors namely; Prof. A. R. Oyi, Prof. A. B. Isah and Dr T. S. Allagh who provided guidance and support to ensure that this work is completed. I am also indebted to Prof. A. K. Bansal and his team at National Institute for Pharmaceutical Education and Research (NIPER), Mohali, India who were gracious to host me in their lab for six (6) months for part of the work to be carried out. I appreciate the contributions of the staff of Central Instrumentation Laboratory (CIL), NIPER, Mohali, who assisted me greatly with theanalysis. I acknowledge the input of the Tertiary Education Trust Fund (TETFUND) for providing the grant that facilitated my travel to undertake the bench work far away in India.

I appreciate God for my parents (Mr and Mrs F. H. S. Apeji) who thought it wise to invest in my education from childhood. I must thank my siblings and In-laws who granted me moral support while I was pursuing this programme.I wish to thank every member of staff of the Department of Pharmaceutics and Pharmaceutical Microbiology for creating an environment conducive for research and learning.

Finally, I must commend my darling wife (Alice) and lovely kids (Jotham and Rehoboth) who put up with my absenteeism from home in the last two years in order to conclude my research. May the Lord keep usalive to enjoy the dividends of our labour.

ABSTRACT

The concept of co-processing as a particle engineering technique has been used as a tool to improve the functionality of many existing excipients. This study was designed to improve the functionality of cassava starch as excipient for direct compression by co-processing with gelatin and colloidal silicon dioxide.

The Design of Experiment (DoE) approach was employed to optimize the percentage ratios of the primary excipients for the co-processed excipient. Fourteen experimental formulations containing varying proportions of the primary excipients were prepared by the method of co-fusion and twelve tablets each weighing 400 mg each were produced for each formulation using the Hydraulic Carver Press. The compressed tablets were kept for 24 h in the desiccator and evaluated for tensile strength and disintegration time. The data obtained from the tabletswere suitably analysed using the Design Expert software and fittedto a special quartic model that correlated the effect of varying the proportions of the excipients in the different formulations on tablet properties.The composition of the co-processed excipient that produced tablets of desirable characteristics after optimization was found to be cassava starch (90 %), gelatin (7.5 %) and colloidal silicon dioxide (2.5 %).

The optimized co-processed excipient subsequently known as "*StarGelaSil*" (SGS) was prepared in large quantities and stored in an airtight container for further studies. Solid-state characterization was conducted on SGS to determine its particle size, shape, distribution, surface morphology, degree of crystallinity, hygroscopicity, compatibility etc using established analytical techniques. Powder properties of SGS were also determined by measuring its flowability using the angle of repose, bulk and tapped densities, porosity, dilution potential, lubricant sensitivity ratio etc. The compaction behaviour of SGS was analysed using Heckel and Kawakita equations and the

compressibility, tabletability, compactability (CTC) profile was determined in comparison to the physical mixture of the primary excipients (SGS-PM). Tablets were formulated by direct compression using Ibuprofen as the drug of choice and compared with tablets produced using Prosolv® and StarLac® as reference standards.

The results revealed that co-processed particles of SGS were largelyamorphous and spherical in shape with rough surfaces. There was no incompatibility between the excipients used for co-processing and between drug and co-processed excipient. Flow properties were enhanced as a result of co-processing. A superior CTC profile was obtained for SGS when compared with SGS-PM. The tablets produced by SGS conformed to the specifications of USP (2009) and compared well with those of the reference excipients in terms of tensile strength, disintegration time and drug-release profile.

This study concluded that co-processing was able to improve the functionality ofcassava starch as excipient for direct compression. Hence, the excipient can be developed for usein pharmaceutical industry as a choice material for direct compression.

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LIST OF ABBREVIATIONS

A	Intercept of the linear portion
API	Active Pharmaceutical Ingredient
AR	Angle of Repose
BD	Bulk Density
BI	Bonding Index
BSS	British Standard Size
CD	Circular Dichroism
CI	Carr's Index
CLSM	Confocal Laser Scanning Microscopy
CMS	Chitin Metal Silicate
CPE	Co-processed Excipient
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CS	Cassava Starch
CSD	Colloidal Silicon Dioxide
CTC	Compressibility, Tabletability and Compactability
D	Relative Density
DC	Direct Compression
DG	Dry Granulation
DoE	Design of Experiment
DSC	Differential Scanning Calorimetry
DT	Disintegration Time
DVS	Dynamic Vapour Sorption
ε	Porosity

FDA	Food and Drug Administration
FITC	Fluorescein isothiocyanate
FRC	Functionality related Characteristics
FT-IR	Fourier Transform Infrared Spectroscopy
GEL	Gelatin
H_2O	Water
HCl	Hydrochloride
HR	Hausner's Ratio
HSM	Hot-stage Microscopy
ICH	International Conference on Harmonization
IPEC	International Pharmaceutical Excipient Council
K	Slope of the linear portion
LSR	Lubricant Sensitivity Ratio
MCC	Microcrystalline Cellulose
MHH	Mannitol Hemihydrate
MN/m^2	Mega Newton per square metre
MPa	Mega Pascal
NaCl	Sodium Chloride
NaCMC	Sodium Carboxymethylcellulose
NaOH	Sodium Hydroxide
NDA	New Drug Application
NMR	Nuclear Magnetic Resonance
P	Applied Pressure
PEG	Polyethylene glycol
PSV	Prosolv

PVP	Polyvinylpyrrolidone
PXRD	Powder X-ray Diffraction
P_Y	Yield Pressure
QbD	Quality by Design
SC	Simple Centroid
SCMC	Sodium Carboxymethylcellulose
SEM	Scanning Electron Microscopy
SGS	StarGelaSil
SGS-PM	StarGelaSil physical mixture
SLC	StarLac
SMCC	Silicified Microcrystalline Cellulose
SP	Spheronization
TD	Tapped Density
TGA	Thermo Gravimetric Analysis
TS	Tensile Strength
USP/NF	United States Pharmacopoeia-National Formulary
WG	Wet Granulation
ρ	Relative density
ρ_c	Critical density
σ	Pressure

CHAPTER ONE

1.0 INTRODUCTION

1.1 Solid Dosage Forms

Tablets account for more than 80 % of all dosage forms in the market (Khomane and Bansal, 2013)because of the following properties:

(i) They are easy to dispense,

(ii) Offer dosage accuracy,

(iii) They are amenable to mass production at a relatively cheap cost,

(iv) Tamper resistant compared to capsules, and

(v) Offer better stability to heat and moisture compared to liquid and semi-solid formulations (Jivraj *et al.*, 2000; Pucelj, 2014).

The European Pharmacopoeia (2002) defines tablets as solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. Despite the long and continuing history of the development of new technologies for administration of drugs, the tablet form remains the most commonly used dosage form (European Pharmacopoeia, 2002).

1.2 Excipients

The formulation of tabletsusually consists of the active pharmaceutical ingredient (API) and excipients. The International Pharmaceutical Excipient Council (IPEC) has defined

excipients as “substances other than the API in finished dosage form, which have been appropriately evaluated for safety and are included in drug delivery systems to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability. They assist in product identification, or enhance any other attributes for the overall safety and effectiveness of the drug delivery system during storage and use” (Daraghmeh, 2012; Pucelj, 2014).

They may serve either as diluents, binders, disintegrants, lubricants, glidants, or release control agents (Rashid *et al*., 2013). They have earlier been labelled as the “functional components” of a formulation (Moreton, 2004). They may be classified as natural (i.e. cellulose, starch, chitosan etc), inorganic (dicalcium phosphate), synthetic (polyvinylpyrrolidone) and semisynthetic (hydroxypropylmethylcellulose) on the basis of their source and chemical nature.

More than 70 % of all formulations contain excipients in concentrations higher than that of the API, affirming the contribution of excipients in the design of dosage forms(Nachaegari and Bansal, 2004; Saha and Shahiwala, 2009). It is therefore obvious that excipients contribute in significant terms toward the processing, stability, safety and performance of solid dosage forms.

1.2.1 Types of excipients

In tablet formulation, a range of excipient materials is normally required along with the active ingredient in order to furnish the tablet with the desired properties. For example, the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficiently strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients

will affect all these properties. Based on their function, excipients have been grouped into the following classes:

1.2.1.1 Diluents/Fillers/Bulking agents

A diluent is any material that is added to a tablet formulation to fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use by increasing the bulk volume of the formulation. Hence, the final product has the proper volume for patient handling. A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively cheap, compactable, and preferablytasteless or pleasant tasting (as in chewable tablet). Examples of diluents are lactose, dicalcium phosphate dihydrate, sucrose, glucose, mannitol, sorbitol, calcium sulphate, starch etc.

1.2.1.2 Binders

Bindersareoften added to the granulation liquid during wet granulation to improve the cohesiveness and compactability of the powder particles, which assists in the formation of agglomerates or granules.Materials with high bonding ability can be used as binders to increase the mechanical strength of the tablet. A binder is usually a ductile material prone to undergo plastic (irreversible) deformation (Klevan, 2011). They act by reducing interparticulate distances within the tablet, thereby improving bond formation. If the entire bulk of the binder particles undergo extensive plastic deformation during compression, the interparticulate voids will, at least partly, be filled and the tablet porosity will decrease. This increases the contact area between the particles, which promotes the creation of interparticulate bonds and subsequently increases the tablet strength (Sun, 2011).

It is commonly accepted that binders added in dissolved form, during a granulation process, is more effective than incorporating as a dry powder during direct compression. Typical examples of binders include starches, gelatin, acacia, sucrose, sodium alginate, polyvinylpyrrolidone (PVP), carboxymethylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose etc. Water and alcohol have been usedasmoisteningagents.

1.2.1.3 Disintegrating agents

Disintegrants are normally added to facilitate the rupture of bonds and subsequent disintegration of the tablets (Daraghmeh*et al.*, 2015). Disintegrants are usually added for the purpose of causing the compressed tablet to break up into smaller fragmentswhen placed in an aqueous medium, thereby facilitating dissolution and making the active ingredients ready for absorption in the digestive tract. The most conventionally used disintegrants are: corn starch, potato starch, and alginic acid. Other substances which swell in water can be used as disintegrants such as gelatin, sodium carboxymethylcellulose, microcrystalline cellulose, and bentonite.

Superdisintegrants are rapid acting disintegrants which are effective at low concentration and have greater disintegrating efficiency than the conventional disintegrants. They act by swelling and due to swelling pressure exerted in the outer direction or radial direction, they cause tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration. Commercially available superdisintegrants includes sodium starch glycolate, cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose.

1.2.1.4 Glidants, antiadherents and lubricants

Glidants are added to increase the flowability of the powder mass, reduce interparticulate friction and improve powderflow in the hopper shoe and die of the tableting machine. Antiadherents can be added to decrease sticking of the powder to the faces of the punches and the die walls during compaction, and lubricants are added to decrease friction between powder and die, facilitating ejection of the tablet from the die. However, addition of lubricants (also including glidants and antiadherents) can exert negative effects on tablet strength, since the lubricant often reduces the creation of interparticulate bonds. Further, lubricants can also slow the drug dissolution process by introducing hydrophobic films around drug and excipient particles(Patel*et al.*, 2006). These negative effects are especially pronounced when long mixing times are required. Therefore, the amount of lubricants should be kept relatively low and the mixing procedure kept short, to avoid a homogenous distribution of lubricant throughout the powder mass.Lubricants such as magnesium stearate, calcium stearate, stearic acid, talc and colloidal silicon dioxide are the most frequently used lubricants in tablets or hard gelatin capsules.

1.2.1.5 Flavours, sweeteners and colorants

Flavours and sweeteners are primarily used to improve or mask the taste of the drug, with subsequent substantial improvement in patient compliance. Typical examples of flavours commonly used are volatile oils which include clove, fennel, orange and wintergreen oil while sweeteners include sucrose, sorbitol, mannitol, xylitol, saccharin and aspartame.

Colorants are added to provide tablets with good aesthetic value, and can improve tablet identification, especially when patients are taking a number of different tablets. The

common colorants used in tableting include erythrosine, tartrazine, sunset yellow, brilliant blue, indigotine and fast green.

1.2.2 Functionality of an excipient

The quality of medicines depends not only on the active drug and production processes, but also on the performance of the excipients. The traditional concept of the excipient as any component other than the active substance has undergone a substantial evolution from an "inert" and cheap vehicle to an essential constituent of the formulation(Moreton, 2004).

More than a thousand raw materials are available from a wide variety of sources and have been adapted for use in the pharmaceutical industry. Their chemical structures vary from small molecules to complex natural or synthetic polymeric mixtures. Excipients are now incorporated as functional components to perform a wide variety of functions to guarantee the stability and bioavailability of the drug substance from the drug product and its potential for manufacture on a production scale. Beyond the dosage form necessities, excipients are required to perform important and specific technological functions particularly in the domain of solid dosage forms.

The functionality of an excipient is best described as its' contribution to a dosage form's stability, identity, delivery and processability which does not depend solely on the excipient's inherent properties but also on its application, formulation and process(Moreton, 2004).

A good number of excipients relevant to tableting are multifunctional in nature, i.e. having the ability to combine two or more functions in a formulation. A typical example is microcrystalline cellulose (MCC) which is available in various grades. MCC is highly compactable and can also aid disintegration due to its ability to take up water by

wicking action(Rumman, 2009). The use of a multifunctional excipient reduces the number of excipients incorporated in a formulation to the barest minimum thereby simplifying the final formulation and the manufacturing process.

The European Pharmacopoeia (2008) has developed a list of functionality-related characteristics (FRC) for some of the excipient monograph. These tests have been described as non-mandatory but highly recommended because of their importance to the excipient's performance in many applications.

Characterization studies on excipients must go beyond the simple tests for identity, purity and safety as recommended in the Pharmacopoeial monographs and extend to testing the technological functionality of the excipient, which is usually employed in the solid state. The functionality of an excipient is defined by the physical, physico-mechanical and biopharmaceutical properties. The characterization of the solid state and surface parameters is therefore fundamental first to assess and then guarantee the behaviour of the excipient in the formulation and production phases. Analytical techniques such as infra-red spectroscopy and nuclear magnetic resonance (NMR) can be used to determine molecular structure and possible chemical interactions.

Thermo gravimetric analysis (TGA) and differential scanning calorimetry (DSC) are often employed to clarify the stability, compatibility, degree of crystallinity and phase transitions occurring in the excipient. The structure of the single crystal or the powder can be examined with absolute certainty by powder x-ray diffraction (PXRD).

A thorough understanding of the specific properties of a material gives us insight as to which of them will be crucial to the stability, bioavailability and easy manufacturability of the formulation (Zhou and Qiu, 2010).

1.2.3 Powder compaction and particle bonding process

Excipients for direct compression are required to form solid compacts when mixed with poorly compressible drugs. Mechanical properties of direct compression excipients determine success of the powder compaction and the deformation behaviour of material is a property that mainly affects the tableting ofpowders (Roberts and Rowe, 1986).

The compaction process is a series of several events: particle movement into void spaces, partial fracture, elastic deformation, plastic deformation and cohesion between particle surfaces. These events occur simultaneously, but not necessarily to the same degree at any stage of the compression process (Patel *et al*., 2006; Zhou and Qiu, 2010).

During consolidation of a powder bed, a reduction in porosity occurs. This reduction in compact volume brings particles into close proximity to each other. The reduced distance between the particles facilitates creation of bonds and makes the particles adhere together to form a coherent compact.

Two different types of interactions are normally considered in direct compression of pharmaceutical materials; intermolecular interactions and mechanical interlocking. Van der Waal forces are probably the most important intermolecular forces responsible for bond formation in tablets. Hydrogen bonding is another example of intermolecular forces that act over a short distance between particles. The nature of these forces depends on the chemical composition of the material(Patel *et al.*, 2006).

Bonding by hooking or twisting of particles depends on the surface texture and shape of the particles. The dominant bond type depends on various factors, including the degree of compression and the inherent properties of the material. In the high porosity range, the principal attraction between particles has been suggested to be intermolecular forces; whereas in the low porosity range, solid bridges play a major role (Adolfsson

and Nystrom, 1996). Usually, solid bridges connect particles by spanning, sintering, melting and crystallization (Klevan, 2011).

1.2.3.1 Compaction models

The assessment of powder compressibility can be determined by studying the relationship between compact porosity and compression pressure. If high pressures are applied to a powder bed, low porosities of the resulting compacts can be achieved. When the porosity of the tablet is close to zero, the structure of the tablet should be different from the structure at normal porosities (5-25 %) (Adolfsson and Nystrom, 1996).The final porosity reduction may eventually represent a transformation to a new physical structure, where the solid constitutes the continuous phase. Thus, the bonding structure of the resulting compact may also be altered. Knowledge of the volume reduction ability of a powder makes it possible to predict the compaction behaviour of a pharmaceutical material (Zhou and Qiu, 2010).

A compaction equation shows the relationship between the state of consolidation of a powder such as porosity, volume (or relative volume), density, or void ratio, as a function of the compression pressure. The most widely used equation relating the porosity (ε) of the powder bed during compaction to the applied pressure (P) is the Heckel equation. This equation is based on the assumption that densification of the powder under pressure follows first-order kinetics. It is given as:

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad -----Eq.1$$

where$D$ is the relative density of the tablet (ratio of tablet density to the true density of the powder) at applied pressure, P and K is the slope of the straight line portion of the Heckel plot. The reciprocal of the slope (K) of the linear portion of the Heckel curve is referred to as the mean yield pressure, P_Y. The P_Y can be used to indicate the mechanism

occurring during compression. From the value of *A* (intercept), the total relative density, D_A (D_A= *1* - e^{-A}) or powder solid fraction due to die filling and particle rearrangement can be calculated (Roberts and Rowe, 1986).

Kuentz and Leuenberger (1977) postulated a modified Heckel equation which allows the description of the transition between the states of a powder to the state of the tablet. The modified Heckel equation is given as follows:

$$\sigma = \frac{1}{C}\left[\rho_C - \rho - (1 - \rho_C)\ln\left(\frac{1-\rho}{1-\rho_C}\right)\right] - - - - - Eq.2$$

whereσ is the pressure, ρ is the relative density, ρ_c is the critical density, and *C* is a constant.

Powders have been classified into three types A, B, and C on the basis of the Heckel plot and the compaction behaviour of the material (Wong and Pilpel, 1990). The graphical illustration of the three plots is given as Figure 1.1.

With type ‘A’ materials, a linear relationship is observed, with plots remaining parallel as the applied pressure is increased indicating deformation apparently only by plastic deformation. A typical example of a type ‘A’ material is sodium chloride. They are comparatively soft and readily undergo plastic deformation retaining different degrees of porosity depending on the initial packing of the powder in the die. This is usually influenced by the size distribution and shape of the original particles.

For type ‘B’ materials, there is an initial curved region followed by a straight line. This indicates that the particles are fragmenting at the early stages of the compression process i.e. brittle fracture precedes plastic flow. Type ‘B’ Heckel plots are usually seen with harder materials with higher yield pressures which undergo compression by fragmentation to achieve a densely packed arrangement e.g. lactose.

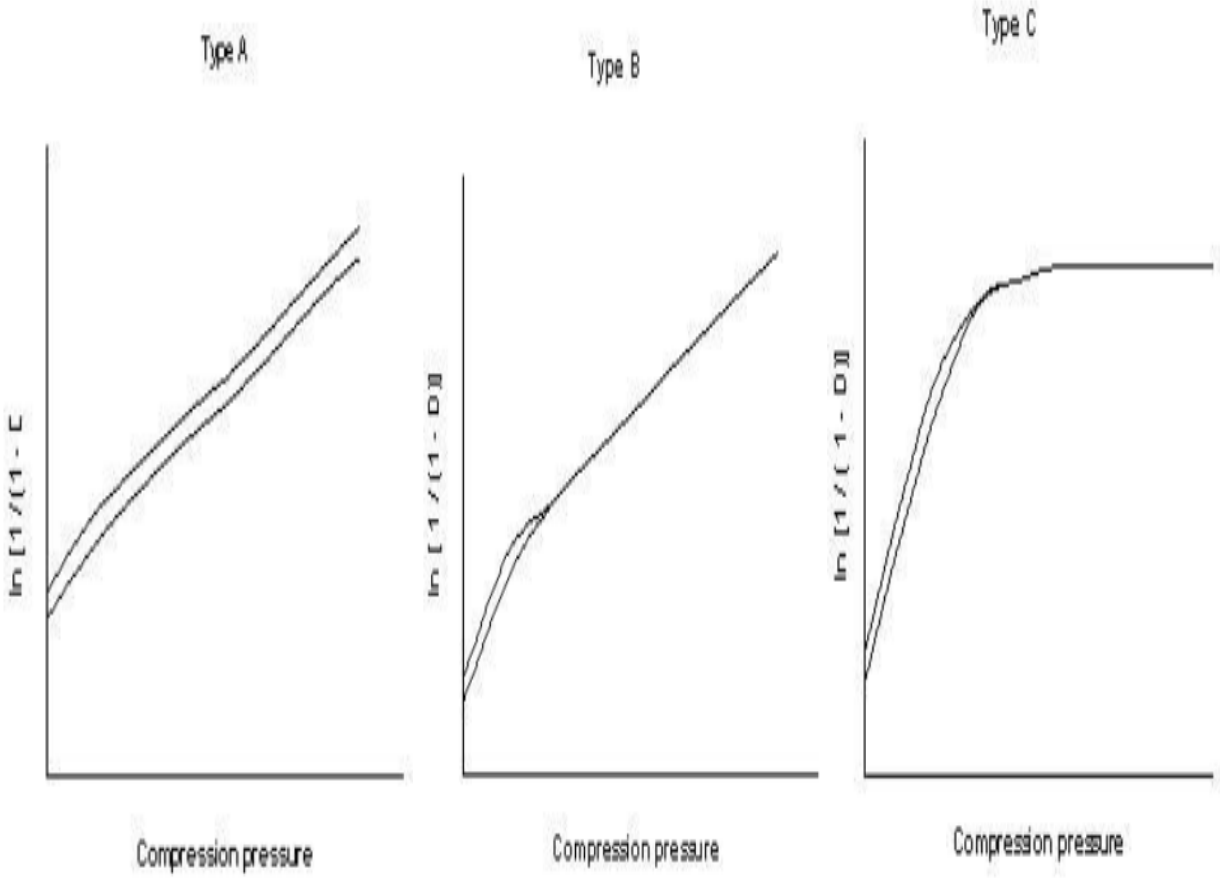

Figure 1.1: Different types of Heckel plots(Odeku, 2007)

In type ‘C’ materials, there is an initial steep linear region which become superimposed and flattens out as the applied pressure is increased. Wong and Pilpel (1990) explained this behaviour to be due to the absence of a rearrangement stage and densification is due to plastic deformation and asperity melting.

There are two methods used to obtain density-pressure profiles: the in-die and out-of-die (or ejected tablets) methods. In the out-of-die method, the compact volume is measured after the tablet is ejected from the die having undergone partial elastic recovery. Conversely, the in-die method measures the compact densification in the die by evaluating punch displacement(s) relative to the increase in compression pressure. This method is faster and consumes less material than the out-of-die method, which requires a new compact for each compression pressure. However, the in-die density measurement contains an elastic component leading to falsely low mean yield pressures, which is a limitation when using the information to prepare a tablet formulation (Egart *et al.*, 2014).

The Kawakita linear model is another porosity-pressure function used to characterize powder compressibility. It is based on the assumption that the particles are subjected to compressive load in equilibrium at all stages of compression, so that the product of pressure term and volume term is constant. It is expressed as:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad ------ Eq.3$$

$$C = 1 - \frac{\rho_0}{\rho_a} \quad ------ Eq.4$$

where$P$ is the applied pressure and C is the degree of volume reduction, ρ_0 is the bulk density, ρ_a is the compact apparent density, ‘a’ is indicative of powder compressibility and ‘b’ is a constant that is inversely related to the yield strength of particles. The plot

of P/C vs P gives a straight line. The constants '*a*' and '*b*' can be determined from the slope and intercept, respectively. This equation is applicable for soft fluffy powders, and is best used for low pressures and high porosity situations.

1.3 Tableting Methods

Tablets have been produced by three main methods namely wet granulation, dry granulation and direct compression.

1.3.1 Wet granulation

Wet granulation typically involves wet massing a blend of active pharmaceutical ingredients (API) and excipients in a wet granulator followed by subsequent wet screening and finally drying(Martinello*et al.*, 2006). The most commonly used liquid for wet granulation is water although non-aqueous solvents such as ethanol and isopropyl alcohol may be used when water is unsuitable. While water is extremely economical and environmentally friendly, wet-granulation techniques are labour intensive and process times are inherently long due to wetting and drying stages.

Wet granulation, encompassing low- and high-shear mixing, fluid-bed mixing (spraying) and wet-mass extrusion, is an extremely versatile technique that has several advantages over dry methods, including improved control of drug content, better uniformity for highly potent drugs (low-dose APIs) and production of granules with superior bulk density and compactibility (high- and low-dose APIs).

1.3.2 Dry granulation

Dry granulation typically involves the compaction of powder blends through slugging or roller compaction. Slugging involves the manufacture of a large compressed tablet whereas roller compaction pushes powder blends through two counter-rotating rolls,

producing a sheet of agglomerated material. In both cases, the formed solid compact is milled to produce granules of the desired particle size range for compression or filling.Dry granulation is a suitable alternative to wet granulation particularly when the API or excipients are sensitive to water/moisture and non-ambient temperatures, conditions that are typical for wet granulation.

Interestingly, dry granulation processes produce granules with an extremely high bulk density and low intra-granular porosity in comparison with granules produced using alternative techniques(Patel*et al.*, 2008). Furthermore, dry-granulated materials exhibit better gravimetric flowability; however, the high-density granules produced using this process have been shown to suffer from loss of tabletability, due to the significant number of particle defects and loss of plasticity introduced during processing. This is extremely important, as the quality of the final dosage form is significantly influenced by the compaction properties of the granular material(Joiris*et al*., 1998). In addition to loss of tabletability and possible phase transformation during compression, dry granulation may alsoresult in high levels of dust (problematic for potent API), poor compaction homogeneity and high levels of adhesion to the production equipment.

The significant lack of process understanding of dry granulation has limited its use in tableting though it is conceptually very simple and relatively cost effective. These disadvantages combined with a willingness to accept static agglomeration processes have led to wet granulation remaining the preferred and most widely accepted method for size enlargement within the pharmaceutical industry.

1.3.3 Direct compression

Direct compression is by far the simplest means of production of tablet dosage forms. It only requires that the drug is properly blended with appropriate excipients before

compression (Rashid *et al.*, 2013). This procedure involves fewer processing steps, less time and energy thereby reducing cost of production. It is also suitable to formulate heat and/or moisture sensitive drugs (Avachat and Ahire, 2007). Changes in dissolution profiles and the possibility of microbial growth on storage are also less likely to occur in tablets made by DC compared to those prepared by wet granulation due to the absence of moisture during processing. Compacts made by DC disintegrate into primary particles, rather than granules, and hence, can provide faster API release (Saha and Shahiwala, 2009).

A recent report states that around 80 % of new drug application (NDA) projects utilize wet granulation. The decision is driven by timelines rather than costs, since this is the most likely process to succeed. Employing direct compression which might appear as a rapid formulation procedure may have a higher chance of failure since it might not work for poorly compressible drugs with challenging physicochemical properties (McCormick, 2005). Less than 20 % of actives can be compressed directly into tablets (Harden *et al.*, 2004). For some APIs, the doses are too small to be compressed into a tablet directly without needing a bulking agent, i.e. folic acid (5 mg).

Although simple in terms of unit processes involved, the direct compression process is greatly influenced by the characteristics of the powder blend (Rojas*et al.*, 2013). The physico-mechanical properties of excipients required for a smooth DC process include good flowability, low or no moisture sensitivity, low lubricant sensitivity, good compressibility, optimum dilution potential, and good adaptability to high-speed tableting machines (Saha and Shahiwala, 2009).

The choice of the excipient grade can be a challenge in DC. Selecting an improper grade of an excipient could lead to segregation and greater lubricant sensitivity (Almaya and Aburub, 2008). For example, Avicel® PH-200 (180 µm) is more sensitive to the

addition of magnesium stearate than Avicel® PH-101 (50 µm) and Avicel® PH-102 (100 µm) because it has more regularly-shaped particles which are easily covered by magnesium stearate leading to less particle bonding (Camargo, 2011). In addition, wide variations between the excipients and APIs particle shape and size may lead to inconsistent die filling, preferred orientations in particle bonding, non-homogeneous particle slippage and differences in pressure transmission within the powder bed, all resulting in tablet lamination and capping. Lamination occurs when there is separation of a compact into two or more distinct horizontal layers, whereas capping occurs when the upper or lower segment of the compact separates horizontally from the main body (Chow *et al.*, 2008).

1.3.3.1 Characteristics of an ideal direct compression excipient

The manufacture of a tablet dosage form usually involves a diluent, disintegrant, binder, lubricant and glidant (flow enhancer). Functionality describes the activity of an excipient. A multifunctional excipient is defined as a material that has more than one functional property (Camargo, 2011). A glidant improves flowability of the powder mixture; while a lubricant is added to reduce the friction between the powder and tablet tooling. The latter also enhances tablet efficiency and reduces punch - and – die wear. The filler (diluent) is used to increase the bulk of the tablet or capsule to the desired size/volume, easy compact handling and administration. A binder allows the formation of granules or tablets of adequate tensile strength, whereas the use of a disintegrant allows the tablet break into particles when it comes in contact with water. Compressibility is expressed as the relative volume reduction of the powder bed in response to the applied pressure, and compactibility is the ability to form a compact with sufficient strength when a compression force is applied (Khomane*et al.*, 2013; Upadhyay*et al.*,2013).

Carrying capacity or dilution potential is defined as the minimum amount of the excipient that when mixed with a drug shows no change in its compressibility, flow rate and ability to form hard compacts at low pressures (Flores *et al.*, 2000; Camargo, 2011; Rojas *et al.*, 2013)

In order to ensure a robust and successful manufacture of tablets, an ideal direct compression (DC) excipient should possess the following characteristics: excellent compressibility, adequate powder flow, resistance to segregation during handling and storage, fast compact disintegration, a broad range of bulk densities, low sensitivity to lubricants, should be easily scaled up and allow higher drug loading even at low usage levels and should be easily prepared (Zeleznik and Renak, 2005; Jacob *et al.*, 2007).

In addition to the above requirements, a DC multifunctional excipient should be characterized by the following properties (Chang and Chang, 2007; Thoorens *et al.*, 2008):

i. Physiologically safe and not affect drug bioavailability.

ii. Be physically and chemically stable to heat, moisture and air.

iii. It should not interfere with the functional properties of other excipients and API.

iv. Be compatible with the packaging material.

v. It should have comparable particle size distribution with the API.

vi. Good compactibility even in high speed tableting machines (low dwell times).

vii. Ability to be reworked without loss of flow or compactibility.

viii. Be cost effective and available preferably from multiple suppliers.

ix. Have pleasant organoleptic properties, be well characterized and accepted by the industry and regulatory agencies.

x. Not contribute to microbiological load of the formulation.

xi. Preferably white.

There is no single excipient currently available that meets all the requirements listed for an ideal direct compression excipient (Patel and Patel, 2007). Hence, it has become necessary to develop novel excipients with a wider spectrum of functionality via co-processing.

1.4 Co-processing

Co-processing was introduced as an intervention strategy to develop excipients that will supply the functionality required in direct compression. It is a particle engineering technique that combines two or more excipients at the sub-particle level with the aim of improving the functionality of the final product while minimising the short-comings of the individual excipients (Nachaegari and Bansal, 2004). This procedure has shown promise in providing improved performance of the co-processed excipient over and above its physical mixture(Kittipongpatana and Kittipongpatana, 2012).

This study aims to develop a co-processed excipient with multifunctional application by combining three excipients in optimum proportions.

1.5 Statement of Research Problem

Native starch from a wide variety of sources have been used in tablet production either as a filler, disintegrant, binder or lubricant (Odeku and Itiola, 2007; Kadajji and Betageri, 2011). This is associated with the fact that starch, in one hand, can provide essential tablet properties for drug release; on the other hand, the nature of starch has made it amenable to modification to serve different functions (Jivraj *et al.*, 2000).

Native starch offers two main benefits to a formulation namely, a rapid disintegrating property and ability to add bulk to the drug formulation (as filler) (Zhang *et al.*, 2003; Rashid*et al.*, 2013). In spite of these properties, starch possesses limited functionalities with regard to powder compression, tensile strength, and flow properties in solid dosage form preparations (Alebiowu and Itiola, 2002; Adedokun and Itiola, 2010). These short-comings have restricted the use of native starch in direct compression formulations and subsequently in high-speed tableting machines.

Owing to the limitations above, a number of chemical and physical modifications were applied to transform native starch into a DC excipient with a wider spectrum of functionalities (Atichokudomchai and Varavinit, 2003; Apeji *et al.*, 2011). Again, there was a limit to which modification improved its potential for direct compression coupled with the safety and toxicity issues associated with chemical modification. Hence, it became imperative to seek another route for developing starch-based excipients with improved functionalities. Co-processing is a strategy that has been adopted to improve the functionality of starch for direct compression in combination with other excipients.

1.6 Justification for the Study

This study has become necessary because of the following reasons

i. Starch is readily available in abundant supply from diverse sources. This makes it a good candidate for co-processing.

ii. Cassava is grown in industrial quantities in Nigeria. Hence, it can be harnessed to develop home-grown excipients for our pharmaceutical industries.

iii. Currently, a sizeable proportion of co-processed excipients available to the pharmaceutical industry are either lactose-based or cellulose based (i.e. StarLac®, Prosolv®, Ludipress® etc.) with a limited number of starch-based excipients.

iv. The inclusion of gelatin into the structure of cassava starch during co-processing will fuse the starch particles resulting in an increase in particle size. This will enhance flow properties and improve the overall compressibility of the excipient.

v. There is no single-based excipient that can deliver all the performance requirements for a robust direct compression process.

vi. Co-processing will limit the number of excipients added to a formulation thereby reducing the incidence of incompatibility.

vii. Co-processing is a cheaper alternative because it involves existing excipients that do not need to be characterised since their properties are already documented.

viii. Co-processing involves manipulation of the physical properties excluding any changes in the chemical nature of the excipients.

1.7 Aim and Objectives

1.7.1 Aim

The aim of this research is to improve the functionality of cassava starch as excipient for direct compression by co-processing with gelatin and colloidal silicon dioxide in optimum proportions.

1.7.2 Objectives

i. To optimize the composition of the co-processed excipient using the Design of Experiment (DoE) approach.

ii. To prepare the co-processed excipient using the optimized formula.

iii. To carry out solid-state characterisation using analytical techniques such as Scanning electron microscopy (SEM), Confocal laser scanning microscopy (CLSM), Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR) and Powder X-ray diffraction (PXRD).

iv. To determine the physico-mechanical properties of the co-processed excipient i.e. particle size analysis, flow properties, bulk, tapped and true densities, moisture content, dilution potential, lubricant sensitivity.

v. To characterize the deformation behaviour of the excipient using compaction models like Heckel and Kawakita equations.

vi. To formulate and evaluate tablets by direct compression using a poorly compactible drug model i.e. Ibuprofen.

vii. To evaluate the performance of the co-processed excipient in comparison to two commercially available co-processed excipient (Prosolv® and StarLac®).

1.8 Research Hypothesis

1.8.1 Null Hypothesis (H_0)

The co-processing of cassava starch with gelatin and colloidal silicon dioxide in optimized ratios will not improve the functionality of starch as a multifunctional excipient in tablet formulation by direct compression.

1.8.2 Alternate Hypothesis (H_a)

The co-processing of cassava starch with gelatin and colloidal silicon dioxide in optimized ratios will improve the functionality of starch as a multifunctional excipient in tablet formulation by direct compression.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Development of novel excipients

More recently, few new excipients have been introduced into the market. The development of novel excipients so far has been market driven (i.e. excipients are developed in response to market demand) rather than marketing driven (i.e. excipients are developed first and market demand created through marketing strategies). One reason for this lack of new excipients is the relatively high cost involved in excipient development, including the toxicity profile. However, with the increasing number of new drug molecules with varying physicochemical, pharmacokinetic, permeation and stability properties, there is a growing interest among formulators to search for new excipients that have minimal scale-up problems, low manufacturing costs, and little environmental impact (Marwaha *et al.*, 2010).

Other factors driving the search for new excipients as reported byNachaegari and Bansal (2004) include the following:

- The growing popularity of the direct compression process and demands for an ideal filler-binder that can replace two or more excipients, avoiding the need for multiple excipients in a formulation (i.e. disintegrant, binder, lubricant etc).
- The increasing speed capabilities of tablet presses, which require excipients to maintain good compressibility and low weight variation even at short dwell times.

- Shortcomings of existing excipients, such as loss of compaction upon wet granulation, high moisture sensitivity and poor die filling as a result of agglomeration.
- The lack of excipients that addresses the needs of a patient, with a specific disease state such as those with diabetes, hypertension, and lactose and/or sorbitol sensitivity.
- The ability to modulate the solubility, permeability, or stability of drug molecules.

2.2 Sources of novel excipients

Excipients with improved functionality can be obtained by developing a new chemical entity, new grades of existing materials or their combinations(Moreton, 2004). An excipient is only considered novel when it is a new chemical entity, a new route of administration is created by its use, a physical/chemical modification of an existing excipient is formed, a co-processed mixture of existing excipients is developed or a food additive is used for the first time for oral drug administration (Larner *et al.*, 2006). In the last three decades, new grades of existing excipients have been developed, but only a few novel excipients have been introduced into the market (Chang and Chang, 2007).

New grades of existing excipients can be obtained by modifying fundamental properties, leading to improved derived (functional) properties (Odeku*et al.*, 2008; Block *et al.*, 2009). Fundamental characteristics, such as morphology, particle size, shape, surface area, porosity and density all determine excipient functional properties such as flowability, compressibility, compactibility, dilution potential, disintegration, and lubrication potential (Camargo, 2011).

Any new chemical entity being developed as an excipient must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and costly process. The requirements of purity, safety, and functionality of the excipients are established and harmonized by the International Pharmaceutical Excipients Council (IPEC). In addition, similar to active ingredients, the excipient must undergo a phase of development, which shortens the market exclusivity period making the investment less attractive.

One of the solutions to the above problem was to develop drug products jointly, in which a new excipient becomes part of the new drug application. Thus, the combined expertise of pharmaceutical and excipient companies can lead to the development of tailor made innovative excipients. For example, Cydex Pharmaceuticals (Lenexa, KS) and Pfizer (New York, NY) worked collaboratively to obtain the approval of Captisol, a solubilizer for intravenous (IV) applications (Marwaha *et al.*, 2010).

In the past four decades, excipients have been physically and chemically engineered for developing new grades, such as pregelatinized starch, Avicel® PH-101, PH-102, and PH-200 (FMC Biopolymers, Newark, DE), spray-dried lactose (Foremost farms, Baraboo, WI) and crospovidone (Polyplasdone®XL and Polyplasdone®XL-10, International Specialty Products, Wayne, NJ). However, functionality can only be improved to a certain extent, because of the limited range of possible modifications that restricts functionality (Nachaegari and Bansal, 2004). Powder density and particle size could be altered to achieve better flow. However, when one attribute is improved, another may be compromised (i.e. flow of Avicel® PH-200 is improved 1.6 fold at the expense of its compactibility and vice versa for Avicel® PH-101) (Lerk *et al.*, 1974; Taylor *et al.*, 2000). However, in the case of native starches, thermal treatment led to an improved binder property (pre-gelatinized starch), attributable to the partially

hydrolysed nature of the granules which made them more hydrophilic (Klinger *et al.*, 1986).

Pregelatinization also provided other functionalities such as excellent flow, self-lubrication, improved use as filler in hard gelatin capsules (5-75 %), and a better binder in wet granulation (5-20 %). Further, this material has improved use as a drug binder for roller compaction and direct compression applications and as a disintegrant in tablets (5-10 %) (Ashish and Neves, 2006; Adedokun and Itiola, 2010).

2.2.1 Particle engineering as a source of new excipients

Particle engineering is a broad concept that involves the manipulation of particle parameters such as shape, size, size distribution, and simultaneous polymorphic changes that occur at the molecular level. All these parameters are translated into bulk-level changes, such as flow properties, compressibility, moisture sensitivity and machinability (York, 2001).

The solid state of a substance can be represented by three levels – molecular, particle, and bulk (Sainio, 2011). The molecular level comprises the arrangement of individual molecules in the solid state, and includes polymorphs, pseudopolymorphs and amorphous forms (Khomane, 2013). A typical example of how variation in the polymorphic form changes the functional properties of a material is lactose. Lactose exists in two forms, α-lactose and β-lactose. α-lactose monohydrate has good flow, small surface pore area, but poor binding properties. Anhydrous α-lactose, on the other hand, has a larger pore area, excellent binding properties (4 times larger) keeping the good flow characteristics. Further, different from the regular structure of α-lactose crystals, β-lactose has a granular form consisting of aggregates of small crystals with better binding properties (Lerk, 1993).

Other modifications at the molecular level involve chemical reactions or cross-linking of the excipient with a low molecular weight substances. These processes are expensive and usually require a need for solvent recovery and determination of residual solvents. Further, cross-linking agents are often toxic and leave traces of by-products (impurities) that could be harmful or degrade *in vivo* to toxic products. For example, microcrystalline cellulose, starch, chitosan, lactose, and other sugars can be easily cross-linked with glutaraldehyde in a complex etherification reaction. However, glutaraldehyde also self-polymerizes, leading to the formation of undesirable by-products which are difficult to remove (Rasmussen and Albrechtsen, 1974). Further, carboxymethylation of potato starch (ether synthesis) followed by neutralization with citric acid produces a superdisintegrant (sodium starch glycolate). Similarly, another type of starch cross-linking produced hydroxyethyl starch, useful for parenteral applications (Camargo, 2011). Cellulose derivatives like ethyl cellulose, methylcellulose and hydroxypropyl methylcellulose are also chemically modified excipients (Krassig, 1996).

The particle level comprises of individual particle properties such as shape, size, size distribution, surface morphology, surface area, and porosity (Brittain, 2001). The fundamental particle properties have a direct bearing on excipient functionalities such as the potential for dilution, disintegration, and lubrication. Hence, the development of a new excipient must begin with the particle design that is most suited to deliver the targeted functionalities (Nachaegari and Bansal, 2004). Particles with special characteristics can be designed by manipulating the conditions like crystallization and drying associated with the preceding level (Gupta *et al.*, 2006).

The bulk level is composed of an assembly of particles, and governs functional properties such as flowability, compressibility, compactibility, dilution potential,

disintegration and lubricant sensitivity, which are critical factors in the excipient's performance (Rojas *et al.*, 2013). This level can be modified by changing particle interaction in the bulk state. The resulting blends will exhibit intermediate properties between those of the two parent materials. In a few instances, the magnitude of these properties is non-ratio dependent (Nachaegari and Bansal, 2004). Particle size, particle size distribution and bulk density of the materials should be similar to prevent segregation during manipulation, handling and storage of the product, and batch-to-batch variability problems (Levin, 2006).

These levels are interdependent, with changes in one level getting reflected in the other level, thus providing a strong scientific framework for the development of new grades and combinations of existing excipients (Nachaegari and Bansal, 2004).

Only a limited functionality improvement is attained by the particle engineering of a single excipient. The spectrum of functionality can be widened by the co-processing or particle engineering of two or more existing excipients. Co-processing involves interaction of two or more excipients at the sub-particle level, aimed at providing a synergy of functionality improvements, as well as limiting the undesirable properties of the individual excipients.

Co-processing is based on the concept of excipient interaction at the sub-particle level. It provides a functional synergy as well as masking the undesirable properties of the individual components (Block *et al.*, 2009). Particles of the minor component can be incorporated either on the surface, or within the core of the excipient particles. This process requires homogenization of the excipients, followed by a co-processing step. As long as the two materials comply with the compendial requirements, the co-processed product does not need toxicity studies required for a new chemical entity.

In the design and development of a drug product, it is not uncommon to use two or more excipients/co-adjuvants to obtain a mixture with adequate tableting properties. The properties of such blends can result in either synergistic or antagonistic effect(s) with respect to various tableting properties (Lerk *et al.*, 1974). For example, a powder blend can be used to formulate rapidly disintegrating tablets from a mixture of Prosolv® SMCC 90, mannitol and a poorly soluble drug (loratadine) compressed at low pressures. Prosolv® can adsorb a sufficient quantity of fine dust of the fast dissolving excipient (mannitol). The resulting compacts are able to disintegrate within 60 s after contact with water or saliva (Beso and Sirca, 2006).

In a few cases, the API can be dispersed among the excipients in a liquid followed by spray drying to form a homogenous blend. For example, acetaminophen can be spray-dried with maltodextrin in water to produce oblong, free flowing particles with good compactibility. In this case, the binary mixture has good compactibility, but its compacts show a capping tendency (Gonnissen *et al.*, 2008). Sometimes it is advisable to diminish the undesirable effects of adjuvants in the bulk simply by changing blending time (i.e. the negative effect of hydrophobic magnesium stearate on plastically deforming materials can be decreased by reducing the blending time to 5 min) (Jivraj *et al.*, 2000).

2.2.2 Co-processing as a tool for developing novel excipients

Over the years, the strategy for developing excipients by co-processing has gained importance. However, the development of such combinations is a complex process because one excipient may interfere with the existing functionality of the other excipient. Co-processing was initially used by the food industry to improve stability, wettability and solubility and to enhance the gelling properties of food ingredients, such as co-processed glucomannan and galactomannan (Modliszewski and Ballard, 1996).

Excipient co-processing in the pharmaceutical industry originated in the early 1980s with the introduction of co-processed microcrystalline cellulose and calcium carbonate (Auguello *et al.,* 1998). Co-processing is a novel concept of altering excipient functionality by retaining the favourable attributes and supplementing with newer ones, by processing the parent excipient with other excipients (Bansal and Nachaegari, 2002; Bansal, 2003; Nachaegari and Bansal, 2004). This leads to the production of added functionality excipients to the formulator's advantage. The added functionality can be in terms of improved processing such as flow properties, compressibility, content uniformity, dilution potential, and lubricant sensitivity, or improved performance such as disintegration and dissolution profile (Nachaegari and Bansal, 2004). The co-processed excipient provides a ready-to-use excipient with predefined multifunctionality.

Excipient co-processing could lead to the formation of materials with superior properties compared to simple physical mixtures (gravity driven blending) of components. The aim of co-processing is to obtain a product with added value by a balance of its functionality and production costs. An excipient of reasonable price, such as diluent, has to be combined with another functional material in order to obtain an integrated product with superior functionality than the simple blend of components. The randomized embedding of the components in the particles minimizes anisotropic behaviour, such that deformation during compression along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of a co-processed excipient as a direct compression material may combine the advantages of wet granulation with the lower cost of direct compression(Joseph *et al.*, 2015).

A major limitation of the co-processed mixture is that the ratio of the excipients in the mixture is fixed. When developing a new formulation, a fixed ratio of the excipients

may not be optimal for a particular API and for the dose per tablet under development (Bolhuis and Chowhan, 1996; Saha and Shahiwala, 2009). Development of a co-processed excipient involves the following stages:

- Identifying the two or three excipients to be co-processed by carefully studying material characteristics and functionality requirements
- Selecting the proportions of excipients to optimize
- Assessing a suitable solvent in which to disperse the excipients
- Selecting an appropriate drying process such as spray drying or flash drying
- Optimizing the process to avoid batch-to-batch product variations

2.3 Role of material science in co-processing

Material science plays a major role in altering the physicomechanical characteristics of excipients, especially with regard to their compression and flow behaviour. Solid materials, with regards to their response to applied pressure, can be classified under the following (Patel *et al.*, 2006; Mahmoodi, 2012):

- ✓ Elastic: Any change in shape is completely reversible, and the material returns to its original shape upon release of applied stress e.g. corn starch
- ✓ Plastic: Permanent change in the shape of a material due to applied stress e.g. microcrystalline cellulose (MCC), corn starch, and sodium chloride (NaCl).
- ✓ Brittle: Rapid propagation of a crack throughout the material on application of stress e.g. sucrose, mannitol, sodium citrate, lactose and dicalcium phosphate.

The predisposition of a material to deform in a particular manner depends on its lattice structure; in particular whether weakly bonded lattice planes are inherently present. In definite terms, most of the materials cannot be classified distinctly into individual

categories. Pharmaceuticals exhibit all three characteristics, with one of them being the predominant response, this making it difficult to clearly demarcate the property favourable for compressibility.

Excipient co-processing offers a valuable tool to alter compression and/or flow behaviour of a material. A combination of plastic and brittle material is necessary for optimum tableting performance (Nachaegari and Bansal, 2004). Ideally, a co-processed excipient exhibits superior properties compared to the simple physical mixture of individual components.

Brittle materials that undergo extensive fragmentation generally result in tablets of relatively high porosity because of the relatively large number of bonding points that are created, which prevents further volume reduction. A ductile material, on the other hand, will often result in tablets of low porosity because of the high degree of plastic deformation enabling the particles to move very close to each other (York, 1992; Garekani *et al.*, 2001).

Co-processing is usually conducted with a plastic and a brittle excipient. The combination of these two types of material prevents the storage of excessive elastic energy during compression, resulting in a small amount of stress relaxation and a reduced tendency for capping and lamination (Jacob*et al.*, 2007). Further, co-processing of these two types of deforming materials produce a synergistic effect, in terms of compressibility, by selectively overcoming individual disadvantages. Such combinations can help improve functional properties, such as compaction performance, flow properties, strain-rate, lubricant and moisture sensitivities, or reduced hornification (ability to form hydrogen bonding). The products so formed are physically modified in a way so that they do not lose their chemical structure and stability. This means that excipients maintain their independent chemical properties, while synergistically

increasing their functional performance (Chow *et al.*, 2008). If the resulting co-processed excipient is porous, segregation is typically diminished since APIs can adhere unto excipient particles, making process validation and in-process control easy and more reliable.

2.4 Methods of Co-processing

Spray drying, wet granulation, spheronization, and co-crystallization can be used for co-processing. Spray drying is a process in which an aqueous or non-aqueous dispersion of the materials are sprayed through a nozzle at high pressures and the droplets formed are rapidly dried and collected as powder.

Wet granulation involves addition of an aqueous dispersion of a binder to a previously mixed powder blend, followed by wet sieving and drying.

In the spheronization process, the wet mixture of the excipients is first extruded to produce homogeneous spaghetti-like rods. The rods are, while wet converted to beads by using a spheronizer.

In co-crystallization, the two materials are dissolved in a solvent (often with heat) in which both are highly soluble followed by cooling at different rates to produce desired co-crystals. Differences in the cooling rates cause changes in the size and shape of the resulting crystals. These crystals can then be milled or passed through sieves to control their particle size.

2.5 Advantages of co-processed excipients

Co-processing enhances the properties of its products thereby conferring the following advantages:

i. Absence of chemical change

There is absence of any chemical alteration during co-processing of excipients resulting only in physical changes. Characterization of silicified microcrystalline cellulose (SMCC) with X-ray diffraction, solid-state and C13 nuclear magnetic resonance imaging (NMR), and infra-red and Raman spectroscopy confirmed the absence of chemical changes, and indicated a similarity to the physicochemical properties of MCC (Tobyn *et al.*, 1998). This reduces the regulatory burden and encourages the formulators to use co-processed excipients during the development phase.

ii. Improved physicomechanical properties

Co-processing has been able to improve significantly the functionality of the products obtained. The details are given below:

a. Improved flow properties

Controlled optimal particle size and size distribution ensures superior flow properties of co-processed excipients and reduced dependence on incorporation of glidants. The powder flow property of SMCC was studied in comparison with the physical mixture of its constituent excipients (Allen, 1996). The particle size range of the two test samples was found to be identical, but the flow of the co-processed excipient was better than that of the physical mixture. The spray-dried co-processed product of cellulose and lactose yielded a product that had a spherical

shape and even surface, which resulted in improved flow properties when compared to its physical mixture. Similarly, mechanical coating of microcrystalline cellulose II with colloidal silicon dioxide resulted in better flow properties (Rojas and Kumar, 2011).

b. Improved compressibility

Co-processed excipients have been used mainly in direct compression tableting because of better flow ability and compressibility, and the excipient formed is a filler-binder. The compressibility of several co-processed excipients such as Cellactose®, SMCC and Ludipress® have been reported to be superior compared to the physical mixtures of their component excipients(Schmidt and Rubensdorfer, 1994a; Allen, 1996; Sherwood and Becker, 1998). The versatility of SMCC has been reported in the manufacturing of high-dose DC formulations, wherein it reduces binder requirement by more than half, and results in overall reduction in excipient requirement (Joshi, 2002).

Co-processing of α-lactose monohydrate with corn starch helped to improve its compressibility, and provided dual benefits of enhanced bonding capacity and better disintegration potential, the attributes associated to starch (Wagner andDressler, 2003). This effect was attributed to the binding of small starch particles together with α-lactose monohydrate crystals into compound particles.

Although DC seems to be the method of choice for tableting, wet granulation is still employed in various products manufacturing because of improved control of drug content, better uniformity for highly potent drugs (low-dose APIs) and production of granules with superior bulk

density and compactibility (Andrews, 2007). Excipients like MCC lose compressibility upon addition of water, a phenomenon called ‘quasi-hornification’ (Staniforth and Chatrath, 1996). This property is improved, however, when it is co-processed into SMCC.

c. Better dilution potential

Dilution potential is the ability of the excipient to retain its compressibility even after dilution with another material in a fixed proportion(Rojas *et al.*, 2013). Most drug substances are poorly compressible, and require excipients to achieve better compressibility to retain good compaction even on dilution. Cellactose was shown to possess a higher dilution potential than a physical mixture of its constituent excipients (Flores *et al.*, 2000).

d. Lowering of lubricant sensitivity

Co-processing lowers the sensitivity of the product toward loss of their functionality in the presence of lubricants. Most co-processed products consist of a relatively large amount of brittle material and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material (Maarschalk and Bolhuis, 1999). The plastic material provides good bonding properties by creating a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity by preventing the formation of a coherent lubricant network, by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

iii. Co-processing gives rise to the development of tailor-made designer excipients with retention of functional and removal of undesirable properties, which can help in faster product development.

iv. It provides a single excipient with multiple functionalities, thereby reducing the inventory burden

v. Offers improvement in organoleptic properties, such as those in Avicel® CE 15, a co-processed excipient of MCC and guar gum, designed for providing chewable tablets with reduced grittiness and tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability.

vi. It provides more robust tablets at low compression force.

vii. Acts as a constant source for development of value-added generic products.

viii. Reduce product cost due to improved functionality (Prosolv Technical Report, 2001) and fewer test requirements compared with individual excipients.

2.6 Co-processed excipients for direct compression

The development of novel excipients by co-processing has increased the range of excipients available for direct compression. The performance requirements of flow and compressibility are two critical properties that have been enhanced by co-processing (Kittipongpatana and Kittipongpatana, 2012). Currently, a large proportion of co-processed excipients that have been developed and commercialized for direct compression are either lactose-based or cellulose-based excipients.

2.6.1 Lactose-based excipients

In solid dosage forms, lactose is the diluent of choice in tablet formulations. However, the inadequate compressibility and poor flow properties of α-lactose monohydrate have placed a restriction on its use as a filler-binder for direct compression (DC).

Many researchers and excipient developers have modified crystalline α-lactose monohydrate to achieve a product exhibiting good compactibility, reduced capping tendency and good flow properties to meet the requirements of excipients for DC (Wagner and Dressler, 2003).

Processing of lactose into small α-lactose monohydrate agglomerates (e.g. Tablettose, Pharmatose DCL 15) or spray-dried lactose was done to improve its direct compression properties. This processed lactose had better fluidity and compactibility than native lactose. However, the compressibility of spray-dried lactose was limited, and furthermore, it had relatively poor dilution potential. Spray-dried lactose was not amenable to being reworked as it tends to lose its compressibility after initial compaction (Shangraw, 1990).

Much later, binary mixtures of crystalline α-lactose monohydrate with microcrystalline cellulose (MCC), povidone or starch were tried but the results only led to an increase in compressibility of the mixture with no concurrent improvement in its flow properties as compared to pure α-lactose monohydrate (Wagner and Dressler, 2003). Hence, efforts have been geared towards development of co-processed lactose.

Co-processing of α-lactose monohydrate with povidone (PVP) and crospovidone produced Ludipress® (BASF AG, Ludwigshafen, Germany), making it suitable filler for direct compression on high-speed tableting machines. It is an odourless, tasteless, white free-flowing granules designed specifically for direct compression but equally suitable

as a filler for hard gelatin capsules. The formation of a layer of PVP and crospovidone on the surface of lactose powder imparted excellent flowability and low degree of hygroscopicity to lactose. Similarly, the hardness of the tablets produced was independent of machine speed. The binding properties of Ludipress®, both unlubricated and lubricated with 1 % magnesium stearate was good and was found to be better than the physical mixture (Bolhuis and Chowhan, 1996). Tablets containing Ludipress® had a much longer disintegration time in comparison to tablets containing α-lactose monohydrate, anhydrous β-lactose, spray-dried lactose or Tablettose. This prolonged disintegration was adduced to the presence of PVP (Baykara *et al.*, 1991). Ashrafi *et al.*(2005) had also reported the sustaining effect of Ludipress® when used in large concentrations in a formulation.

Ludipress® exhibited a better flow rate when compared to Avicel PH 101 and possessed the highest flow index among various lactose-based compressible excipients (Cellactose, Tablettose) as extrapolated from its lower static and dynamic angle of repose (Munoz-Ruiz *et al.*, 1992; Munoz-Ruiz *et al.*, 1993).

The ability of Ludipress®to form tablets was similar to Cellactose and Avicel PH 200, whereas tablets made from the physical blend were much softer. At a compaction pressure of 100 MPa, friability of Ludipress® compacts was ~ 0.2 %. A compaction load of 200 MN/m^2 was necessary to obtain similar values for tablets prepared with Tablettose. Ludipress® displayed high potential multipurpose excipient in the formulation of low-dose drugs because Ludipress based tablets exhibited optimum disintegration time and compression pressure independent dissolution of glibenclamide (Schmidt and Rubensdorfer, 1994b).

Schimdt and Rubensdorfer(1994a; 1994b) evaluated the powder and tableting properties of Ludipress and found that Ludipress samples exhibited a good batch-to-batch

uniformity and flow characteristics compared with the physical blends and other excipients investigated.

To further improve the compressibility of lactose, crystalline α-lactose monohydrate has been co-processed with powdered cellulose (Cellactose, Meggle) (Armstrong *et al.*, 1996)or microcrystalline cellulose (Microcelac, Meggle) (Saha and Shahiwala, 2009) to obtain products with improved bonding ability and excellent flow properties (Wagner and Dressler, 2003).

Cellactose was designed primarily for direct tableting and it combines the filler and binding properties of lactose and cellulose resulting in better tablet performance at lower cost. It has excellent flowability attributed to its regular particle shape and favourable particle size distribution (Armstrong *et al.*, 1996). The improved compactibility of Cellactose is explained by the consolidation mechanism of plastic deformation of cellulose and brittle fracture of lactose (Garr and Rubinstein, 1991). Also, Cellactose was shown to have a higher dilution potential than the physical mixture of its constituent excipients (Flores *et al.*, 2000). The presence of cellulose fibres in the macroporous particles provides good disintegration properties to Cellactose. The moisture sorption capacity of Cellactose is much lower than that of cellulose alone as it is coated with lactose (Bolhuis and Chowhan, 1996).

Improved tablet strength with Cellactose was attributed to the enhanced interparticle bonding in this co-processed excipient. Reduction of interparticle bonding by the presence of a lubricant film on the particles and the relaxation of lubricated tablets was higher than that of unlubricated tablets in which interparticle attractions are large. However, the negative effect of magnesium stearate on interparticle bonding of Cellactose particles is smaller than the physical mixture particles (Arida and Al-Tabakha, 2008).

The process of melt granulation technique was used to prepare a directly compressible co-processed excipient composed of lactose and MCC (3:1) base, incorporating 12.5 % of the melted basis of the polymer blend of PVP: PEG (1:9) as binder (Gohel and Jogani, 2003a). The prepared agglomerates were evaluated for percentage fines, Carr's index and compressed tablets were evaluated for tensile strength, friability and disintegration time. It was concluded by the authors that melt granulation technique can successfully replace the traditional wet granulation and spray drying for the development of multi-functional directly compressible adjuvant for use in pharmaceutical formulations.

Microcelac 100 is another marketed spray-dried product containing α-lactose monohydrate (75 %) and MCC (25 %) (Michoel *et al.*, 2002).A study conducted by Muzikova and Zvolankova (2007) revealed that the tablet strength of pure Cellactose 80 compacts was lower than that of Microcelac 100, both with and without lubricant at compression force of 6 and 8 kN. Disintegration time of the tablets from Cellactose 80 was longer than those of Microcelac 100, except for tablets containing 0.4 % sodium stearyl fumarate with a compression force of 6 kN(Muzikova and Zvolankova, 2007). Michoel *et al*(2002) demonstrated that Microcelac 100 has superior flow and binding properties and remain unchanged on addition of folic acid. These improved characteristics were explained by spray-drying (Michoel *et al.*, 2002).

Another lactose-based excipient that was developed recently is StarLac. It is a co-processed filler-binder consisting of 85 % α-lactose monohydrate and 15 % native corn starch. Starch is a bifunctional excipient, used as a binder and disintegrant; however, it exhibits the lowest elastic recovery at high binding capacity. When starch was co-processed with α-lactose monohydrate, it resulted in a product with excellent compactibility (Wagner and Dressler, 2003).

The deformation behaviour of StarLac was found to be dependent on the lactose properties. Flowability of StarLac is dependent on the spray-drying process. The presence of starch imparts a rapid disintegrating property to the product. StarLac was proven to have improved compactibility and flowability when compared to starch and its physical mixtures (Hauschild and Picker, 2004).

Gohel and Jogani (2003b) demonstrated the use of several linear regressions in the development of co-processed lactose and starch. They concluded that as the lactose:starch ratio increased, Carr's index of the product and crushing strength of the tablets increased simultaneously with a corresponding decrease in friability. The percentage of starch paste had an inverse effect on the friability.

Co-processing of anhydrous lactose (95 %) with lactilol (5 %) into Pharmatose DCL 40 reduced the sensitivity of lactose to moisture. The flow properties were enhanced because of its spherical shape and favourable particle size distribution. The water uptake of Pharmatose DCL 40 was found to be very low at increasing relative humidity. Its binding capacity and dilution potential were much better than those of all known lactose-based products (Bolhuis and Chowhan, 1996). A list of commercially available co-processed excipients is given below in Table 2.1.

Table 2.1:List of commercially available co-processed excipients

Type	Brand Name	Manufacturer	Ingredients	%	Processing
Starch-based	StarCap® 1500	Colorcon	Corn Starch	90	Spray-drying
			Pregelatinized starch	10	
Cellulose-based	Avicel® HFE	FMC	MCC	90	Spray-drying
			Mannitol	10	
	Avicel® RC-591	FMC	MCC	89	Milling, spray-drying
			NaCMC	11	
	Avicel® RC-581	FMC	MCC	89	Milling, spray-drying
			NaCMC	11	
	Avicel® CL-611	FMC	MCC	85	Spray-drying
			NaCMC	15	
	Avicel® CE 15	FMC	MCC	85	Spray-drying
			Guar gum	15	
	Prosolv® SMCC 50	JRS Pharma	MCC	98	Spray-drying
			Colloidal silicon dioxide	2	
	Prosolv® SMCC 90	JRS Pharma	MCC	98	Spray-drying
			Colloidal silicon dioxide	2	
Lactose-based	Cellactose®	Meggle Pharma	α-lactose monohydrate	75	Spray-drying
			Crospovidone	25	
	Ludipress®	BASF AG	α-lactose monohydrate	93.4	Roller drying
			Crospovidone	3.4	

		PVP	3.2	
Microcellac®	Meggle Pharma	α-lactose monohydrate	75	Spray-drying
		MCC	25	
Pharmatose® DCL 40	DMV Vengel	β-lactose	95	Spray-drying
		Anhydrous lactitol	5	
StarLac®	Meggle/Roquette	α-lactose monohydrate	85	Spray-drying
		Corn starch	15	

(Source: Camargo, 2011)

2.6.2 Cellulose-based excipients

Microcrystalline cellulose (MCC) is a direct compression binder with good lubricity and low hygroscopicity. When compressed, MCC particles deform plastically due to the presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macroscale (Shangraw, 1990). However, MCC loses its compressibility in the presence of water during wet granulation. This phenomenon is known as "quasi-hornification" (Nachaegari and Bansal, 2004). This becomes a real challenge when MCC occupies a greater percentage in a tablet.

The fluidity of MCC is poor compared to other direct compression fillers because of its relatively small particle size. Co-processing of MCC (98 %) with fumed colloidal silicon dioxide (2 %) into SMCC (Prosolv®) improves the strength of tablet compacts and reduced the sensitivity of MCC to wet granulation (Nachaegari and Bansal, 2004; Sherwood and Becker, 1998). SMCC exhibited better flow than MCC alone (Luukkonen *et al.*, 1999). Tobyn *et al* (1998) had earlier reported that there was 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. In spite of the similarity in structure, analytical techniques such as IR have not been able to provide reasons for the improvement in compressibility of SMCC over MCC. Internal bonding in SMCC accounts for change in compressibility from MCC after wet granulation (Buckton *et al.*, 1999).

A study was carried out by Luukkonen *et al* (1999) on the rheological behaviour of the wet powder masses of SMCC (Prosolv®), and standard grades of MCC (EMCOCEL 50 and Avicel PH 101) as a function of mixing time using a mixer torque rheometer. They

found out that SMCC had improved flow properties and specific surface area with reduced swelling capacity compared to standard MCC grades.

Rojas and Kumar (2011)reported a small negative effect of colloidal silicon dioxide on the interparticle bonding strength of unlubricated SMCC. The strength of SMCC tablets increased significantly with increasing compression force (Muzikova and Novakova, 2007). The superior behaviour of SMCC was observed when cohesive, poorly compressible drugs were formulated into directly compressed tablets (Lahdenpaa *et al.*, 2001).

Kachrimanis *et al*(2003) observed a slight increase in the tensile strength but a significant increase in the disintegration time of Prosolv® compared with Avicel® in the packing fraction range of 0.7 – 0.9, the range for pharmaceutical tablets. The inclusion of silicon dioxide acted as a barrier for the moisture sorbed only for relative humidity up to 52 %. At higher relative humidity (72 %), the incorporated silicon dioxide did not increase the particle deformation and resulted in more extended disintegration time owing to its probable saturation.

Avicel CE 15 is a co-processed excipient of MCC and guar gum, mainly used in chewable tablets (Rowe *et al.*, 2005). Avicel CE I5 offers improved palatability, creamier mouth feel with less grittiness and reduced tooth packing (Rowe *et al.*, 2005). When MCC was co-processed with mannitol, there was an improved compactibility profile, lubricant sensitivity and ejection profile compared to MCC (Li *et al.*, 2008).

An excipient with low lubricant sensitivity was developed from the co-processed combination of MCC and calcium carbonate ranging from a weight ratio of 75:25 to 35:65. The compression profile remained relatively unchanged when various lubricants were employed, irrespective of the lubricant concentration (Mehara *et al.*, 1988). Limwong *et al*(2004) developed composite particles of rice starch and MCC by spray

drying technique and investigated its direct compression functionality. These composite particles demonstrated good compressibility and flowability while its tablets had low friability and good self-disintegrating property.

2.7 Studies carried out on other investigational co-processed excipients

Other excipients with improved functionality have been developed via co-processing which have not been commercialized. Many researchers home and abroad have invested much effort in exploring the potentials of co-processing. Some of their findings are documented below.

Adeagbo and Alebiowu (2008) assessed the lubricant potential of cocoa butter co-processed with magnesium stearate plus talc in comparison with magnesium stearate plus talc using flow and compressional characteristics of paracetamol granules and mechanical properties of their tablets. The authors concluded that cocoa butter was an effective and viable lubricant that can be co-processed with magnesium stearate/talc mixture for an efficient lubrication of granules and may be useful in reducing lamination and capping tendencies in formulations that are susceptible to these defects. The consolidation and flow properties of a novel excipient were enhanced by co-processing neem gum with either rice starch or lactose in varying proportions in a study carried out by Ogunjimi and Alebiowu (2013).

Gohel *et al* (2007a) processed crospovidone and sodium starch glycolate as a co-processed superdisintegrant, producing good flow and compression characteristics. When this excipient was used in the formulation of cefixime trihydrate and ibuprofen tablets, a quick disintegration and improved dissolution rate were observed. Similarly, the same authors have shown that co-processed superdisintegrant of croscarmellose

sodium and crospovidone has better flow, crushing strength, disintegration time and drug dissolution when compared to the physical blend (Gohel *et al.*, 2007b).

Physically modified chitosan has been co-processed with silicon dioxide to yield a novel super disintegrating agent in a study carried out by El-Barghouthi *et al* (2008). The intimate physical association between chitosan and silica created an insoluble, hydrophilic, highly absorbent material responsible for the superior performance in water uptake, water saturation for gelling formation, and compactability among other superdisintegrant. The excipient exhibited the best functionality in wet granulation formulations and was noted as the only disintegrant that was effective at all concentrations in tablet formulation.

A co-processed excipient was prepared from commercially available crystalline mannitol and α-chitin using direct compression as well as spray-drying, wet, and dry granulation (Daraghmeh *et al.*, 2010). α-chitin processed with mannitol formed non-hygroscopic, highly compactable, disintegrable compacts. Optimal physicochemical properties of the excipient were obtained using a co-processed mannitol-chitin (2:8,$^{w}/_{w}$) mixture prepared by wet granulation. This co-processed excipient was found to be useful for the formulation of poorly compressible, high-strength, and low-strength active pharmaceutical ingredients.

Novel chitin metal silicate (CMS) co-precipitate was developed by Hamed*et al* (2010) and employed as a single multifunctional excipient in the formulation of tablets either by direct compression or wet granulation. The tablets produced met the official requirements for acceptable tablets and confirmed the potential of this excipient as filler, binder, and superdisintegrant, all-in-one, in the design of tablets by direct compression as well as wet granulation methods.

Al-Akayleh *et al* (2013) have equally developed a novel, multifunctional co-processed excipient via roller compaction of α-lactose monohydrate and magnesium silicate. The investigated co-processed excipient demonstrated plastic deformation upon compression, good flowability and crushing strength and a shorter disintegration time. The suitability of this excipient as a single multifunctional excipient was confirmed by formulating tablets of Mebeverine HCl and Losartan Potassium. The tablets produced were characterized by rapid disintegration and dissolution profiles in comparison to the marketed drugs.

Orally disintegrating tablets were prepared by a co-processed mixture of micronized crospovidone and mannitol using a ball mill to improve compactability and tablet stability. The tablets produced showed good stability for six months under humid conditions with rapid disintegration (< 30 s) and increased hardness of the tablets (tensile strength > 1.0 MN/m^2) (Katsuno *et al.*, 2013).

2.8 Research output on starch-based co-processed excipients

Most of the co-processed excipients that have been developed and commercialized are either lactose-based or cellulose-based products. The only co-processed excipient with a greater proportion of starch that has been marketed is StarCap 1500®. StarCap 1500® is a unique co-processed mixture of globally accepted excipients, corn starch and pregelatinized starch, designed for use in capsules and tablets. It is an inert, free-flowing, low dust excipient with disintegration and dissolution properties independent of the medium pH. It possesses better flow properties than MCC. It allows for minimal dusting or adherence to contact surfaces, leading to a cleaner filling operation and lower tablet variation. StarCap 1500® at > 75 % level makes the release profile of propranolol pH dependent and at 24.75 % level allows for the release of 90 % Gabapentin within 6 min (Gulian *et al.*, 2006).

Novel co-processed excipients of maize starch and acacia (StarAc) were formulated in various mixing ratios and evaluated as a direct compression excipient (Olowosulu *et al.*, 2011). The results obtained from the study revealed that the co-processed excipient prepared by partial pregelatinization method produced better tablets in terms of crushing strength, friability and disintegration time when compared to tablets produced by the fully pregelatinized co-processed excipient.

Shittu *et al* (2012) designed and developed a two-component composite filler-binder containing microcrystalline tapioca starch and α-lactose monohydrate for direct compression. The novel co-processed excipient showed improved functionality over the physical mixture of the primary excipients and performed better than StarLac® in terms of compaction properties.

The tablet properties of StarCap 1500® were evaluated in comparison to Starch 1500®. The results revealed a better compressibility of StarCap 1500® when compared to Starch 1500® and a lower elastic component of energy. The tablets were stronger and disintegrated more rapidly, but the substance possessed a higher sensitivity to lubricant addition than Starch 1500® (Muzikova and Eimerova, 2011; Rojas *et al.*, 2012).

Several researchers have continued to develop starch-based co-processed excipients at investigational level with improved functionality. A study was carried out recently by Kittipongpatana and Kittipongpatana (2012) to develop directly compressible co-precipitated powder composed of rice starch and colloidal silicon dioxide (CSD) mixed at five different ratios (8:1, 4:1, 2:1, 4:3, and 1:1), with three concentrations of sodium hydroxide (NaOH) (0.5, 1.0, and 2.0 M) employed in the dispersion of colloidal silicon dioxide. The co-precipitated powders exhibited improved flowability, compactibility, superior bulk and tapped densities compared to that of native starch and physical mixtures. The optimum ratio of starch: colloidal silicon dioxide to yield powder with

good flow and compactibility was found to be 4:1, with the use of either 0.5 or 1.0 M NaOH to disperse CSD. It was therefore concluded from the study that the co-precipitated powder has potential for use as a directly compressible excipient in tablet formulation.

Eraga *et al* (2014) developed a novel multifunctional co-processed excipient by processing gelatinized maize starch, sodium carboxyl methylcellulose (SCMC) and microcrystalline cellulose (MCC) in a ratio of 2:1:1. The co-processed excipient exhibited excellent flow properties reflected by the angle of repose, high moisture content, good swelling index and hydration capacity. Paracetamol tablets produced by direct compression using this excipient were acceptable with regard to weight, crushing strength, drug content and disintegration time.

Co-precipitates of corn starch with different silicates (Mg, Ca, Al) have been developed and evaluated as a tablet superdisintegrant by Singh *et al* (2014). The study revealed that there was an improvement in the flow properties and the tablets disintegrated very rapidly. The workers thus concluded that this excipient can be used as an effective adjuvant to existing tablet superdisintegrant.

Tapioca starch and mannitol were co-processed together, employing two methods (co-fusion and co-grinding) and used as disintegrants in an orally disintegrating paracetamol tablet formulation (Adeoye and Alebiowu, 2014b). The tablets produced were evaluated for mechanical and release properties. The results obtained revealed that the novel disintegrant enhanced the mechanical properties of the tablets with reference to friability and tensile strength. The flow, packing and compaction characteristics of the excipient were enhanced (Adeoye and Alebiowu, 2014a).

2.9 Constituent excipients for co-processing

Three excipients have been selected for this study on the basis of their properties. They are cassava starch, gelatin and colloidal silicon dioxide. Based on their response to applied pressure, cassava starch deforms by plastic deformation with some degree of elastic recovery occurring during decompression while gelatin and colloidal silicon dioxide deform by brittle fracture. The goal of combining these three candidates is to develop a multifunctional excipient that integrates the disintegrating ability of starch, the binding strength of gelatin and the enhanced flow contributed by colloidal silicon dioxide in an optimized manner.

2.9.1 Starch

Starch, $(C_6H_{10}0_5)_n$ is a carbohydrate polymer that is naturally available in abundant quantities next to cellulose and chitin. Owing to its large availability and low cost, native starch has found application in the food and non-food industries alike. As an auxiliary raw material of choice, starch has exceeded other similar biopolymers, such as cellulose in its versatility and usefulness. Starch has been rated as one of the best-known excipients in the various pharmaceutical formulations (Rashid *et al.*, 2013).

Starch forms the major component in tropical root and tuber crops and hence these crops are highly valued (Ghosh *et al.*, 1988; Chadha and Nair, 1994). The starch content ranges from 15 – 40 % on fresh weight basis. The starch content in cassava is among the highest in starch yielding crops. It is easy to extract and is obtained in pure form by simple extraction. The bland taste, higher paste clarity and fewer tendencies to retrograde compared to cereal starches makes cassava starch the preferred choice for food purposes.

Untreated native starches are structurally too weak and functionally too restricted with some undesirable properties i.e. poor flowability and compressibility. Processing is necessary to widen the spectrum of functionality and improve its rating in the pharmaceutical industry. Several approaches have been adopted to modify starch. The most common is the reaction of starch with various chemicals to alter the arrangement of the glucose chains in the starch granules, or to introduce additional chemical groups, such as phosphate or acetate to starch. These modifications modulate the behaviour of starch making it adaptable for a particular purpose. The modified starches are a major resource for the pharmaceutical industry.

2.9.1.1 Description

Starch occurs as a fine, white powder that is odourless and tasteless, composed of very small spherical or elliptical granules. The botanical origin of the starch material determines the granule shape and size. It is insoluble in alcohol, most solvents and cold water. Gelatinization temperatures vary from starch to starch, but range from 60 – 75 ºC (Hoover, 2001). Starch granules lose their characteristic shape as gelatinization proceeds.

Starch is a semi-crystalline polymer. The linear amylose molecules are amorphous in nature, but the branched amylopectin portion has been reported as partially crystalline (French, 1984). It is believed that the crystalline regions in the starch granule are interspersed in a continuous amorphous phase (French, 1984). PXRD studies have revealed that starch exists in three crystal forms designated as A, B and C (Ring *et al.*, 1988). These forms are dependent on the botanical source of the starch. Pattern A is observed for cereal grain starches, whereas pattern B is characteristic of tuber, fruit, and stem starches. Pattern C is intermediate between A and B patterns and has been attributed to mixtures of A and B crystallites.

The crystalline order in starch granules is often the basic underlying factor influencing functional properties. The presence of amorphous and crystalline regions in the starch granules creates more opportunities for starch modification.

2.9.1.2 Pharmaceutical uses of starch

Starch is widely used in the pharmaceutical industry because, among its other properties, it is readily available, inexpensive, white and inert. Currently, starch is being employed as a tablet/capsule diluent, disintegrant and binder in solid dosage form development(Alebiowu, 2001;Odeku and Akinwande, 2012; Odeku, 2013). Physical and chemical modifications have also been used to alter the granule structure of starch and modify their functional properties to eliminate some of its drawbacks, making them adaptable for specific uses (Alebiowu and Itiola, 2003; Lee *et al.*, 2004; Adedokun and Itiola, 2010;Assen*et al.*, 2011).

The functionality of starch in a formulation depends on its mode of application. Starch will function as a disintegrant when it is added in the dry state prior to external lubrication of the granules. It may exhibit both binding and disintegrant properties when it is incorporated either as a paste or dry before granulation with other excipients.

It has been reported that starches densify by plastic deformation during compression but this is largely dependent on the particle size, size distribution and particle shape (Odeku *et al.*, 2008; Adedokun and Itiola, 2010).

A number of starch modifications are used in pharmaceutical applications. pregelatinized or compressible starch has been chemically or mechanically processed to rupture all or part of the granules in water. It is then dried to yield an excipient material suitable for direct compression formulations. Modified starches obtained through chemical derivation such as etherification, esterification, cross-linking, and grafting

have been employed as drug delivery vehicles for controlled release of drugs and other bioactive agents (Prochaska *et al.*, 2009).

2.9.2 Cassava starch

Cassava, *Manihot esculenta* Crantz (Fam. Euphorbiaceae) also known as yucca (Central America), mandioca or manioc (Brazil), tapioca (India and Malaysia), and cassada or cassava (Africa and Southeast Asia) (Grace, 1977; Tonukari, 2004) is an important starchy staple of lowland tropics and a major source of food support for some of the poorest nations of the world. It is one of the world's cheapest and most popular stable crops in countries such as Nigeria, Brazil, and Thailand (Bean and Setser, 1992; Odeku, 2013).

Cassava has become a dependable substitute for barley and wheat for countries that do not produce barley and wheat. Cassava starch is an important carbohydrate in tropical countries worldwide. It has a characteristic bland flavour and gives a stringy cohesive paste when gelatinized (Moorthy, 2001).

Cassava ranks very high among crops that convert the greatest amount of solar energy into soluble carbohydrates per unit area. Among the starchy staples, cassava gives a carbohydrate production which is about 40 % higher than rice and 25 % superior to corn, making cassava the cheapest source of calories for both human nutrition and animal feeding. Typical composition of cassava root is moisture (70 %), starch (24 %), fiber (2 %), protein (1 %) and other substances including minerals (3 %) (Tonukari, 2004). The granule size of cassava starch ranges from 5 to 40 μm with a shape that is close to spherical. Table 2.2 shows the USP specifications of cassava starch.

Table 2.2: USP specifications of cassava starch

Properties	Observations
Appearance	White
Physical state	Powder
Odour	Odourless
Particle size (μm)	5-35
Shape	Round, spherical
pH	4.5-7.0
Solubility	Insoluble in water
Loss on drying (% $^{w}/_{w}$)	≤ 16
Bulk density (g/mL)	0.623
Tapped density (g/mL)	0.873
True density (g/mL)	1.48
Amylose content (%)	24.73
Gelatinization temperature (°C)	≈ 63

(Source: USP/NF, 2009)

Cassava starch has been shown to deform mainly by plastic flow during compression in a similar manner to official corn starch, suggesting that cassava starch could replace corn starch in tablet formulations (Itiola, 1991). A study of the packing and cohesive properties of cassava starch has revealed that cassava starch, having a round and more regular shape possessed the lowest shape factor which could promote tight packing of particles and could be useful in the production of capsules (Itiola and Odeku, 2005). When incorporated as a binder in a paracetamol tablet formulation, cassava starch exhibited stronger binding potential than gelatin BP (Itiola and Amoo, 1998).

The quality of tablets produced by modified cassava starch has been evaluated (Nwanekezi *et al.,* 2000). Tapioca starch was modified by cross-linking in the presence of alkaline sodium trimetaphosphate solution followed by hydrolysis using 6 % w/v HCl solution at room temperature for 192 h. The native, cross-linked, and acid-modified tapioca starches were spray-dried to allow the formation of agglomerated starch granules with better flowability suitable for direct compression. It was observed that cross-linking did not increase the relative crystallinity or the melting enthalpy of tapioca starch while acid hydrolysis resulted in an increase in the crystallinity of both starches by the removal of the amorphous regions. The native and cross-linked tapioca starches produced tablets with very low crushing strength, while the acid-modified starches produced tablets with higher crushing strength. Acid-modified and acid-modified cross-linked tapioca starches were shown to be useful as fillers in direct compression tablet preparation (Nwanekezi *et al.,* 2000; Assen *et al.,* 2011).

2.9.3 Colloidal silicon dioxide

Colloidal silicon dioxide or fumed silica or anhydrous silicic acid is a white, amorphous, fluffy powder consisting of primary particles in the nanometre range (10 – 40 nM), resulting in a very large specific surface area (50 – 400 m^2/g). The primary

particles are not isolated but are fused together in relatively stable chain-like aggregates, which in turn form larger agglomerates in the micrometre range. It has low bulk and tapped densities and can produce dust if not properly handled.

It is manufactured by the hydrolysis of silicon tetrachloride in a hydrogen/oxygen flame according to the chemical reaction given below:

$2H_2 + O_2 \rightarrow 2H_2O$

$\underline{SiCl_4 + 2H_2O \rightarrow SiO_2 + 4HCl}$

$2H_2 + O_2 + SiCl_4 \rightarrow SiO_2 + 4HCl$

Gaseous $SiCl_4$ reacts in a gas flame burner (1000 °C) with just formed H_2O to produce SiO_2 in the separation chamber. The HCl that remains adsorbed onto the colloidal silicon dioxide surface is removed in the deacidification chamber by washing with water vapour. The colloidal silicon dioxide product is collected in a silo, tested and packaged.

Upon production, colloidal silicon dioxide is hydrophilic, containing silanol (-Si-OH) and siloxane (-Si-O-Si-) groups on its surface. Silanes such as methyltrichlorosilane or trichlorosilane can also be used, either alone or in combination with tetrachlorosilane, as precursor materials.

Colloidal silicon dioxide is widely used in the pharmaceutical field for its glidant activity. It is normally used at a concentration of 0.2 – 1.0 % to improve the flow properties of cohesive powders and granulates. When applied to tableting operations, colloidal silicon dioxide improves flow into the hopper and dies cavity of the tablet press. It decreases unit weight variation and minimizes the tendency of powder or granule components to separate or segregate due to excessive vibrations.

The addition of 0.5 % colloidal silicon dioxide yields greater tablet hardness and density thereby reducing tablet chipping and breakage during handling, coating, packaging and shipping.

Most of the filler/binders used in pharmaceutical formulations are not free flowing; hence small amounts of glidants are incorporated into the mixtures to improve the flow properties of the powders. Glidants used in pharmacy include talc, colloidal silicon dioxide, calcium phosphates and to a certain extent various metallic stearates.

Several groups have investigated the addition of glidants to a variety of powders and noted that silica-type glidants are the most effective because of their small particle size (Lieberman and Lachman, 1989; Jonat, 2005). A summary of the physical and chemical properties of colloidal silicon dioxide is given below in Table 2.3.

Table 2.3: Physical and chemical properties of colloidal silicon dioxide

Properties	**Observations**
Appearance	White powder
Odour	None
Particle size	12 nM
Specific surface area	200 ± 25 m^2/g
Moisture content	≤ 1.5 %
Ignition loss	≤ 1.0 %
pH	3.6 – 4.5
Boiling point range	2230 °C
Melting point range	1700 °C
Solubility in water	Insoluble
Density	2.2 g/cm^3 @ 20 °C
Bulk density	≈ 30 g/cm^3
Tapped density	≈ 50 g/cm3
SiO_2	≥ 99.8

(Source: Material Safety Data Sheet, Cabot Corporation, Germany)

2.9.4 Gelatin

Gelatin is a protein substance derived from collagen, a natural protein present in the tendons, ligaments, and tissues of mammals. It is produced by boiling the connective tissues, bones and skins of animals, usually cows and pigs. The ability of gelatin to form strong, transparent gels and flexible films that are easily digested, soluble in hot water, and capable of forming a binding action have made it a valuable commodity in food processing, pharmaceuticals, photography, and paper production(PB Gelatins, 2009).

Based on the method of processing, it may exist either as type ‘A’ (acid-cured tissues) or type ‘B’ (lime-cured tissues). The chemical structure of gelatin is given below:

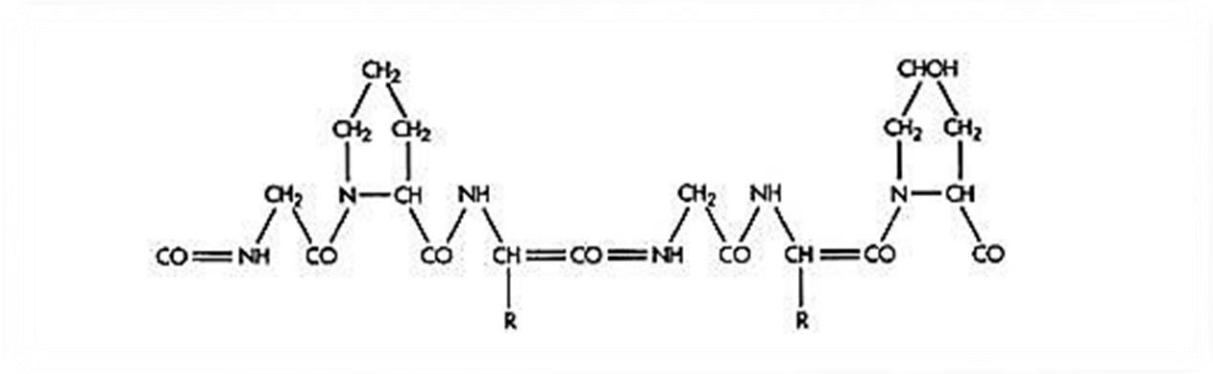

Figure 2.2:Chemical structure of Gelatin

(https://www.researchgate.net/figure/51832364_fig7_Chemical-structure-of-Gelatin**)**

Gelatin has been selected as a constituent excipient for co-processing because it gives texture and stability to the finished products due to its binding ability. It has been used as a delivery vehicle for the release of bioactive molecules (Young *et al.*, 2005). The physicochemical properties of gelatin are given below in Table 2.4.

Table 2.4: Physicochemical properties of gelatin

Properties	Observations
Physical state	Solid
Form	Flakes or powder
Colour	Off-white
Odour	Musty odour
Solubility	Insoluble in cold water, soluble in warm water
Chemical stability	Material is stable under normal conditions
pH	3.8 – 7.6
Gel strength	125 – 145 g
Loss on drying	≤ 15 %

(Source: Avantor Performance Materials, USA)

2.9.5 Ibuprofen

Ibuprofen is a chiral propionic acid derivative belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDS). Due to its analgesic, antipyretic and anti-inflammatory actions, it is used in the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, mild and moderate pain, dysmenorrhea, vascular headache and fever. It occurs as a white, crystalline powder with a characteristic odour. Melting point ranges from 75 – 78 ºC and its solubility in phosphate buffer pH (7.2) is 5.2 mg/ml. The physicochemical properties are summarized in Table 2.5.Ibuprofen was selected as the drug of choice for this study because it is poorly compressible with a high tendency for capping when compressed at high speed (Nokhodchi *et al.*, 1995). The empirical formula of ibuprofen is given as: $C_{13}H_{18}O_2$, with a molecular weight of 206.28 g/mol. The chemical structure is given below:

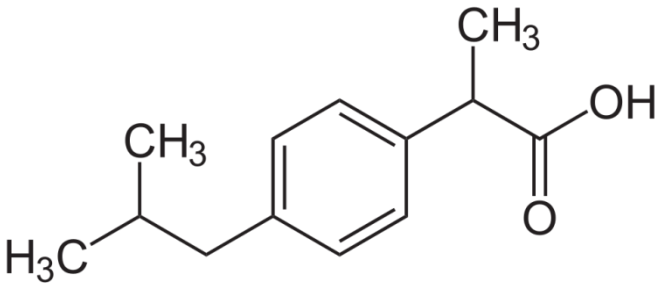

Figure 2.3:Chemical structure of Ibuprofen (Buschmann *et al*., 2010**)**

Table 2.5: Physicochemical properties of Ibuprofen

Properties	**Observations**
Appearance	Crystalline powder
Colour	White
Odour	Characteristic
Solubility in phosphate buffer 7.2 (37 °C)	5.2 mg/ml
Melting point range	75 – 78 °C
Particle size	≈ 50 μm
Bulk density	0.34 g/ml
Tapped density	0.6 g/ml

(Source: BASF, USA)

2.10 Pharmaceutical Quality by Design (QbD)/Design of Experiment (DoE)

The concept of QbD was first mentioned in the International Conference of Harmonization (ICH) Q8 guidance, which states that "*quality cannot be tested into products; instead, quality should be built in by design*" (FDA, 2006). Product testing only confirms product quality. Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality (Yu, 2008).

QbD identifies characteristics that are critical to quality from the perspectives of patients, translates them into attributes that the drug product should possess, and establishes how the critical process parameters can be optimized to consistently produce a drug product with the desired characteristics (Yu, 2008).

Design of Experiment (DoE) is a structured and organized method to determine the relationship among factors that influence the outcome of a process. It is an optimization technique meant for products and/or processes, developed to evaluate all potential factors simultaneously, systematically and speedily. Its' implementation invariably encompasses the use of statistical experimental designs, generation of mathematical equations and graphic outcomes, portraying a complete picture of variation of response(s) as a function of the factor(s)(Singh*et al.*, 2011).

It has been co-opted into studies by several researchers to gain knowledge about combinations and interactions of input variables (e.g. formulation and process variables) and to establish a design space (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human use, 2009). DoE is used both in

the development of new products and for the optimization of existing processes as the goal of DoE is to optimize quality and performance of the product (Larsen*et al.*, 2014).

When DoE is implemented in a pharmaceutical process, the factors are the raw materials attributes (e.g. particle size) and process parameters (e.g. speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness and friability. The outcome of DoE when applied can help to identify optimal conditions, the critical factors that most influence critical quality attributes (CQA) and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPP can be determined. Within the QbD, design space is defined as the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide quality assurance. The application of DoE to product development has resulted in reduced production cost and improved product quality.

Several works have reported the use of DoE in optimizing process and product development. Martinello *et al* (2006)applied experimental DoE in the development and optimization of tablet formulations containing high amounts of paracetamol (more than 70%) and manufactured by direct compression.The physicochemical propertiesobtained from the optimized formulation were very close to those from the regression analysis, demonstrating that DoE is a great tool for the research and development of new formulations.

Design of experiment approach was employed by Larsen *et al*(2014)to examine the effects of formulation and processing variables on the formation of mannitol hemihydrate (MHH) in freeze-dried protein formulations. The successful application of

DoE revealed that the most significant factors promoting the formation of MHH were a high protein concentration, low relative mannitol content and annealing at – 20 °C.

In a study carried out by Kurmi*et al*(2014), DoE was applied for optimization of forced degradation conditions and development of a stability-indicating method for furosemide. Based on the DoE results, an optimized method was obtained wherein a total of twelve degradation products were separated successfully.

The optimization of lipid based oral formulations for cucurmin loading and post dilution droplet size was carried out by design of experiment (DoE) approach with Box-Behnken design (Pawar *et al.*, 2012).

The present study has employed the DoE concept to optimize the composition of the co-processed excipient to deliver desirable tableting properties in the product.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials

3.1.1 Chemicals

The following chemicals as listed in Table 3.1 were used for the entire study.

Table 3.1: List of Chemicals/Excipients and their various manufacturers

Name	Manufacturer/Supplier
Cassava starch	Quality Starch and chemicals (India) Private Ltd, Tamil Nadu, India
Gelatin	May and Baker Ltd, Dagenham, England
Silicon dioxide (CAB-O-SIL)	Cabot GmbH, Rheinfelden, Germany
Ibuprofen	Himedia laboratories Ltd, Mumbai, India
Magnesium stearate USP/NF	Signet chemical corporation, Mumbai, India
Silicified Microcrystalline cellulose (Prosolv®)	JRS Pharma GmbH & Co.KG, Rosenberg, Deutschland
StarLac®	Roquette Pharma, France
Potassium dihydrogen orthophosphate	Rankem (Avantor Performance Materials India Ltd), Gujarat, India
Sodium hydroxide pellets GR	Loba Chemie PVT Ltd, Bombay, India
Ultrapure water	In-house supply, NIPER, Mohali
Demineralised water	In-house supply, NIPER, Mohali

3.1.2 Instruments/Equipment

Instruments and equipment used during the course of this project are listed in Table 3.2.

Table 3.2: List of Instruments/Equipment used

Instrument/Equipment	Model and Manufacturer
Electronic balance	CPA2P, Sartorius AG, Germany
Analytical balance	Mettler-Toledo AG 285, Switzerland
Analytical balance	Sartorius GM 1202, Germany
IR-Moisture balance	Mettler Toledo LP 16, Switzerland
pH meter	Cyberscan 510, Eutech Instruments Ltd, Switzerland
Ultrapure water system	Maxima, USF ELGA, England
Shaker water bath	SW 23, Julabo Labortechnik, Germany
Fluid bed dryer	TG 100, Retsch, Germany
Rimek rotary tablet press	Mini II D, Karnavati Engineering Pvt Ltd., India
Punches and dies	12 mm D-tooling, Karnavati Engineering Pvt Ltd., India
Hydraulic press	Model 3912, Carver Inc., USA
Ultra Turrax® Homogeniser	T 25 basic, Ika-werke, India
Optical microscope	DMLP, Leica, Germany
Scanning electron microscope	S-3400, Hitachi Ltd., Japan
Differential scanning calorimeter	DSC 2000, TA Instruments, USA
Dynamic vapour sorption	Q5000 SA, TA Instruments, USA
Powder X-ray diffractometer	D8 Advance, Bruker, Germany
FT-IR spectrometer	Spectrum 400, Perkin Elmer Instruments, USA
CD spectrometer	J-815, Jasco, Japan
True density meter	Pycno 30, Smart Instruments, Mumbai, India

Surface area analyser	Smart sorb 92/93, Smart Instruments, Mumbai, India
Tapped density tester (USP)	ETD 1020, Electrolab, India
Tablet hardness tester	TBH 20, Erweka, Germany
Granulate flow tester	GTB, Erweka, Germany
Friabilator (USP)	EF-2, Electrolab, India
Disintegration tester (USP)	ED-2L, Electrolab, India
Dissolution tester (USP)	TDT-08L, Electrolab, India
UV/VIS spectrophotometer	Lambda 35, Perkin Elmer Instruments, USA

3.2 Methods

3.2.1 Selection and optimization of the composition of the co-processed excipient using Design of Experiments (DoE)

A simple centroid (mixture) experimental design was used to select a desirable combination of the three excipients comprising the co-processed mixture. The content of cassava starch (factor A) was varied from 90 – 98 % while the limits for gelatin (factor B) and colloidal silicon dioxide (factor C) were kept at 1 – 9 %. The effect of these independent variables (factors A - C) on dependent variables (Y_1: tensile strength of tablet and Y_2: disintegration time of tablet) was studied using Design Expert® software version 9 (Stat-Ease Inc., USA). A total of 14 experimental formulations were designed by the software with 4 centre points. Experiments were run in random order to increase the predictability of the model. A batch size of 30 g was prepared for each experimental formulation.

Tablets were prepared using Hydraulic Carver Press by compressing 400 mg powder at 2000 PSI (53.28 MN/m^2) with a dwell time of 30 s using a flat-faced 13 mm punch and die set. The tablets were kept for 24 h to allow for elastic recovery before evaluation of physical properties.

Table 3.3 shows the concentration range by weight expressed in percentagefor each excipient utilized in the experimental design to optimize the composition of the co-processed excipient.

Table 3.3: The constituent excipients and their various concentration ranges utilized in the experimental design

Component	Name	Experimental design	Concentration range (% $^{w}/_{w}$)
A	Cassava Starch	Mixture	90 – 98
B	Gelatin	Mixture	1 – 9
C	Colloidal Silicon dioxide	Mixture	1 – 9

3.2.2 Preparation of co-processed excipient (CPE)

Cassava starch dispersion (40 % $^{w}/_{w}$) was prepared in distilled water and mixed with corresponding quantities of solubilized gelatin and colloidal silicon dioxide for 5 mins. The mixture was subsequently transferred to a shaker water bath (Julabo SW 23, Seelbach, Germany) set at a temperature of 54 ± 2 °C for 15 min (60 rpm). The mixture was then homogenized afterwards for 5 min at a speed of 11,000 rpm (Ultra Turrax T 25 basic Ika® Werke, India), allowed to air dry partly at room temperature (25 ± 2 °C) for 60 min to remove excess moisture and then drying completed in the Fluid bed dryer (Retsch TG 100, Germany) at 40 °C for 10 min. The product was passed through BSS 30 (sieve size: 500 µm) and packed into tight sealed containers before storing in the desiccator sequel to further studies.

3.2.3 Solid-state characterization

3.2.3.1 Optical and polarized microscopy

Microscopical characterization was done to observe the particle shape and birefringence pattern of powder samples under optical and polarized light mode. Particle size distribution of the powder samples was determined by measuring diameter along the longest axis of at least 500 particles. This study was carried out with the aid of Leica DMLP polarized microscope (Leica Microsystems Wetzlar GmbH, Germany). Images were captured using JVS colour video camera and analysed using Linksys 32 software.

3.2.3.2 Hot stage microscopy (HSM)

HSM of the co-processed excipient was carried out using Leica DMLP polarized microscope (Leica Microsystems, Ernst-Leitz-Strasse, Germany) equipped with Linkam LTS 350 hot stage (Leica Microsystems, Ernst-Leitz-Strasse, Germany). Samples were mounted on the slide and heated from 25 to 300 °C at the heating rate of 20 °C/min.

Images were captured using JVS colour video camera and analysed using Linksys32 software.

3.2.3.3 Scanning electron microscopy (SEM)

SEM was performed using a scanning electron microscope (S-3400, Hitachi Ltd., Tokyo, Japan) operated at an excitation voltage of 10 kV at different magnifications. Powders were mounted onto steel stage using double sided adhesive tape and coated with gold using ion sputter (E-1010, Hitachi Ltd., Japan).

3.2.3.4 Dynamic vapour sorption (DVS)

The moisture sorption behaviour of the powder samples were analysed using DVS (Q 5000 SA, TA Instruments, USA) at 25 °C to measure hygroscopicity. Approximately 5 – 15 mg of sample was placed in the sample holder and exposed to increasing humidity from 0 – 90 % at a step rate of 10 % for every 30 min. The sample weight was recorded at each RH throughout the experiment. Data analysis was done using Universal Analysis® software (version 4.5A).

3.2.3.5 Confocal laser scanning microscopy (CLSM)

CLSM was used to visualize the distribution of FITC-labeled gelatin in the co-processed excipient and the pictures evaluated using an image analysis system. A 488-nm line of Krypton-Argon laser and a laser power of 0.15 mW were employed.

3.2.3.6 Differential scanning calorimetry (DSC)

DSC study of the samples was conducted using DSC, Model Q2000 (TA Instruments, New Castle, USA). DSC cell was purged with 50 mL/min dry nitrogen. Accurately weighed samples (2-4 mg) were heated in standard Tzero aluminium pans in temperature range of 25 to 250 °C at a heating rate of 20 °C/min. Data analysis was performed using Universal® Analysis 2000 (version 4.5A) software. Prior to analysis,

calibration of the instrument was performed using zinc (Zn) and indium (In). Modulated differential scanning Calorimetry (mDSC) was carried out to obtain a better resolution of the glass transition event occurring in the starch-based materials.

3.2.3.7 Powder X-ray diffractometry (PXRD)

PXRD patterns of samples were recorded at room temperature on Bruker's D8 advance diffractometer (Bruker, Germany) with Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter. Analysis was performed in a continuous mode with a step size of 0.01 ° and step time of 1 sec over an angular range of 2 – 40 ° 2θ, using zero background holder. The obtained diffractograms were analysed with DIFFRAC plus EVA (ver.9.0) diffraction software.

3.2.3.8 Fourier transform infra-red (FT-IR) spectroscopy

The FT-IR spectra of all powder samples were recorded from 4000 to 650 cm^{-1} on Perkin Elmer Spectrum 400 spectrometer. Analysis of FT-IR spectra was performed using Spectrum® v3.02.01 (version 3.02.01) software.

3.2.3.9 True density

The true density of powder samples were determined in triplicate by helium pycnometry (Pycno 30, Smart Instruments, India) at 25 ± 2 °C/40 ± 2% RH.

3.2.3.10 Circular dichroism (CD) spectroscopy

CD spectra was recorded at 25 °C on a Jasco 815 spectrometer (Jasco, Tokyo, Japan) equipped with a temperature control unit using a 1 cm path length quartz cell. Samples containing pure gelatin, gelatin in co-processed excipient and FITC-labelled gelatin in the co-processed excipient were scanned at a wavelength of 200 – 250 nm in the presence of distilled water. The concentration of each sample was 0.1 % $^{w}/_{v}$.

A reference spectrum containing distilled water was also recorded. CD spectra was analysed using the spectra analysis software (Jasco Corporation, Japan).

3.2.4 Physico-mechanical properties

3.2.4.1 Bulk density, Tapped density, Carr's index and Hausner's ratio

Bulk density (BD) was calculated by carefully adding accurately weighed powder (100 g) to 250 mL measuring cylinder. The corresponding volume was read off to get the bulk density. Tapped density (TD) was calculated using USP Tap density apparatus (Electrolab, Mumbai, India) as per USP II method (2009). Carr's index (CI) and Hausner's ratio (HR) were calculated using the equations given below:

$$CI = \frac{TD - BD}{TD} \times 100\ \% \ldots\ldots\ldots\ldots\ldots\ldots Eq.5$$

$$HR = \frac{TD}{BD} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.6$$

3.2.4.2 Angle of repose (°)

The angle of repose of the powder samples was measured using the granulate flow tester (GTB, Erweka, Germany). 20 g powder was poured into the stainless steel funnel and allowed to flow out by the opening of the shutter. The height and diameter of the heap of powder formed was measured using a laser device and the data collected was used to generate the angle of repose automatically. A mean of three determinations was recorded (n=3).

3.2.5 Compaction Studies

3.2.5.1 Heckel and Kawakita analysis

Approximately 400 mg powder was weighed individually for each tablet and compressed on a Hydraulic press (Model 3912, Carver Inc., USA) at pressures ranging

from 8.8 – 106.56 MN/m^2 using a flat-faced punch and die set at a dwell time of 30 s. A minimum of three tablets were compressed at each pressure. The tablets were kept in the desiccator for 24 h to allow for elastic recovery prior to analysis. The thickness and diameter of the tablets were measured using a digital micrometre screw gauge (Mitutoyo, Japan). The equations given below were used to calculate the volume, density, relative density and porosity of the tablets respectively.

$$Volume = \pi r^2 t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.7$$

$$Apparent\ Density\ (\rho_A) = \frac{mass\ (g)}{volume\ (mL)} \ldots\ldots\ldots\ldots\ldots Eq.8$$

$$Relative\ density\ (D) = \frac{\rho_A}{\rho_T} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.9$$

$$Porosity\ (\varepsilon) = 1 - \frac{\rho_A}{\rho_T} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.10$$

where, t and ρ_T represents the radius of the tablet, thickness of the tablet and true density of the powder respectively.

The data obtained was interpreted to obtain compressibility, tabletability and compactability (CTC) profile, Heckel plot and Kawakita plot. Tabletability is represented by the plot of tensile strength against compaction pressure (Joiris *et al.*, 1998). Compressibility is represented by the plot of tablet porosity against compaction pressure (Joiris *et al.*, 1998). Compactibility is represented by the plot of tensile strength against porosity (Joiris *et al.*, 1998).

Heckel proposed a model for powder compression, which is given by:

$$\ln\left(\frac{1}{1-D}\right) = KP + A \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.11$$

where$D$ is the relative compact density at pressure P, K is the slope of the linear portion of the plot and A the intercept.

The Kawakita model describes the relationship between the degree of volume reduction of the powder and the applied pressure (Kawakita and Ludde, 1971). The Kawakita model is given by:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.12$$

$$C = 1 - \frac{\rho_0}{\rho_a} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.13$$

whereρ_a, ρ_0, C, and P represents the compact apparent density, powder bulk density, degree of volume reduction and compression pressure, respectively. The constant 'a' is the compressibility index, which is related to the total volume reduction for the powder bed, and the constant 'b' is related to the resistant forces (friction/cohesion) to compression (Hedden *et al.*, 2006).

3.2.5.2 Tablet tensile strength

Crushing strength of the tablets was measured using a tablet hardness tester (Erweka, USA). Tablet dimensions were measured using a digital calliper (Digimatic Mitutoyo Corporation, Japan). Tensile strength was calculated using the equation given below to eliminate the undesirable effect of variable tablet thickness on measured breaking force.

$$\sigma = \frac{2F}{\pi dt} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.14$$

Where σ is the tensile strength (MM/m^2), F is the observed breaking force (N), d is the diameter (mm), and t is the thickness of the compact (mm).

3.2.6 Dilution Potential Studies

Binary mixtures of ibuprofen and the co-processed excipient were obtained by mixing in the following ratios: 20:80, 40:60, 50:50, 60:40 and 80:20, using a mortar and pestle for 5 min and compressed into tablets weighing 400 mg on a Hydraulic press at 66.6 MN/m^2 (2500 PSI) and a dwell time of 30 s. The tablets were kept in a desiccator for 24

h prior to evaluation. Tensile strength of the compacts was determined and plotted against the mass fraction of the excipient. The minimum amount of the excipient required to produce tablets of desirable hardness was extrapolated from the graph. A mean of five (5) determinations was obtained for each ratio.

3.2.7 Lubricant Sensitivity Ratio

Powder samples of the co-processed excipient and magnesium stearate (1 $\%^{w}/_{w}$) were mixed in a tumbling mixer for 5 min and compressed into tablets weighing 400 mg on a Hydraulic press at 66.6 MN/m^2 and a dwell time of 30 s. The tablets were kept in a desiccator for 24 h prior to evaluation. Lubricantsensitivity was expressed as a ratio according to the relationship:

$$LSR = \frac{S_0 - S_{Lub}}{S_0} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.15$$

whereS_0 and S_{Lub} are the crushing strengths of tablets prepared without and with lubricant, respectively.

3.2.8 Formulation Studies with Ibuprofen

Tablets were formulated using ibuprofen as the drug of choice. The co-processed excipient was used to prepare tablets by direct compression and compared with two commercially available co-processed excipients, Prosolv® and StarLac®. The target tablet weight was set at 400 mg and a batch size of 200 tablets was prepared for each formulation. The tablet formula is given below in Table 3.4.

Table 3.4: Formula for preparing Ibuprofen tablets using StarGelaSil, Prosolv® and StarLac® as multifunctional excipients

Ingredients	Batch of Tablets					
	I		II		III	
	1 tab (mg)	200 tabs (g)	1 tab (mg)	200 tabs (g)	1 tab (mg)	200 tabs (g)
Ibuprofen (50 %)	200	40	200	40	200	40
SGS (49 %)	196	39.2	-	-	-	-
Prosolv® (49 %)	-	-	196	39.2	-	-
StarLac® (49 %)	-	-	-	-	196	39.2
Mag.stearate (1 %)	4	0.8	4	0.8	4	0.8
Total (100 %)	**400**	**80**	**400**	**80**	**400**	**80**

Key:-

Batch I: StarGelaSil Tablets

Batch II: Prosolv® Tablets

Batch III: StarLac® Tablets

A sample of ibuprofen (40 g) was weighed on an electronic balance and mixed with 39.2 g of the excipient using a mortar and pestle for 5 min. 0.8 g of magnesium stearate was added to the powder mix in a turbula mixer and allowed to mix for another 5 min. Tablets were compressed using the Rimek rotary tablet press fitted with flat-faced 12 mm punch and die tooling. The punches were separated by a distance of 4 mm to maintain the compression force during tableting. The speed of rotation was set at 14 rpm. Tablets were collected and stored away in the desiccator for 24 h at 23 ± 2 °C to allow for elastic recovery to prevent capping or lamination before any further study.

3.2.9 Tablet Evaluation

3.2.9.1 Weight variation

Twenty tablets were weighed individually and the mean weight calculated. The standard deviation was also recorded (USP/NF, 2009).

3.2.9.2 Tablet thickness and diameter

The thickness and diameter of tablets were measured using the digital micrometre screw gauge (Mitutoyo, Japan). The mean of ten (10) determinations was recorded with standard deviation.

3.2.9.3 Tensile strength

Tensile strength of ten (10) tablets was determined as per the method already described above.

3.2.9.4 Friability

Tablet friability was tested according to USP 32/NF 27 specifications (2009). A friabilator was employed to determine tablet friability. Ten tablets were weighed and

placed in a rotating drum at 25 rpm for 4 min. The tablets were de-dusted and reweighed. The percentage friability was calculated using the formula given below:

$$\% \text{ friability} = \frac{W_i - W_f}{W_f} \times 100 \ldots\ldots\ldots\ldots\ldots Eq.16$$

where W_i is the initial weight of tablet and W_f is the final weight of tablets.

3.2.9.5 Disintegration test

Disintegration times of tablets were evaluated 24 h after compaction using six replicates. Measurements were performed on a disintegration apparatus following the method described in the USP 32/NF 27 (2009). The test was carried out without discs in distilled water regulated at 37 ± 2 °C. The tablet was considered disintegrated at the moment when there was no remainder in the basket.

3.2.9.6 In-vitro drug release studies

Prior to dissolution studies, the calibration curve for ibuprofen was obtained by preparing a stock solution of ibuprofen (0.1 mg/mL) in Phosphate buffer (pH 7.2). Serial dilutions of the stock solution ranging from 1 – 10 µg/mL were prepared by diluting with phosphate buffer (pH 7.2). Absorbance readings were taken at 221 nm and a linear plot of absorbance against concentration (µg/mL) was generated. The equation of the straight line (y = 0.0951x) was used to calculate the amount of drug released at specific time intervals during dissolution studies.

Dissolution studies was carried out using the USP Apparatus II (paddle) method (USP 32/NF 27) (2009) on the dissolution tester (USP). 900 mL of phosphate buffer (pH 7.2) was prepared and utilized as dissolution medium. The temperature of the dissolution medium and speed of rotation were set at 37 ± 0.5 ° C and 50 rpm respectively. Five millilitre aliquots were withdrawn at specific time intervals (5, 10, 20, 30, 45 and 60 min) and replaced with equal volume of phosphate buffer (pH 7.2) at the same

temperature for a period of 1 h. Each sample was filtered using a 0.2 µ membrane disc filter and suitably diluted (1 in 10) with phosphate buffer (pH 7.2). The amount of drug released was determined spectrophotometrically by taking absorbance readings at 221 nm using the UV/VIS spectrophotometer (Lambda 35, PerkinElmer, USA).

Similarity factor ($f2$) was used to compare the dissolution profile of the different formulations. The formula is given below:

$$f\mathbf{2} = \mathbf{50} \times \boldsymbol{log}\left\{\left[\mathbf{1} + \left(\frac{\mathbf{1}}{\boldsymbol{n}}\right)\sum(\boldsymbol{R_t} - \boldsymbol{T_t})^{\mathbf{2}}\right]^{-\mathbf{0.5}} \times \mathbf{100}\right\} \ldots\ldots\ldots \boldsymbol{Eq.17}$$

where$f\mathbf{2}$ = Similarity factor

n = number of time points where percentage drug release for both products is ≥ 85 %

Rt = Cumulative percentage dissolved of reference product at time t.

Tt = Cumulative percentage dissolved of test product at time t.

CHAPTER FOUR

4.0 RESULTS

4.1 Selection of an optimized composition using DoE

The Design of Experiment (DoE) approach was used to optimize and select the best possible combination of the three excipients in preparing a co-processed excipient that will deliver the desired response of tensile strength and disintegration in the final formulation using the simple centroid (SC) experimental design. A summary of the tablet responses obtained for each experimental formulation is presented in Table 4.1. The responses obtained ranged from 2.34 – 4.34 MN/m^2 for tensile strength and 0.16 – 4.08 min for disintegration time for all the experimental batches. Formulations having a higher concentration of gelatin in the co-processed mixture produced tablets with higher tensile strength and longer disintegration time.

Table 4.1: Tablet responses for the experimental formulations containing different proportions of the interacting excipients involved in co-processing

Batch code	Factors			Response	
	CS (A) (%)	GEL (B) (%)	CSD (C) (%)	TS (Y_1) (MPa)	DT (Y_2) (min)
1	94	5	1	3.76	1.82
2	91.33	6.33	2.33	2.34	0.6
3	90	5	5	3.84	0.73
4	92.66	3.67	3.67	3.1	0.22
5	94	1	5	2.7	0.23
6	98	1	1	2.59	0.37
7	90	9	1	4.34	4.08
8	94	5	1	3.8	1.79
9	91.33	2.33	6.33	4.22	0.58
10	98	1	1	2.6	0.41
11	90	1	9	3.02	0.16
12	95.33	2.33	2.33	3.19	0.75
13	90	1	9	3.05	0.18
14	90	9	1	4.28	3.98

CS: Cassava starch
GEL: Gelatin
CSD: Colloidal silicon dioxide
TS: Tensile strength
DT: Disintegration time

These responses (dependent variables) were collected in the form of data and analysed using the Design – Expert 9 (trial version) software (Stat-Ease Inc., USA) by fitting a model for each response. The summary statistics of the analysis of the models fitted for each response using ANOVA is presented in Table 4.2.

Table 4.2: Summary statistics of model analysis by ANOVA for each response evaluated from the data collected from the experimental formulations

Response	**Model**	**R^2**	**Lack of Fit *p* value**	***p* value**	***F* value**
Tensile strength	Special Quartic	0.998	0.962	8.4×10^{-8}	1224.8
Disintegration time	Special Quartic	0.999	0.412	2.9×10^{-8}	1858.8

Key:-

R^2: Co-efficient of determination

p value: Level of significance at $p<0.05$

F value: Variance of the group means

The model equations representing the mathematical expression of the relationship between the factors (components, independent variables) and the responses (dependent variables) are given below. Y_1 and Y_2 represent tensile strength and disintegration time respectively. The equations show that gelatin (B) had the most prominent effect on both responses with respect to the magnitude of its coefficient term.

$$\mathbf{Y_1} = 2.60A + 4.31B + 3.04C + 1.31AB - 0.46AC + 0.67BC + 23.48A^2BC - 171.10AB^2C + 116.72ABC^2$$

$$\mathbf{Y_2} = 0.39A + 4.03B + 0.17C - 1.63AB - 0.22AC - 5.50BC + 31.67A^2BC - 133.57AB^2C + 60.03ABC^2$$

The model was further analysed using ANOVA and the *p* values showing the degree of significance of each model term in the equations for tensile strength and disintegration time is given in Table 4.3. All the model terms for tensile strength were significant at $p < 0.05$ indicating that they all contributed to the tensile strength. A similar scenario was observed for disintegration time where all the terms in the equation were significant at $p < 0.05$ except for AC.

Table 4.3: Model terms for each regression equation representing the two responses and the corresponding *p* value showing the degree of significance

	Model terms								
Response	**A**	**B**	**C**	**AB**	**AC**	**BC**	**A^2BC**	**AB^2C**	**ABC^2**
Y_1=Tensile strength	2.60	4.31	3.04	1.31	-0.46	0.67	23.48	-171.1	116.7
p=	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0090	0.0018	0.0002	< 0.0001	< 0.0001
Y_2=Disintegration time	0.39	4.03	0.17	-1.63	-0.22	-5.50	31.67	-133.6	60.03
p=	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.275	< 0.0001	0.0005	< 0.0001	< 0.0001

A = Cassava starch **B** = Gelatin **C**= Colloidal silicon dioxide

A, B, and C: First order terms

AB, AC, and BC: Second order terms

A^2BC, AB^2C, and ABC^2: Fourth order terms

Based on the regression model obtained above, a contour plot was generated for each response to display the effect of the interacting excipients on the tablet responses of tensile strength and disintegration time. The contour plot and its corresponding 3D surface plot for each response are presented as Figures 4.1 - 4.4.

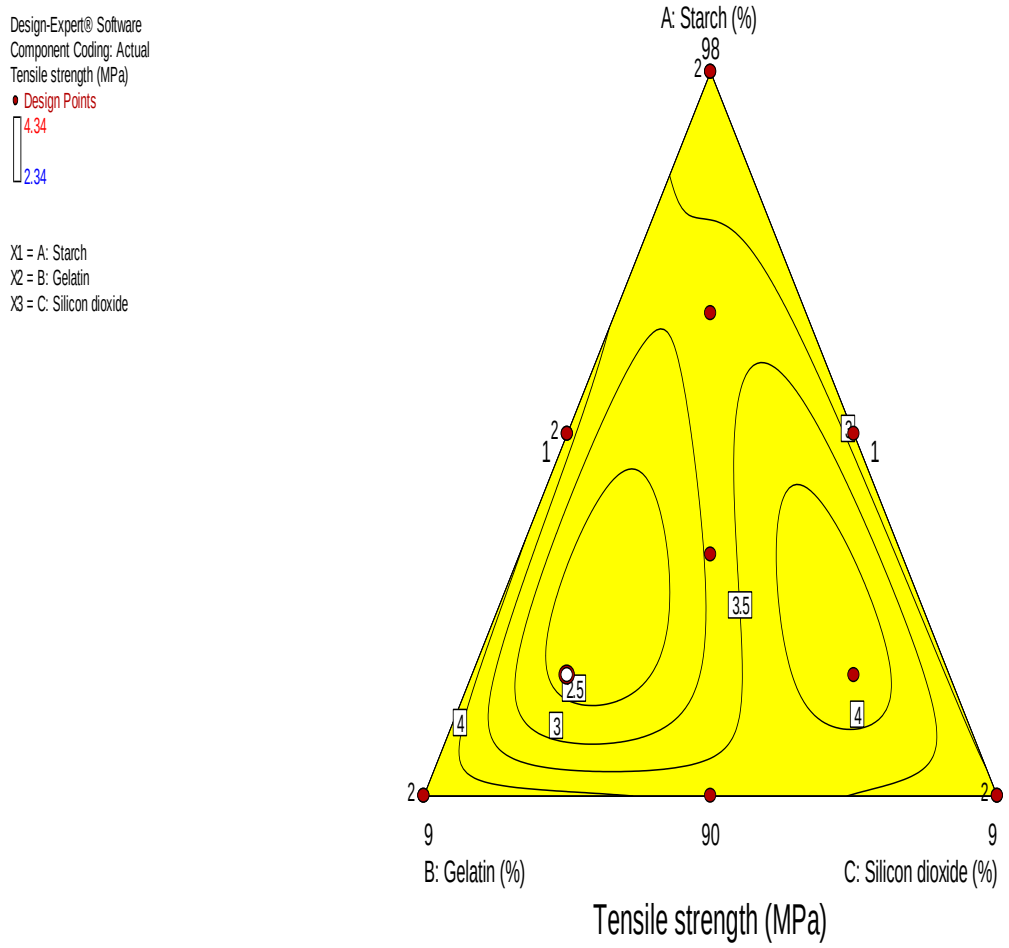

Figure 4.1: Contour plot showing the effect of each excipient on the tensile strength

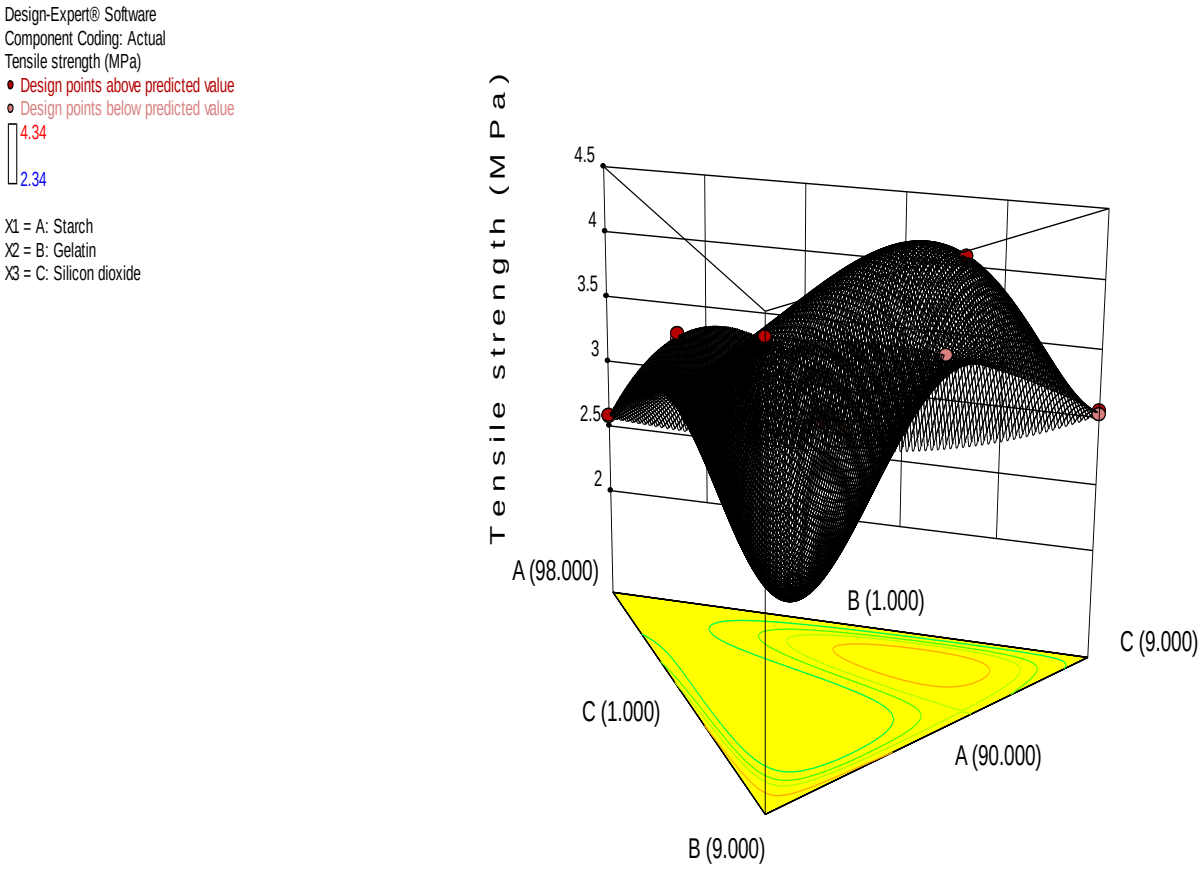

Figure 4.2: Surface plot showing the effect of each excipient on the tensile strength

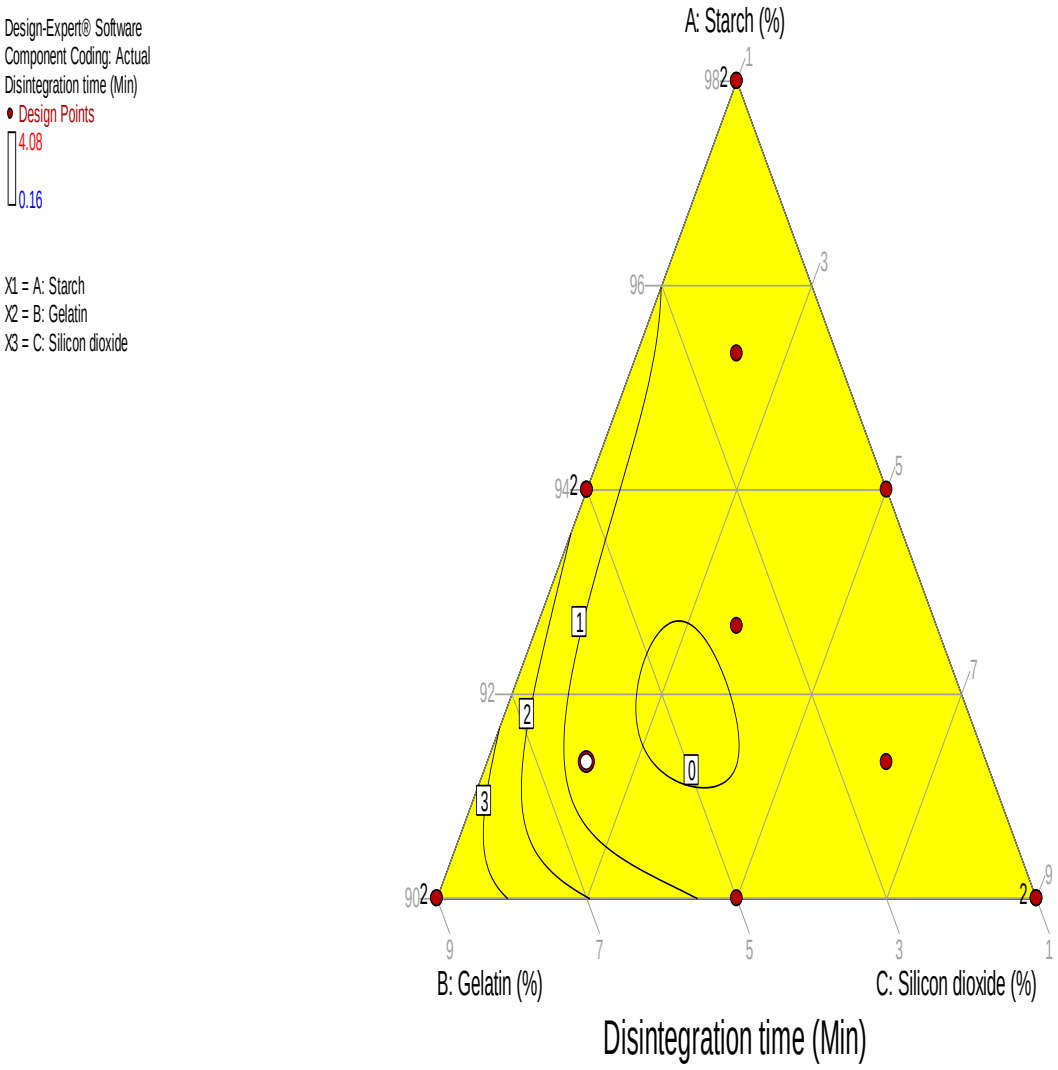

Figure 4.3: Contour plot showing the effect of each excipient on the disintegration time

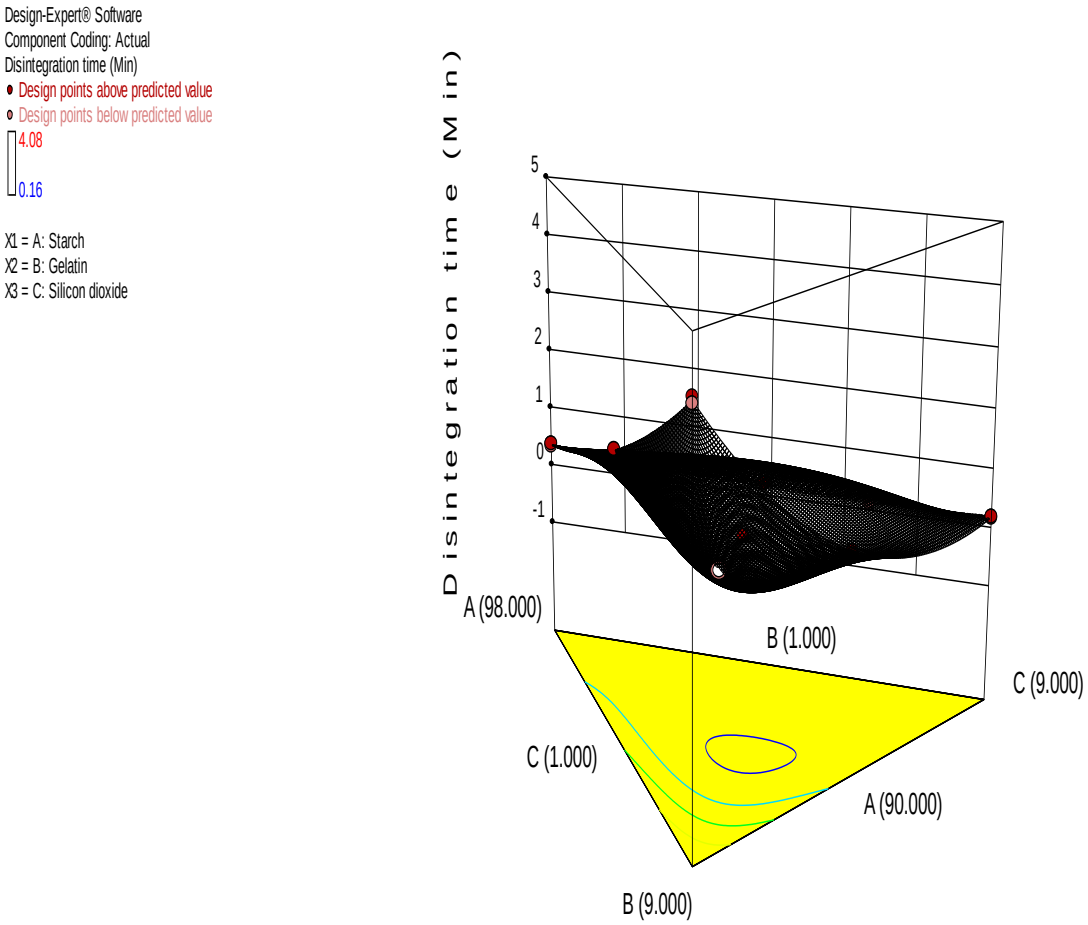

Figure 4.4: Surface plot showing the effect of each excipient on the disintegration time

Following the results of the analysis, numerical and graphical optimization were applied to determine the optimum proportion of excipients required to develop the co-processed excipient that will deliver the desired tablet characteristics as predicted by the Design Expert software. Seven (7) possible combinations were predicted by software and ranked using a desirability scale based on the degree of fitting of each combination to the criteria set during optimization (Table 4.4). Based on the rating of this scale, the first solution with a desirable value of 0.979 was selected by the software as the optimized composition for the co-processed excipient.

Table 4.4: Prediction of the optimized composition of the co-processed excipient showing the possible combinations of interacting excipients and expected responses

Number	Cassava Starch	Gelatin	Colloidal silicon dioxide	Tensile strength	Disintegration time	Desirability scale
1	90	7.5	2.5	4.2	2.5	0.979
2	92.6	6.4	1.0	4.0	2.5	0.961
3	94	5.0	1.0	3.8	1.8	0.843
4	91.6	1.6	6.8	3.9	0.6	0.606
5	95.8	1.7	2.5	3.1	0.7	0.544
6	93	3.0	4.0	3.7	0.6	0.435
7	91.5	1	7.5	2.9	0.2	0.211

A representative overlay contour plot showing the combined responses and the corresponding factor settings is given as Figure 4.5.

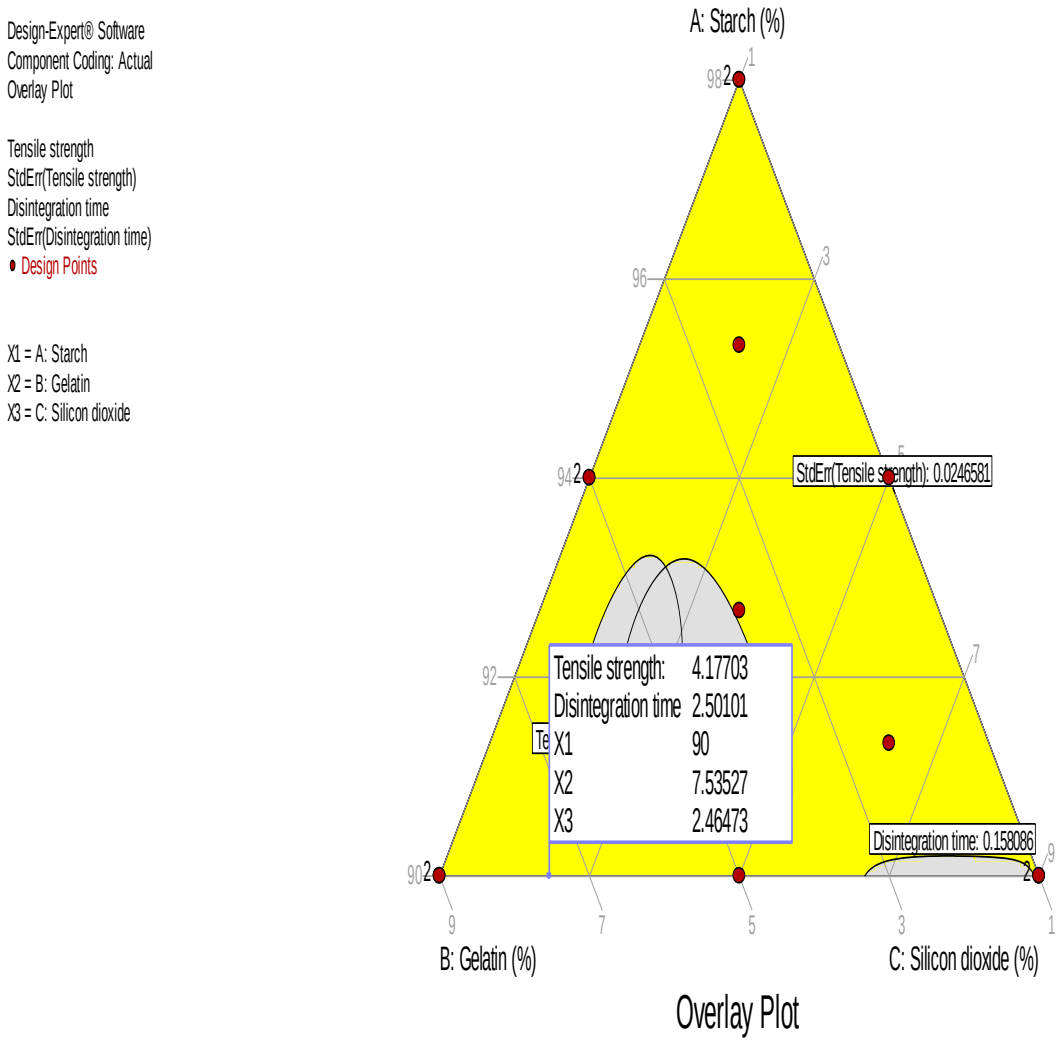

Figure 4.5: Overlay contour plot for tensile strength and disintegration time showing the factor settings (excipients) and the expected responses

Based on the prediction of the software, the first three solutions were selected on the basis of the desirability scale and prepared to formulate tablets. The results obtained from the evaluation of tablet responses are presented in Table 4.5. The values obtained were closely related to the prediction of the software.

Table 4.5: Comparison between the predicted and observed responses of the three selected optimized formulations

	Response			
	Tensile strength (MPa)		Disintegration time (min)	
Solutions	**Predicted**	**Observed**	**Predicted**	**Observed**
SGS-A	4.2 (0.025)*	4.4 (0.15)	2.5 (0.04)	1.6 (0.04)
SGS-B	4.0 (0.025)	4.0 (0.22)	2.5 (0.04)	1.9 (0.08)
SGS-C	3.8 (0.025)	3.9 (0.16)	1.8 (0.04)	1.02 (0.07)

SGS-A: 90/7.5/2.5 * Standard deviation values in parentheses
SGS-B: 92.6/6.4/1.0
SGS-C: 94/5.0/1.0

The results of the supporting studies carried out to select the best possible combination amongst the three selected is presented in Table4.6. Flow properties was assessed by measuring the angle of repose, bulk and tapped densities, Carr's index (CI) and Hausner's ratio (HR).The values obtained for angle of repose was less than 30 ° for the three formulations of the co-processed excipient. The CI and HR ranged from 14.7 – 21.6 % and 1.17 – 1.27 respectively with SGS-A having the least values for both parameters. The lubricant sensitivity ratio (LSR) was ranked in the following order: SGS-C < SGS-A < SGS-B.

Table 4.6: Flow indices and lubricant sensitivity ratio for the three optimized formulations of the co-processed excipient

Excipient	AR (°)	BD (g/mL)	TD (g/mL)	HR	CI (%)	LSR (%)
SGS-A	29.5 (0.15)*	0.44 (0.01)	0.52 (0.02)	1.17 (0.03)	14.7 (2.36)	36.6 (0.43)
SGS-B	28.8 (0.31)	0.41 (0.01)	0.52 (0.02)	1.27 (0.03)	21.6 (2.11)	41.1 (2.63)
SGS-C	27.2 (0.03)	0.42 (0.01)	0.54 (0.02)	1.27 (0.01)	21.1 (0.52)	33.9 (5.88)

AR: Angle of repose
BD: Bulk density
TD: Tapped density
HR: Hausner's ratio
CI: Carr's index
LSR: Lubricant sensitivity ratio
* Standard deviation values in parentheses

The result of the dilution potential studies is displayed as Figure 4.6. The dilution potential plotshowed a marginal difference in the carrying capacity of the three optimized formulations.The compacts of SGS-A had higher tensile strength across the various ratios when compared to SGS-B and SGS-C.

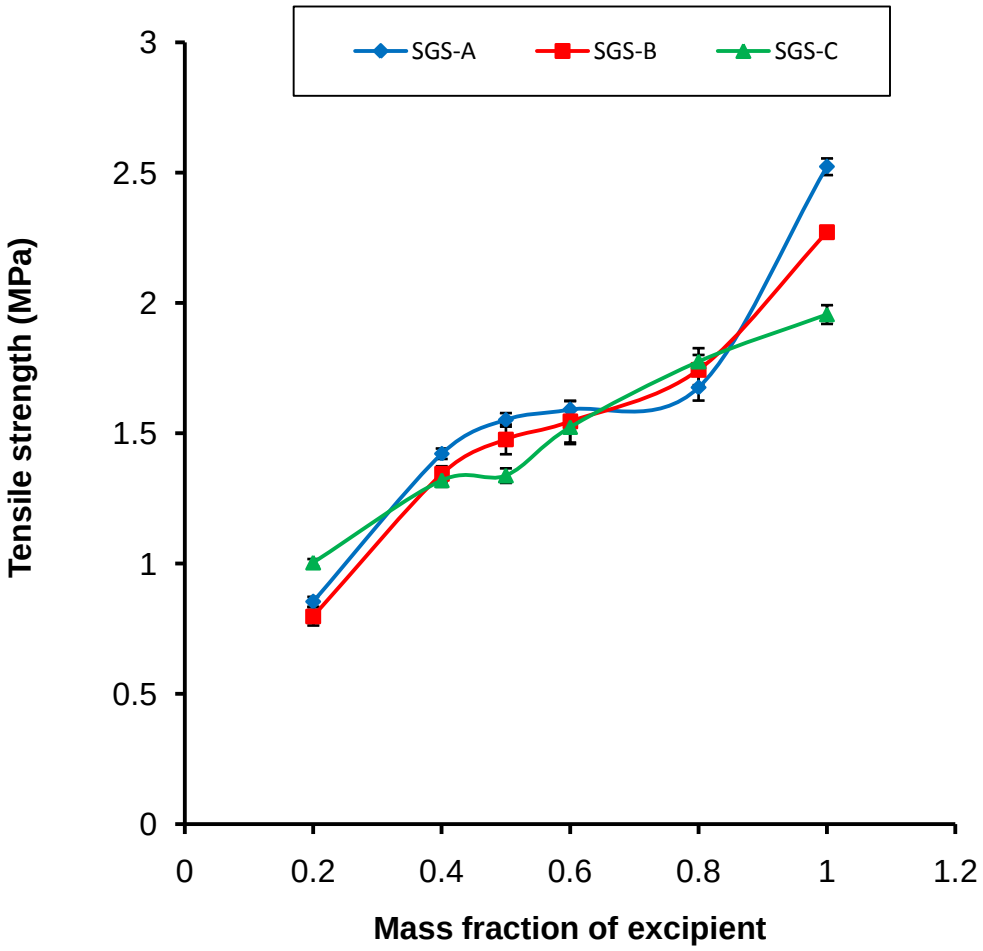

Figure 4.6: Dilution potential plot showing the relationship between the mass fraction of the excipient and tensile strength (MN/m^2)

The results of the dynamic vapour sorptiontest carried out to measure the amount of moisture sorbed by the three optimized formulations is presented in Figure 4.7. The % weight change recorded at 80 % RH was ranked in the following order: SGS-A < SGS-B= SGS-C.

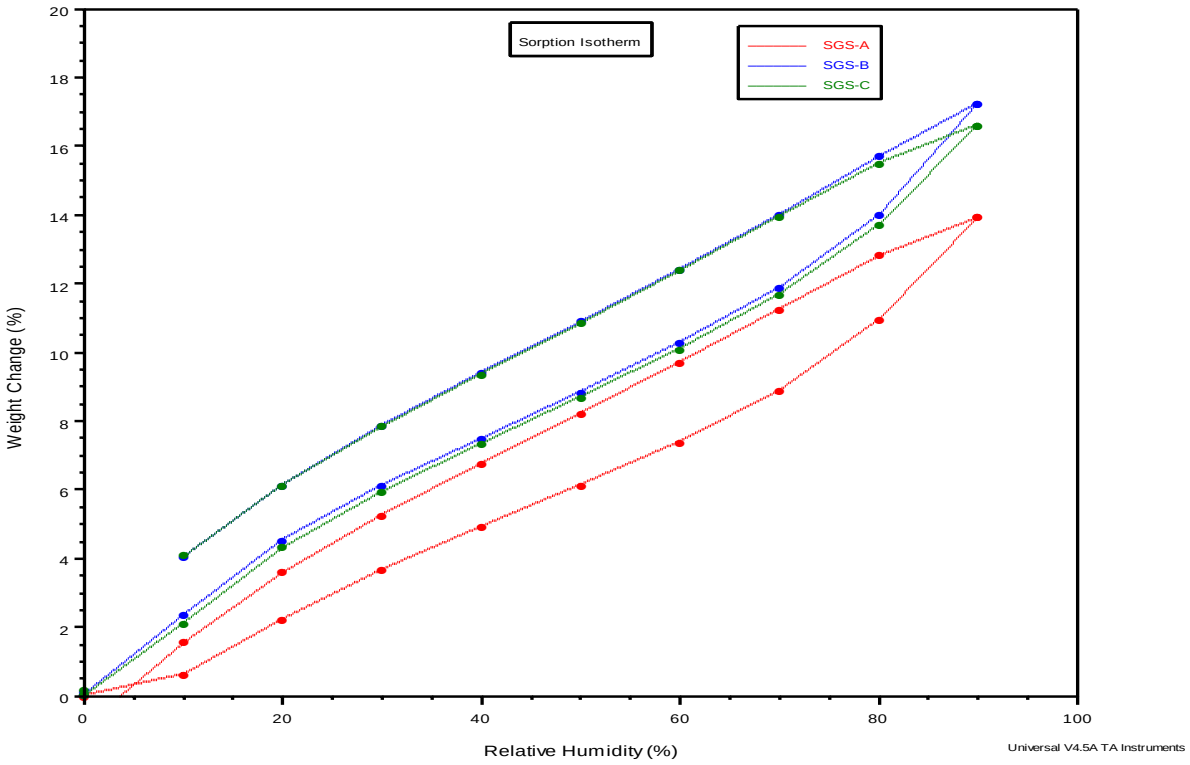

Figure 4.7: Moisture sorption/desorption isotherms of SGS-A, SGS-B and SGS-C showing the relationship between the relative humidity (% RH) and weight change (%)

Based on the findings and observations of the experimental design and other supporting studies, SGS-A was selected as the optimized composition of the co-processed excipient and was carried forward for further studies.

4.2 Solid-state Characterization

4.2.1 Optical and polarized microscopy

The images captured under the microscope for cassava starch (CS) and *StarGelaSil* (SGS) are displayed as Plates I and II respectively. The optical images revealed that both materials are spherical in shape. The polarized images showed birefringence in both materials.

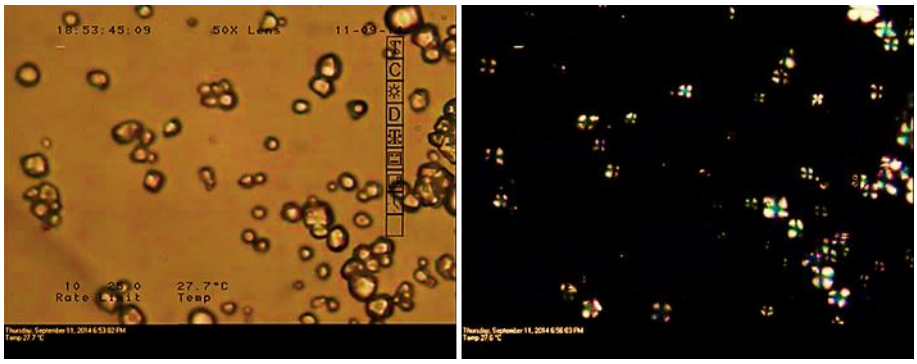

Plate I: Optical and polarized images of CS (x 50)

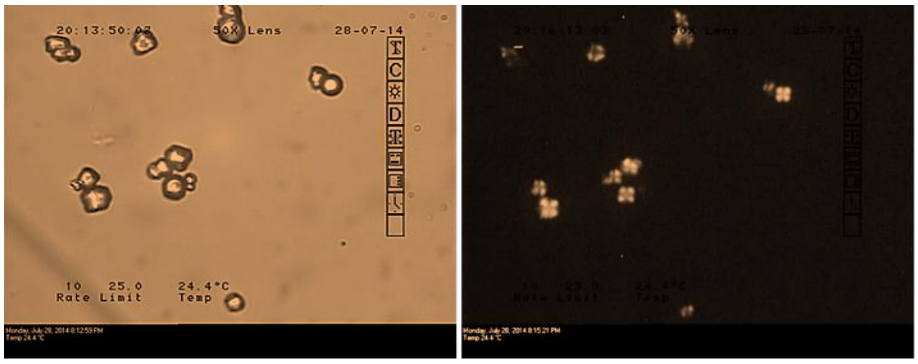

Plate II: Optical and polarized images of SGS (x 50)

Particle size analysis of CS and SGS is presented in Table 4.7. There was an increase in the particle size of SGS as a result of co-processing. The polydispersity index (PDI) of SGS was greater than that of CS indicating a wider variation in particle size distribution.

Table 4.7: Particle size analysis of cassava starch (CS) and *StarGelaSil* (SGS)

	Particle size distribution				
Material	**D_{10}(µm)**	**D_{50}(µm)**	**D_{90}(µm)**	**Range (µm)**	**Polydispersity index (PI)**
SGS	15.5	29	57.8	6.3 - 110.9	1.46
CS	8.9	12.3	16.8	5.6 - 25	0.64

The particle size distribution curves displayed as Figures 4.8 and 4.9 reveal a uniform distribution for CS and a less uniform distribution for SGS.

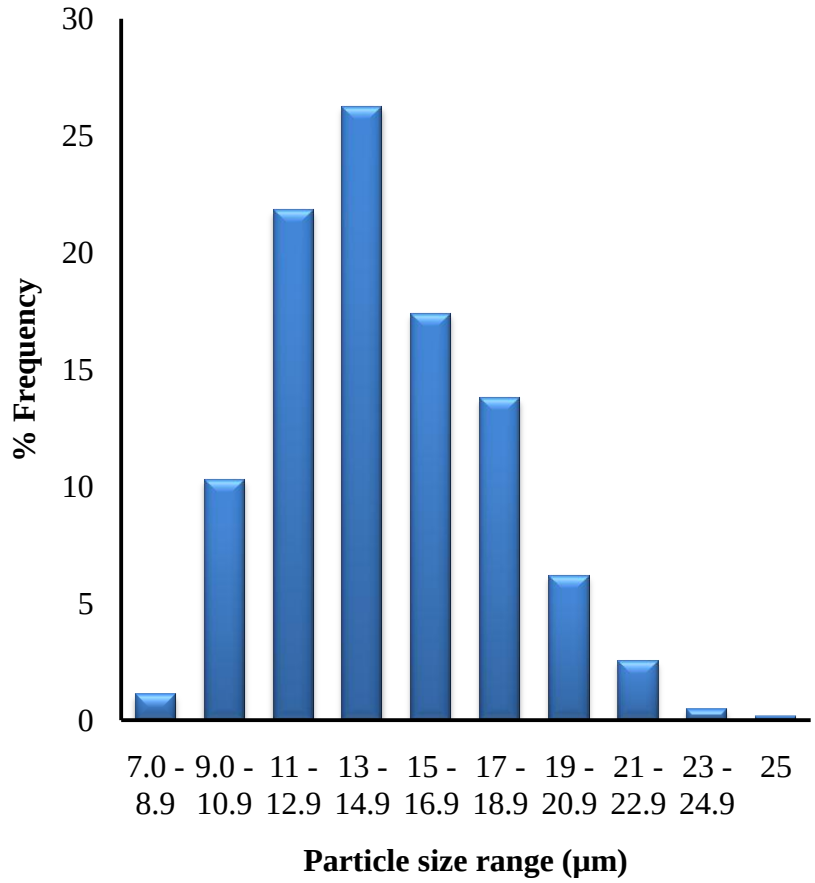

Figure 4.8: Particle size distribution showing the relationship between the particle size range (µm) and % frequency for CS

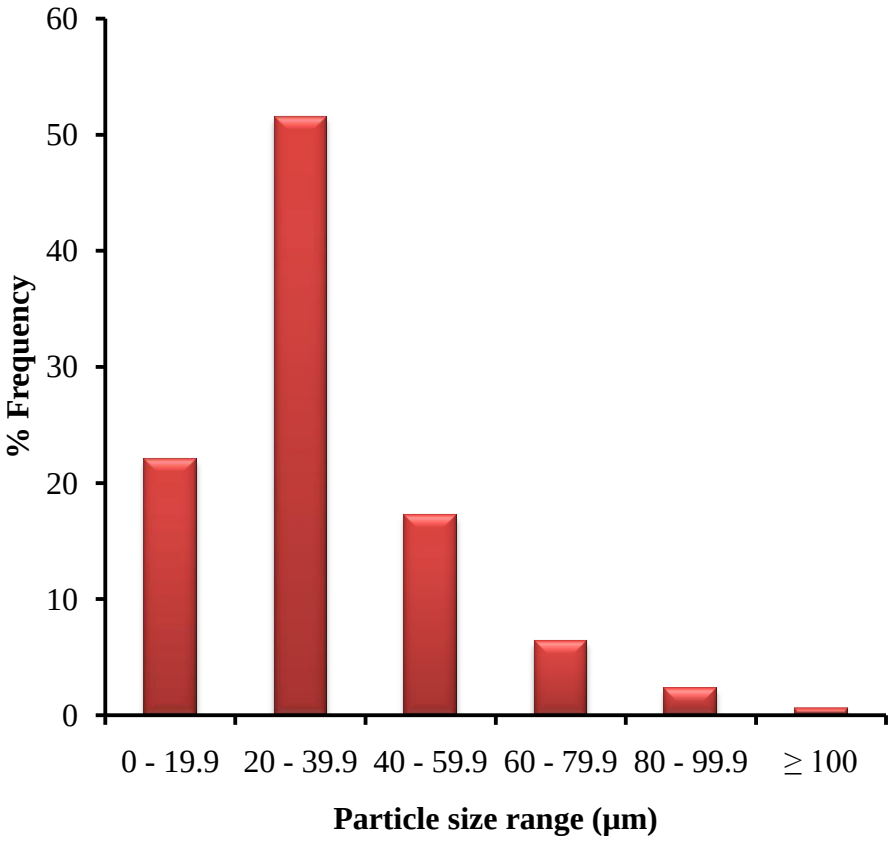

Figure 4.9: Particle size distribution showing the relationship between particle size range (µm) and % frequency for SGS

4.2.2 Hot stage microscopy (HSM)

The images for HSM studies are presented as Plate III. The results reveal that there were no changes in the early stages of heating and onset of degradation occurred at temperatures above 240 ° C. No melting event occurred during heating.

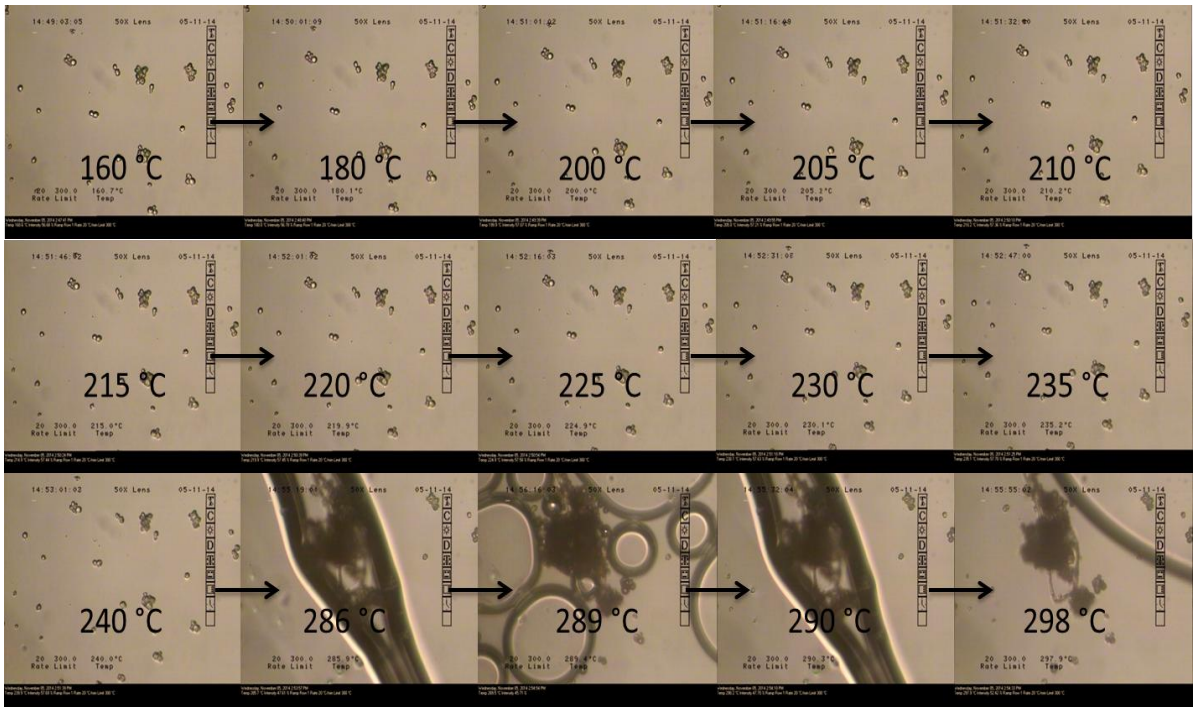

Plate III: HSM images of SGS

4.2.3 Scanning Electron Microscopy (SEM)

The SEM images for CS, GEL, CSD, SGS-PM and SGS is given below as Plate IV. CS particles appeared spherical with smooth surfaces compared to SGS which was equally spherical with rough surface and some degree of irregularity.

The SGS-PM image showed the various particles of the three excipients occurring singly in the mixtureas against the composite particles observed with SGS. Images of GEL and CSD revealed that particles were far from spherical with GEL particles appearing elongated and CSD occurring as flakes.

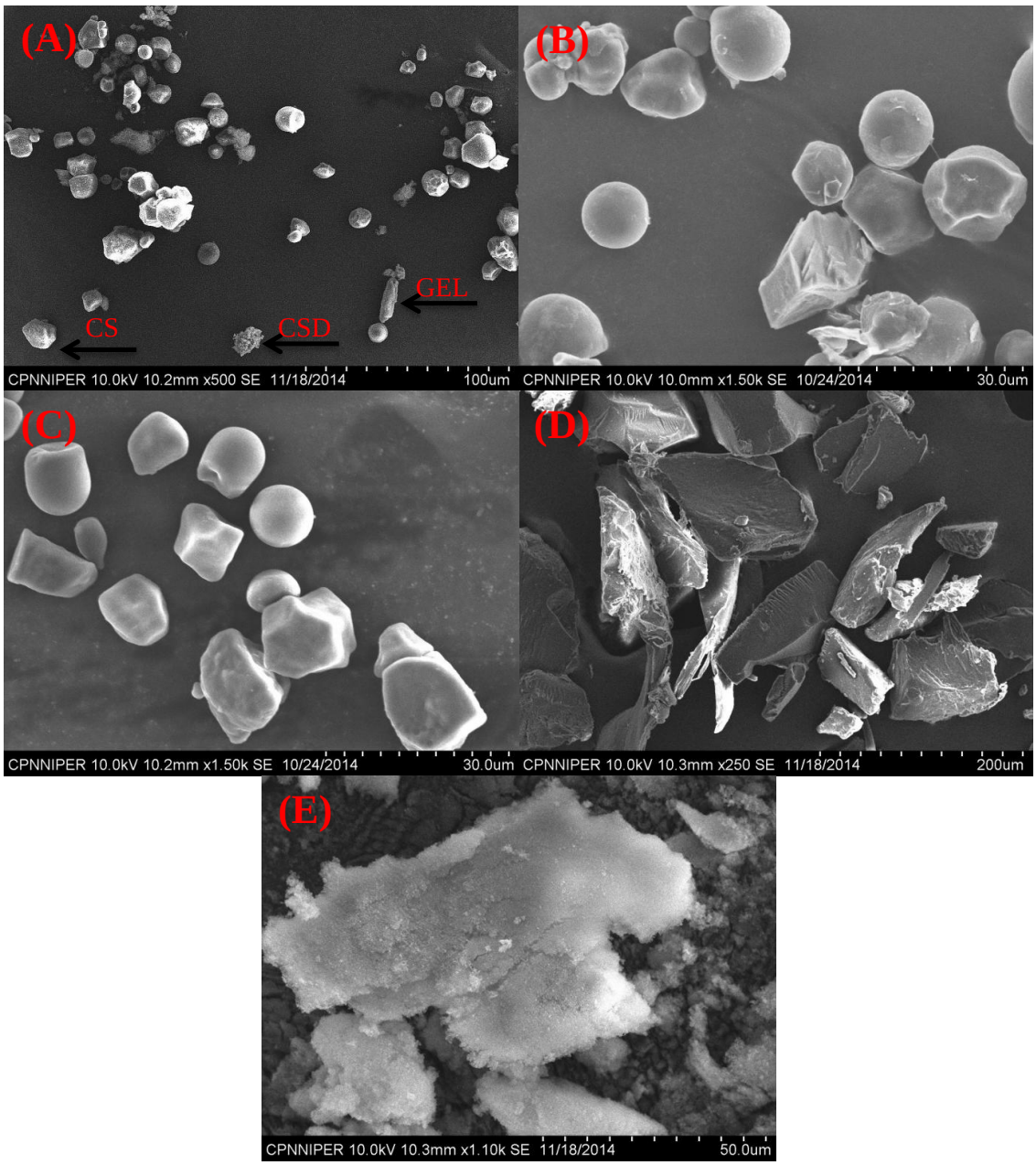

Plate IV: SEM images of (A) SGS-PM, (B) SGS, (C) CS, (D) GEL, and (E) CSD

4.2.4 Confocal laser scanning microscopy (CLSM)

The CLSM image displayed as Plate V shows a uniform spread of gelatin in the co-processed matrix.

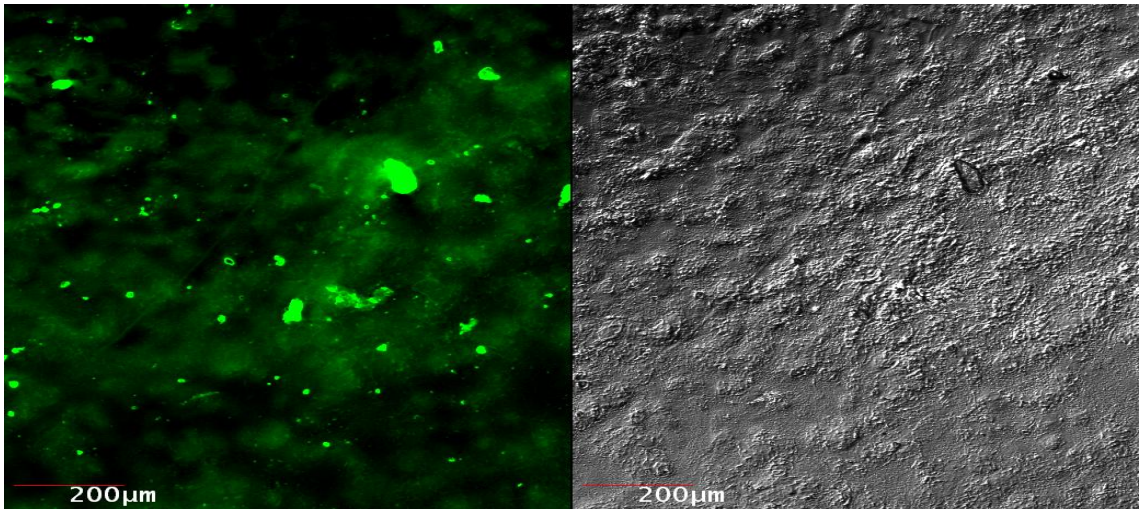

Plate V: CLSM image of SGS prepared with FITC-GEL showing the distribution of gelatin in the co-processed excipient

4.2.5 Differential Scanning Calorimetry (DSC)

Overlay plots of the DSC thermograms of CS, SGS-PM, and SGS and IBU and IBU + SGS are presented as Figures 4.10 and 4.11. The DSC thermogram of CS did not reveal any melting endotherm but a glass transition event that occurred at 256.93°C. Glass transition events also occurred for SGS-PM and SGS respectively at 255.89°C and 254.42°C. The DSC scan confirmed that the glass transition event took place prior to degradation which was observed during the HSM studies.

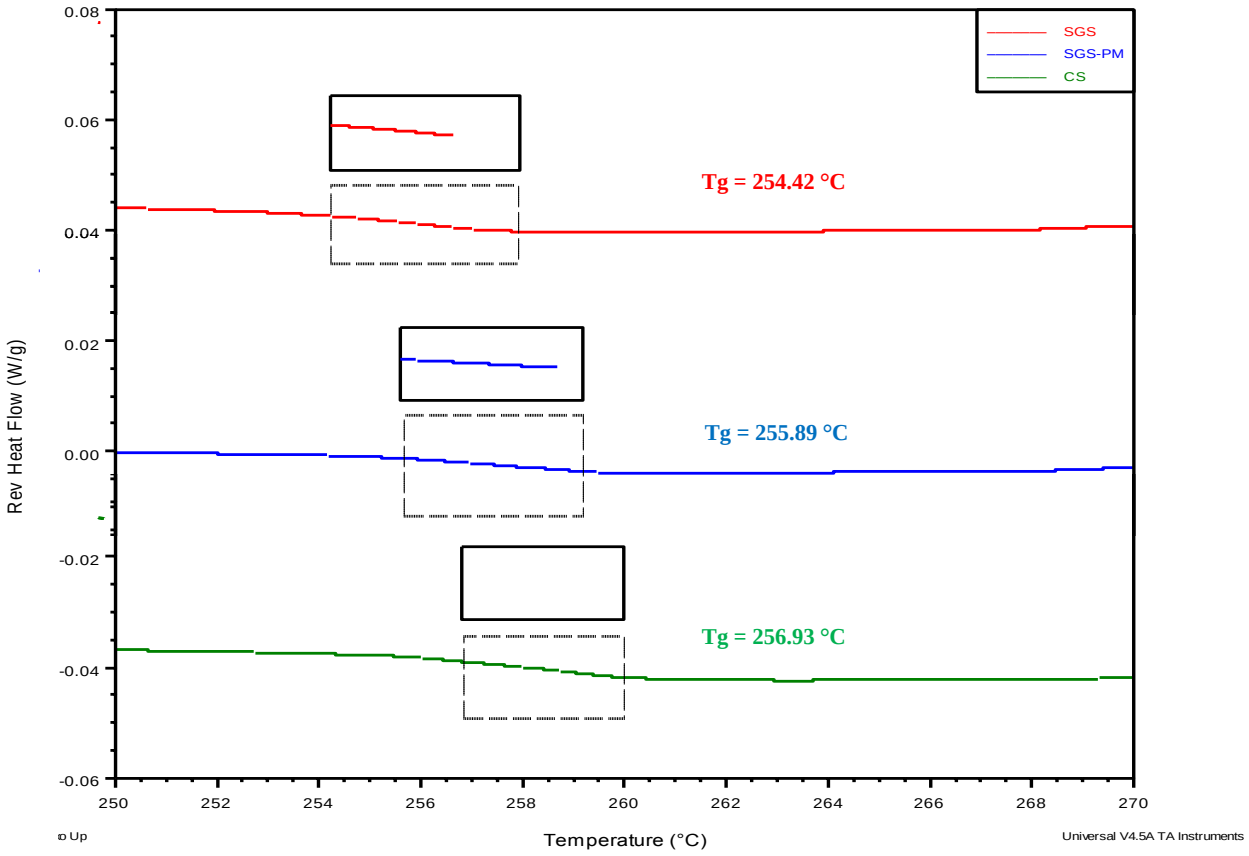

Figure 4.10: Overlay DSC thermograms of SGS, SGS-PM and CS

A melting peak at 79.62 °C was observed in the DSC thermogram of IBU. In the presence of SGS, the melting point was lowered to 78.11 °C. There was a decrease in the intensity of the melting peak of IBU.

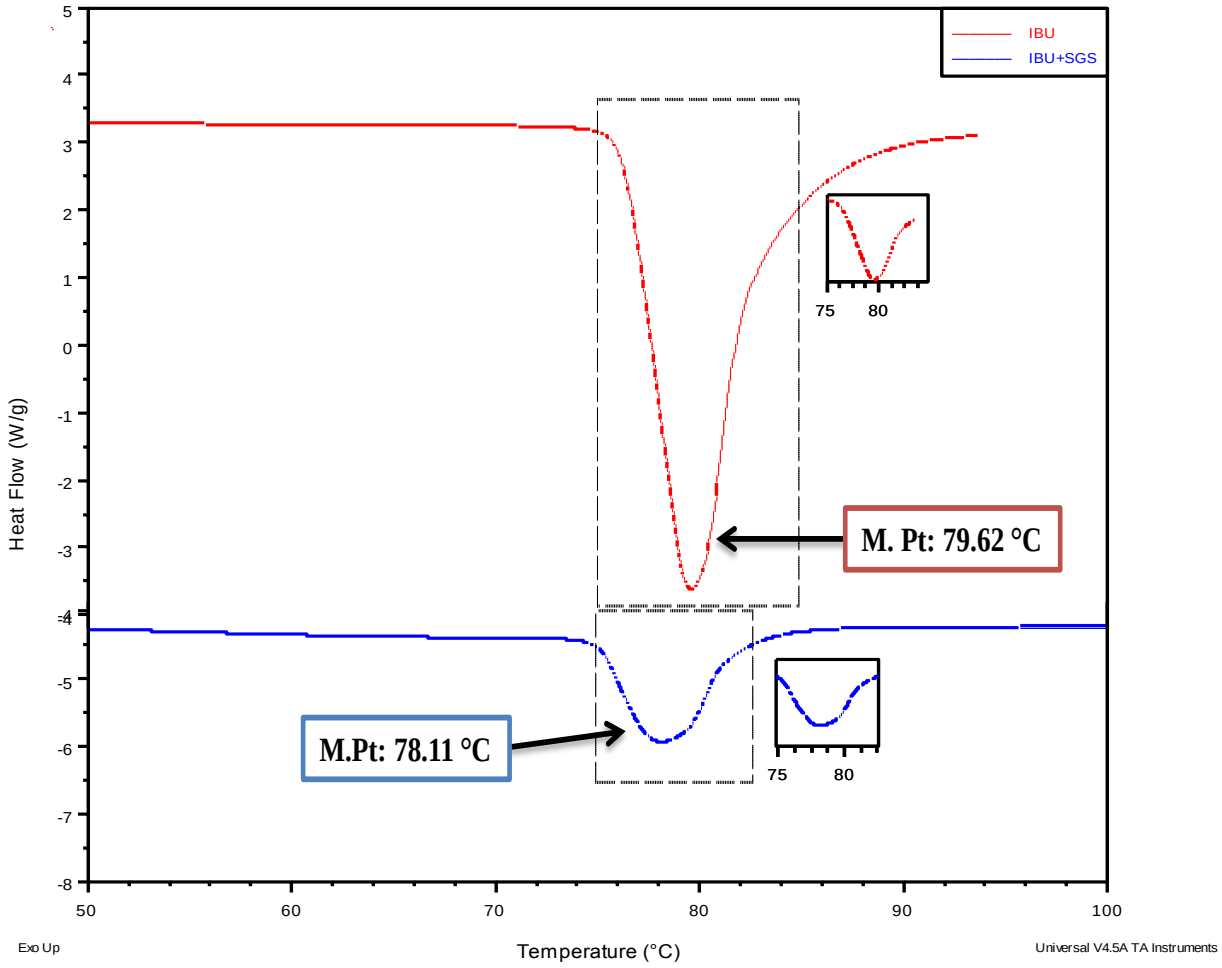

Figure 4.11: Overlay DSC thermograms of IBU and IBU + SGS

4.2.5 Powder X-ray diffraction (PXRD)

The diffraction curves of CSD, GEL, CS and SGS is presented as Figure 4.12. The diffraction curves of GEL and CSD was characterized by a distinct halo pattern with no appearance of distinct peaks. A few broad peaks appeared in the diffraction curve of CS which was maintained in the diffraction curve of SGSpointing to some degree of crystallinity which was observed under polarized microscopy.

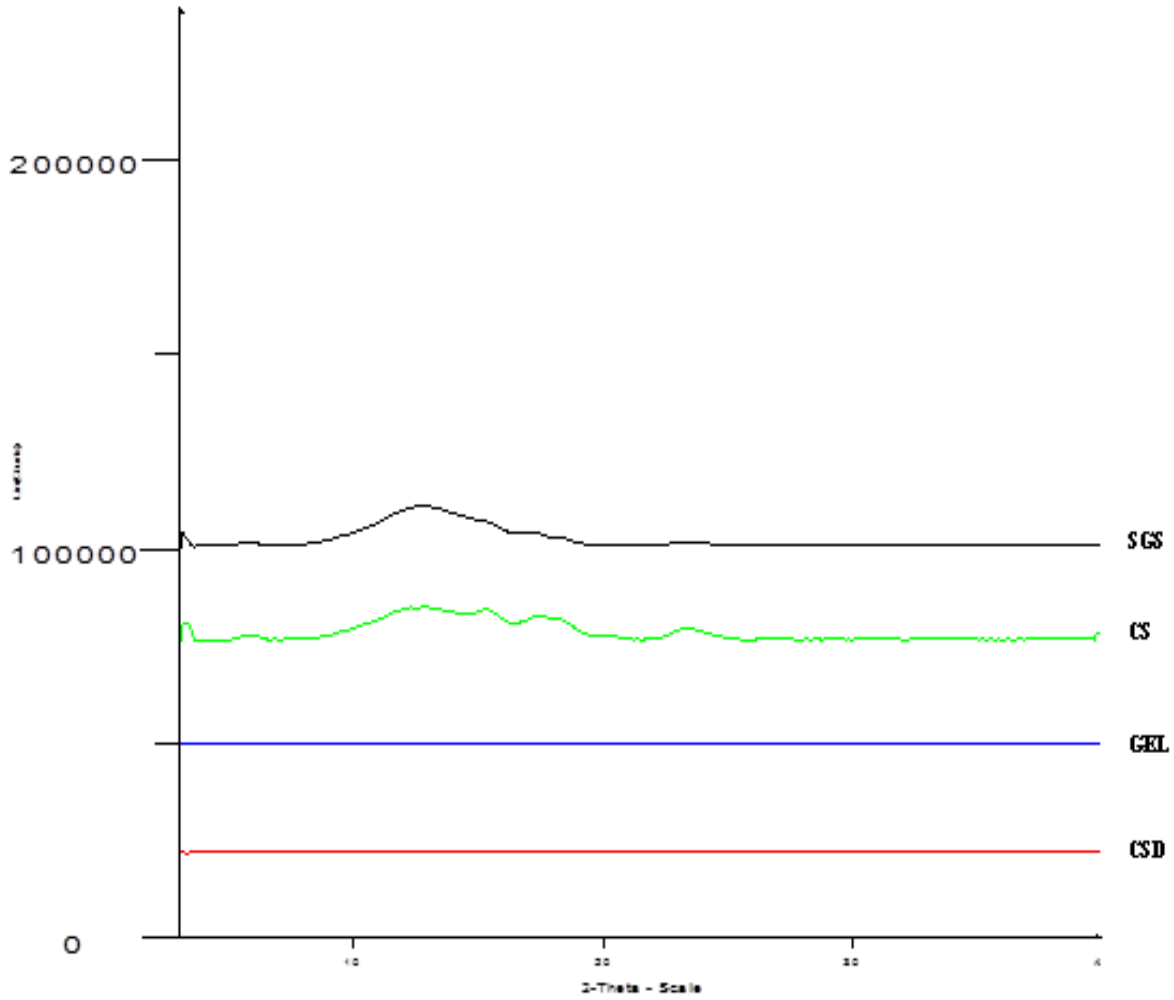

Figure 4.12: PXRD overlay of SGS, CS, GEL and CSD

The diffraction curves of SGS and SGS-PM is presented as Figure 4.13. There was essentially no difference in the diffraction patterns of the two materials. The position and intensity of the peaks were maintained.

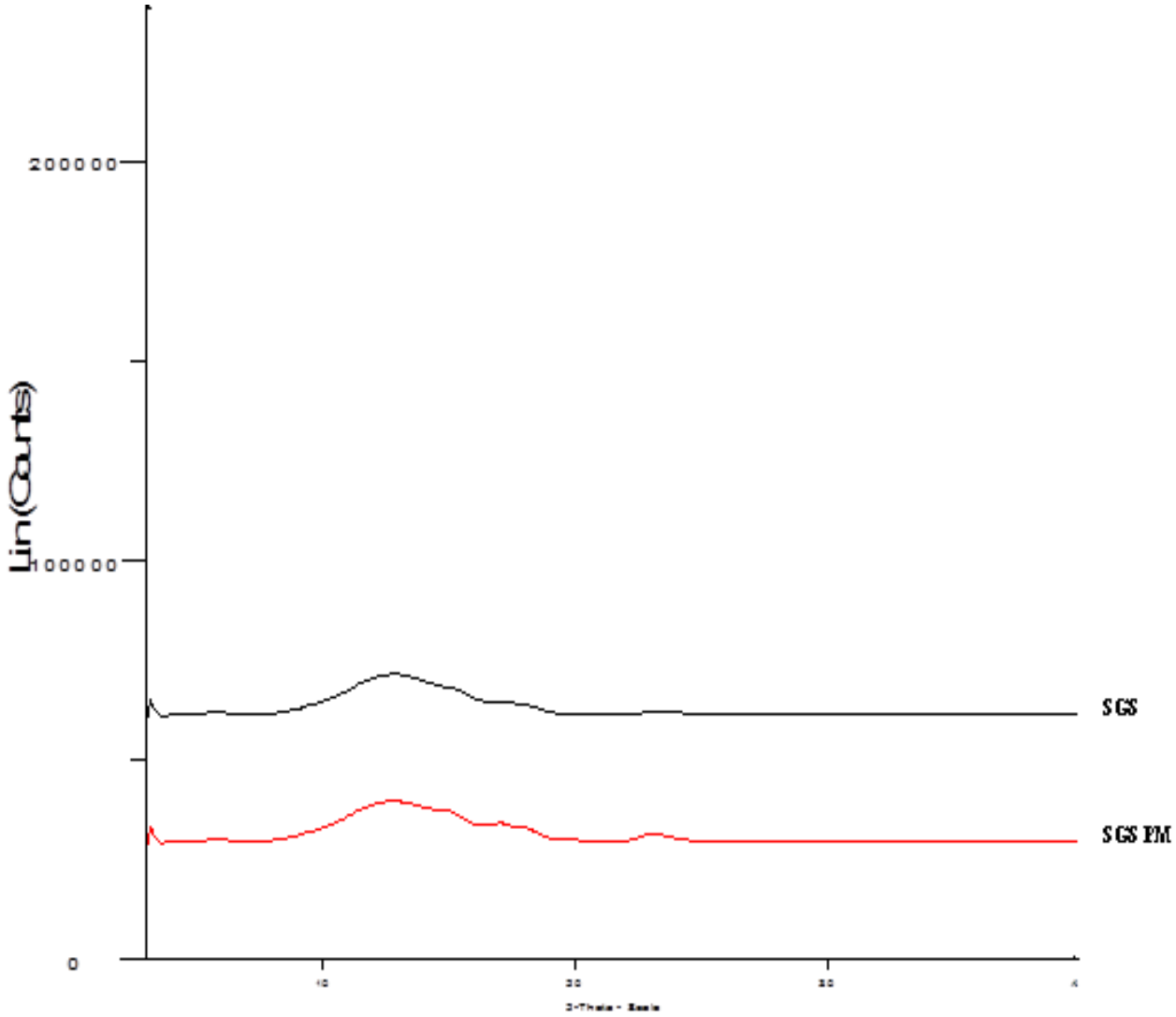

Figure 4.13: PXRD overlay of SGS and SGS-PM

The diffraction curves of SGS, IBU and IBU+SGS is presented in an overlay plot as Figure 4.14. The diffraction curve of IBU is characterized by distinct sharp peaks and these peaks arereflected in the diffraction curve of IBU+SGS occurring at the same positions but with a decrease in intensity.

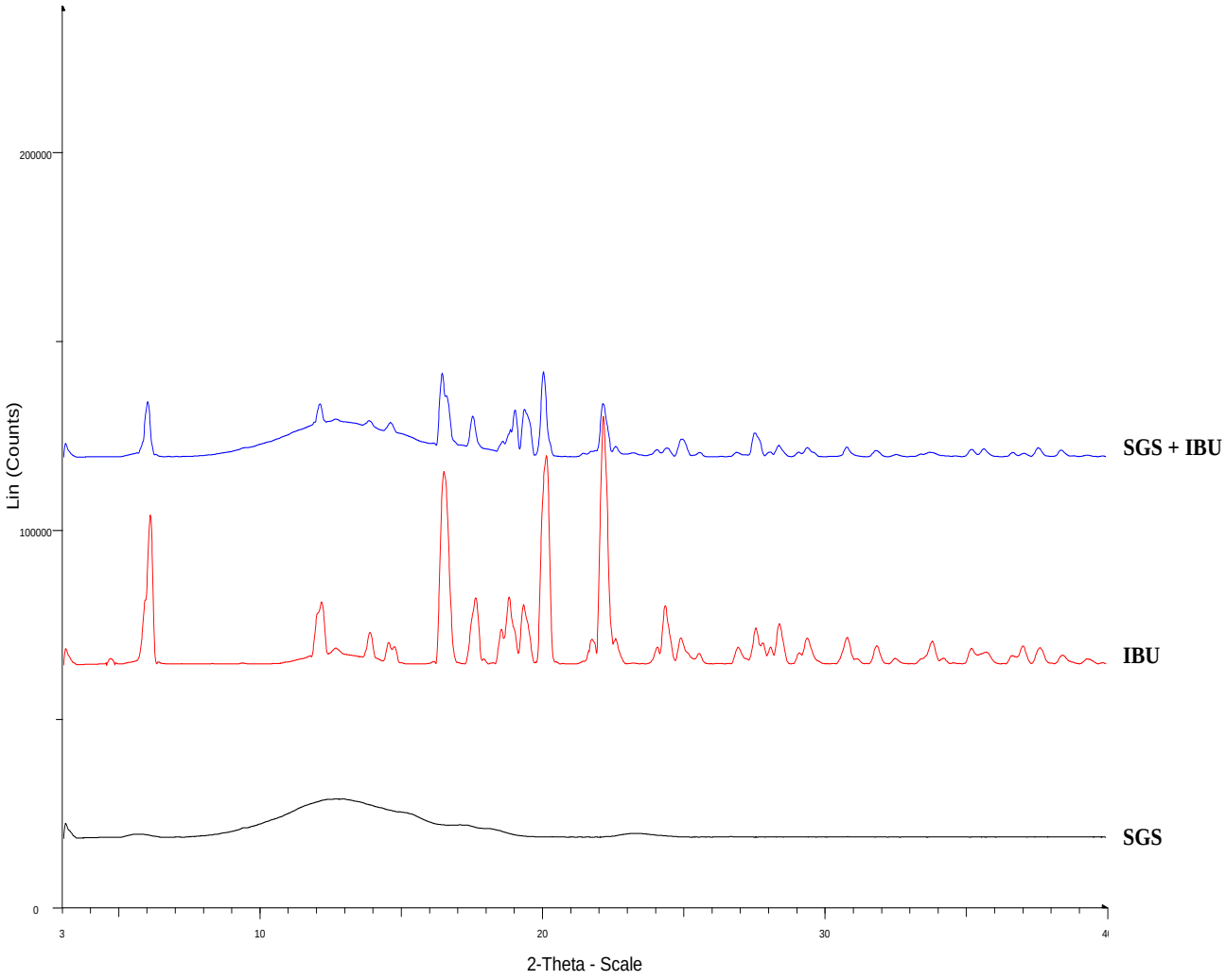

Figure 4.14: PXRD overlay of IBU + SGS, IBU and SGS

4.2.6 Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR spectra of CS, GEL, CSD, and SGS arepresented as an overlay plot in Figure 4.15. The major IR bands occurring in the spectra of the individual excipients are reflected in the spectrum of the co-processed excipient(SGS). The dominance of the IR absorption bands of CS in SGS is as a result of its greater proportion in the mixture blend. A table showing the major IR bands and the associated functional groups for each excipient is given below as Table 4.8.

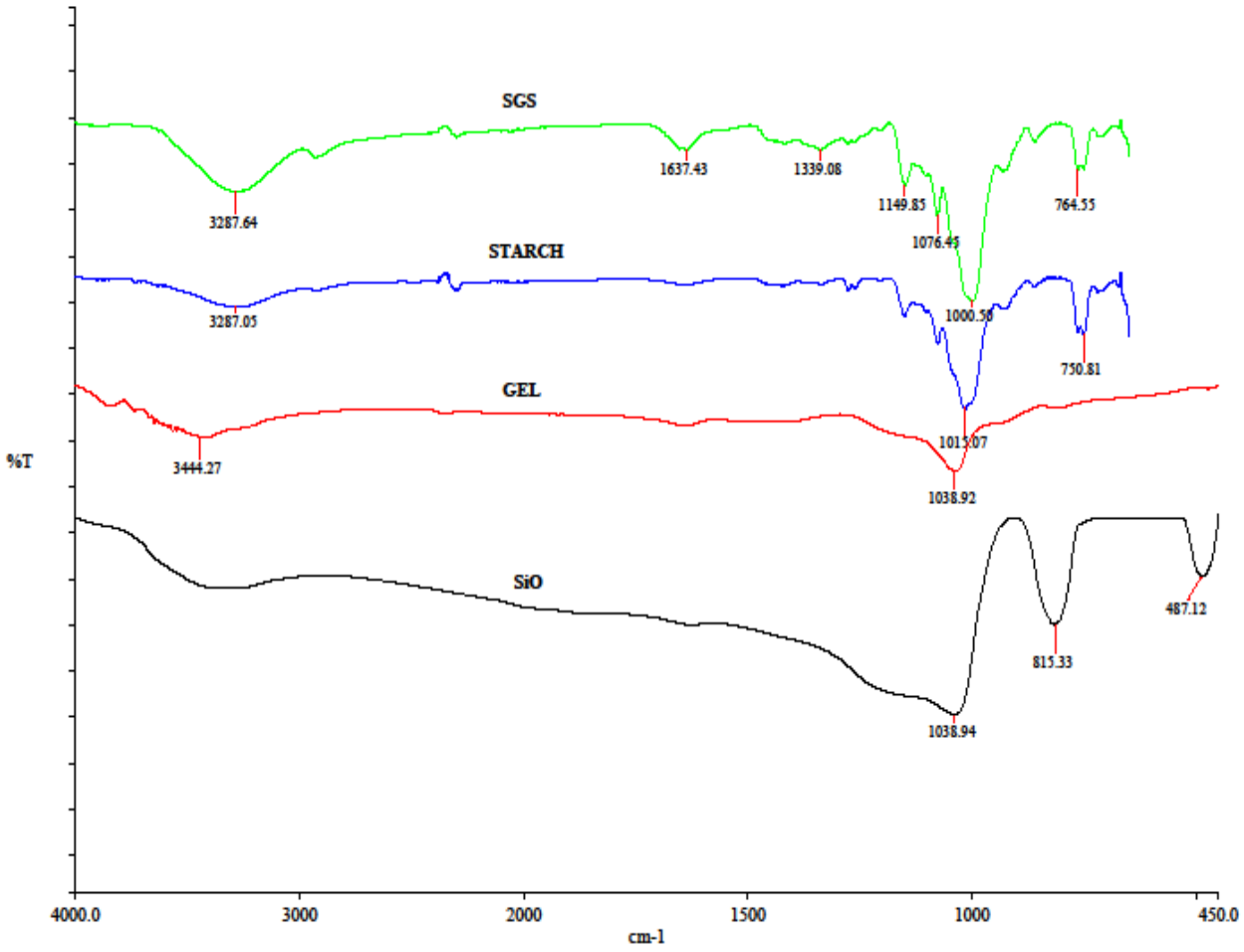

Figure 4.15: FT-IR overlay spectra of SGS, CS, GEL and CSD

Table 4.8: Major FT-IR bands and the corresponding functional groups for the three excipients

Material	IR band (s)	Type of vibration	Functional group (s)
Cassava starch	3287.05	O-H stretch (H-bonded)	Alcohols
	1275.78	C-O stretch	Carboxylic acid
	1150.38	C-O stretch	Carboxylic acid
	1076.43	C-O stretch	Carboxylic acid
	1015.07	C-O stretch	Carboxylic acid
	750.81	=C-H stretch	Alkenes
Gelatin	3444.27	N-H stretch	1°, 2° amides
	1643.24	C═O stretch	Carboxylic acids, Carbonyls (general)
	1038.92	C-N stretch	Aliphatic amines
Colloidal silicon dioxide	3287.23	O-H stretch	Silanol group
	1038.94	Si-O-Si stretch (symmetric)	Silicon Compounds
	815.33	Si-O stretch and Si-O bend (asymmetric)	Silicon Compounds
	487.16	Si-O stretching and Si-O bending (asymmetric)	Silicon Compounds
StarGelaSil	3287.64	O-H stretch (H-bonded)	Alcohols
	2934.01	C-H stretch	Alkanes
	1637.43	C=O stretch	Amides
	1149.85	C-O stretch	Carboxylic acids
	1076.45	C-O stretch	Carboxylic acids
	1000.50	C-O stretch	Carboxylic acids
	860.06	N-H wag	1°, 2° amines
	764.55	N-H wag	1°, 2° amines

The FT-IR spectra of SGS and SGS-PM displayed as Figure 4.16 is a clear superimposition of one on the other. There was no change in the band positions or the appearance of new bands indicating that co-processing did not result in the formation of any new compound.

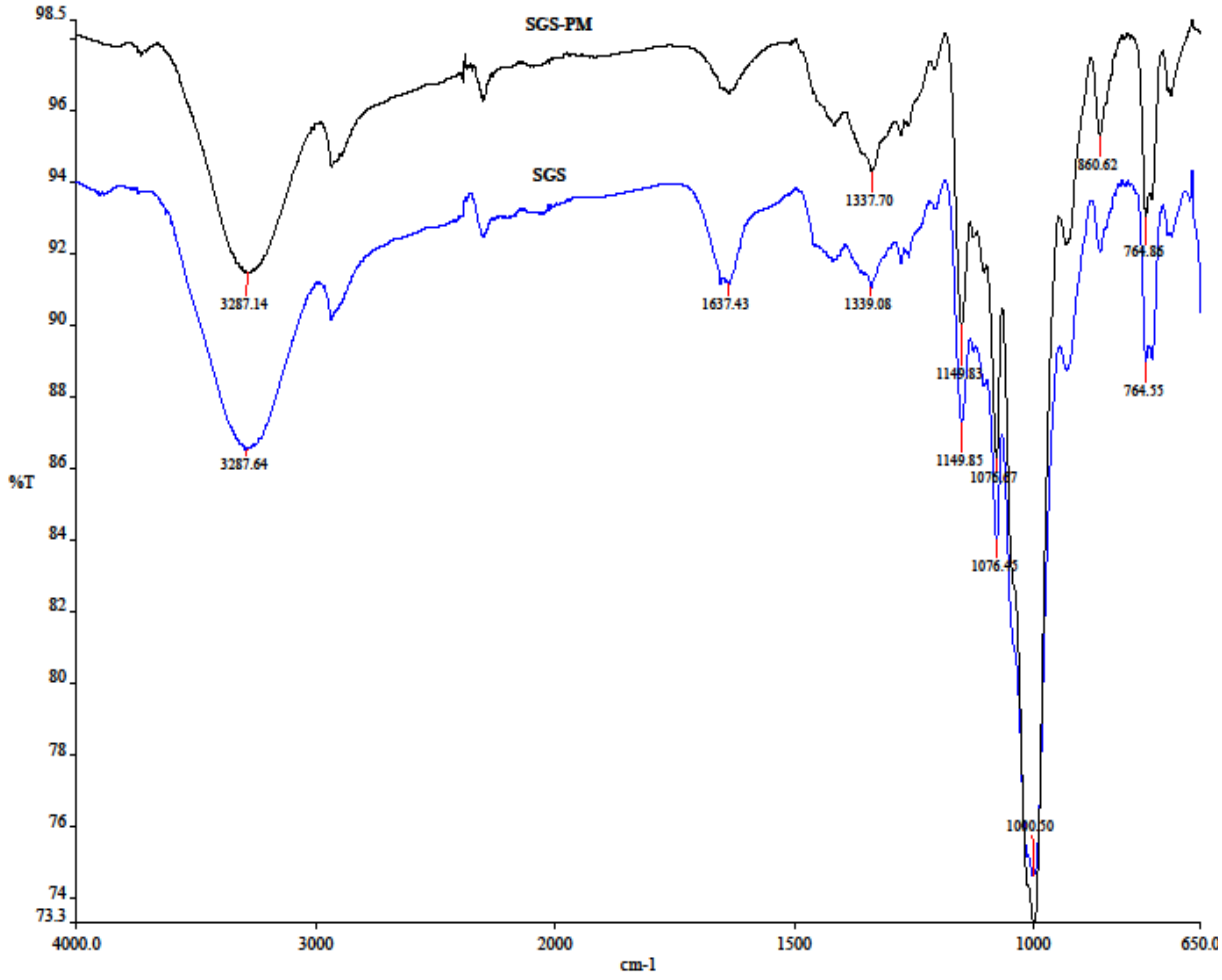

Figure 4.16: FT-IR overlay spectra of SGS and SGS-PM

The FT-IR spectra of IBU, SGS and IBU+SGS displayed as Figure 4.17 showed that the characteristic absorption bands of IBU were reflected in the IR spectrum of IBU+SGS. The various band positions were maintained and there was no appearance of a new band confirming the compatibility between IBU and SGS.

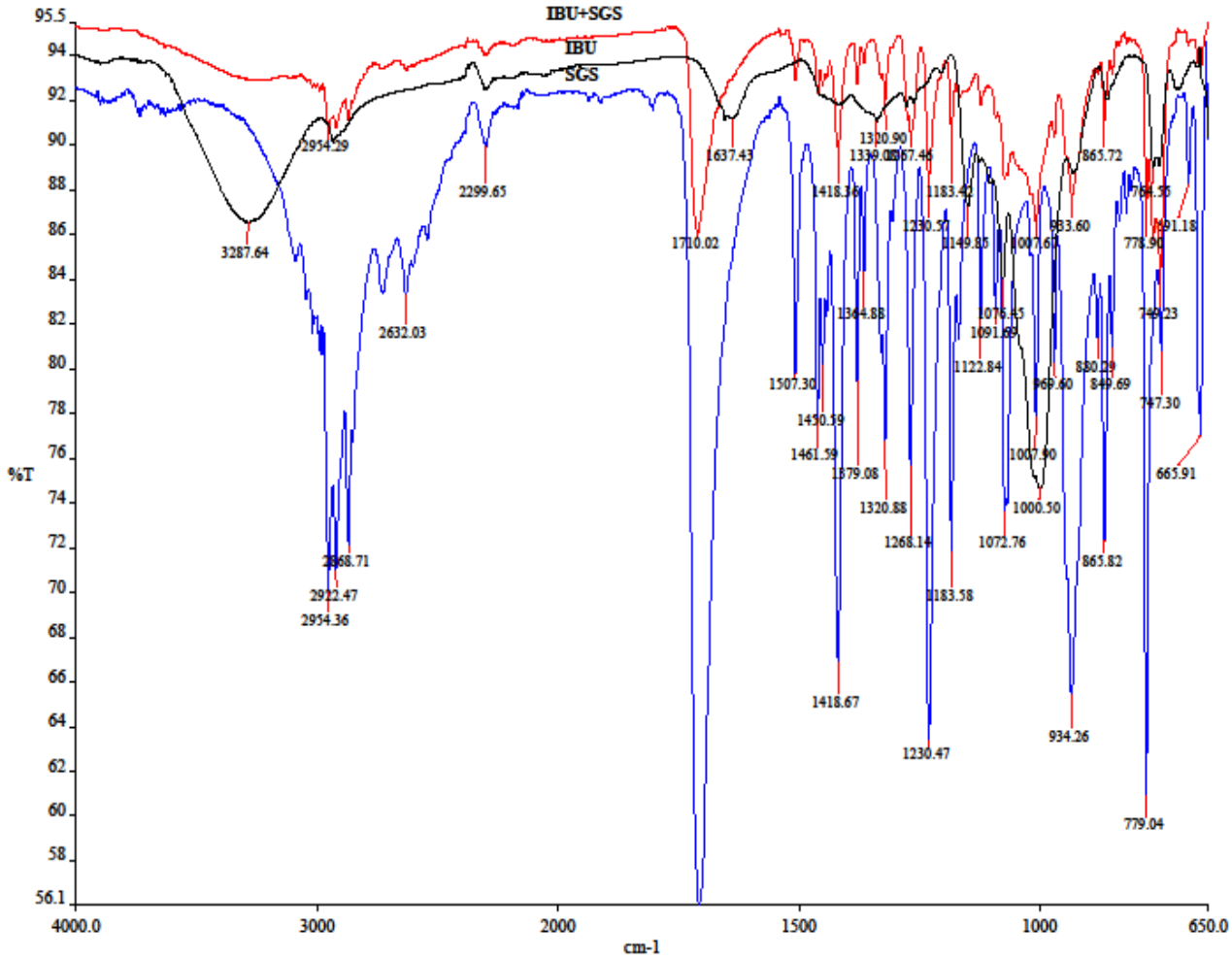

Figure 4.17: FT-IR overlay spectra of IBU + SGS, IBU and SGS

4.2.7 Dynamic Vapour Sorption (DVS) analysis

The moisture sorption isotherms of CS and SGS are presented in Figure 4.18as an overlay plot. The amount of moisture adsorbed by both materials increased steadily with increase in relative humidity.At 80 % RH, the amount of moisture adsorbed by both materials did not exceed 12 %.

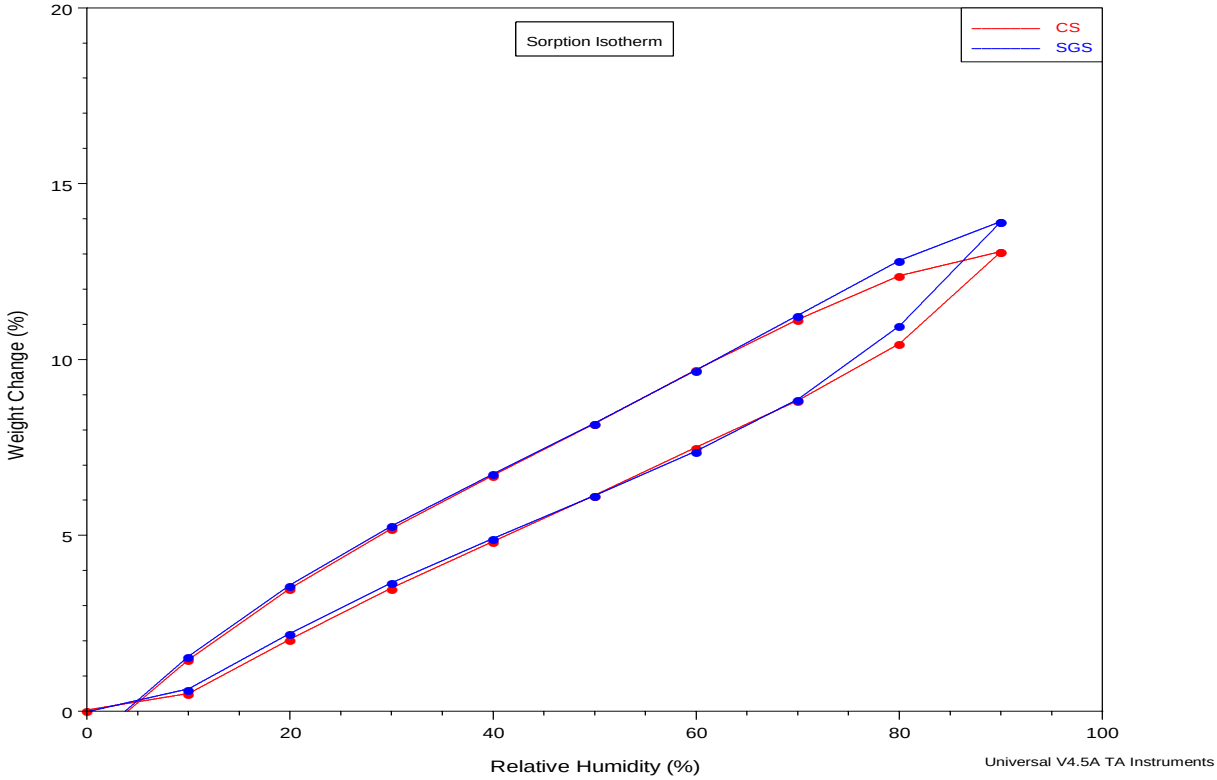

Figure 4.18:Moisture sorption/desorption isotherms of CS and SGS showing the relationship between the relative humidity (% RH) and weight change (%)

The overlay plot displayed in Figure 4.19 compares the moisture sorption profiles of SGS, PSV and SLC. The amount of moisture adsorbed with increasing relative humidity was ranked in the following order: SGS > PSV > SLC. The maximum amount of moisture adsorbed by SGS at 80 % RH did not exceed 12 %.

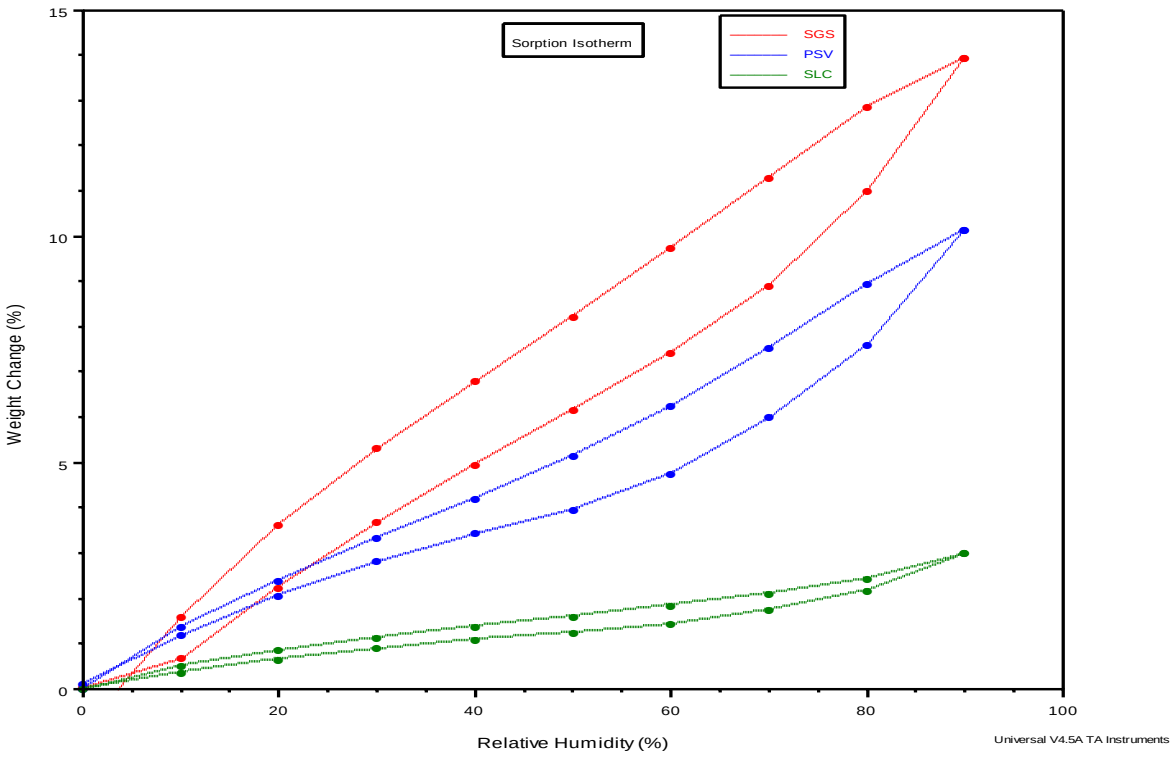

Figure 4.19: Moisture sorption/desorption isotherms of SGS, PSV and SLC showing the relationship between relative humidity (% RH) and weight change (%)

4.2.8 Circular Dichroism (CD) spectroscopy

An overlay plot showing the CD spectra for GEL, SGS and F-SGS is displayed in Figure 4.20. Characteristic peaks of GEL were observed at 208 and 222 nm. Similar patterns of the GEL spectra were obtained for SGS and F-SGS except for slight displacement in the peak positions. The minor changes observed in the SGS and F-SGS suggests that the secondary structure of GEL was not destroyed during processing.

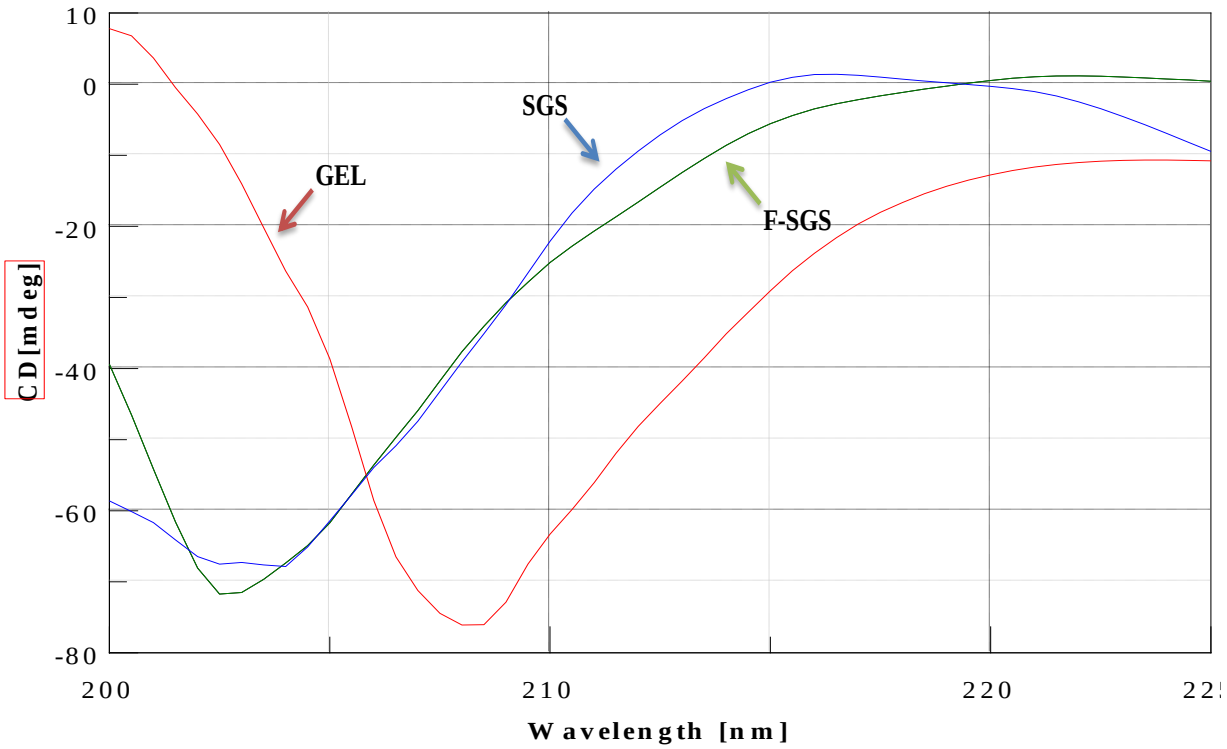

Figure 4.20: Overlay CD spectra of GEL, SGS and F-SGS

Key:-

GEL: Gelatin

SGS: StarGelaSil

F-SGS: StarGelaSil prepared with gelatin stained with fluoroisothiocyanate (FITC)

4.3 Physicomechanical Properties

The results of the physicomechanical properties are presented in Table 4.9. The flow properties estimated by measuring the angle of repose ranged from 21.6 – 27.1 ° with SGS having the least value of 21.6 °. Compared to CS and SGS-PM, flow behaviour was enhanced as a result of co-processing. This was well correlated with the values obtained for CI and HR in the following order, SLC < PSV < SGS for CI and HR respectively. Again, comparing the values obtained with SGS to CS and SGS-PM, there was an improvement in flow properties.

True density values recorded ranged from 1.45 – 1.57 g/cm^3 with SGS having a lesser value compared to CS. The pH values were tending to neutral for all the materials except for SGS which was weakly acidic (pH = 5.5).

The data collected on swelling index shows a marginal increase in swelling of SGS over CS, probably due to the presence of gelatin in the starch matrix. The cellulose derived co-processed excipient (PSV) exhibited the highest degree of swelling while SLC did not swell due to the solubility of lactose in water.

Table 4.9: Physicomechanical properties of CS, SGS, SGS-PM, PSV and SLC

Parameters	Material				
	CS	**SGS**	**SGS-PM**	**PSV**	**SLC**
Angle of repose (°)	Not passable	21.6 (0.29)	Not passable	27.1 (0.1)	25.9 (0.25)
Bulk density (g/cm^3)	0.51 (0.02)	0.48 (0.01)	0.54 (0.02)	0.48 (0.01)	0.64 (0.02)
Tapped density (g/m^3)	0.65 (0.02)	0.57 (0.02)	0.70 (0.03)	0.56 (0.00)	0.71 (0.00)
Carr's index (%)	22 (2.64)	14.7 (2.34)	23.2 (2.76)	12.9 (2.47)	10.6 (3.37)
Hausner's ratio	1.28 (0.04)	1.17 (0.03)	1.30 (0.05)	1.15 (0.03)	1.12 (0.04)
Porosity (%)	66.5	66.6	63.3	69.4	59.3
True density	1.52 (0.02)	1.45 (0.02)	1.46 (0.01)	1.58 (0.01)	1.57 (0.02)
Swelling index (%)	7.14	9.09	ND	55	-16.7
pH	6.4 (0.01)	5.5 (0.01)	ND	6.6 (0.02)	6.5 (0.01)
Effective pore radius (µm)	4.59	5.23	ND	5.54	4.76

ND Not determined

Key:-

CS: Cassava Starch

SGS: StarGelaSil

SGS-PM: StarGelaSil physical mixture

PSV: Prosolv®

SLC: StarLac®

4.4 Compaction Studies

The compaction properties of SGS and SGS-PM were analysed using Heckel and Kawakita equations and the results obtained are presented on Table 4.10 and Figures 4.21 and 4.22 respectively for Heckel and Kawakita plots.

The material yield pressure, P_Y, which is a reflection of the degree of plasticity and the onset of plastic deformation, was extrapolated from Heckel plot using the reciprocal of the slope, K. The results obtained revealed that SGS-PM had a faster onset of deformation due to its lower yield pressure (83.77 MN/m^2). However, greater degree of plastic deformation was obtained with SGS on the basis of D_A (0.903). The extent of fragmentation occurring in SGS was greater than that of SGS-PM due to its higher D_B value of 0.573.

Table 4.10: Heckel and Kawakita parameters for SGS and SGS-PM

	Compaction Analysis						
	Heckel Parameters						
Material	**Slope**	**Intercept**	**P_Y (MN/m^2)**	**R^2**	**D_A**	**D_0**	**D_B**
SGS	0.01	2.33	104.96	0.918	0.903	0.330	0.573
SGS-PM	0.012	1.50	83.77	0.994	0.776	0.369	0.407
	Kawakita Parameters						
Material	**Slope**	**Intercept**	**R^2**	***a***	***b***	***ab***	**$1/b = P_K$**
SGS	1.542	1.953	0.999	0.648	0.790	0.512	1.266
SGS-PM	1.681	3.284	0.999	0.595	0.512	0.305	1.953

Key:-

P_Y: Material's yield pressure

R^2: Coefficient of determination

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

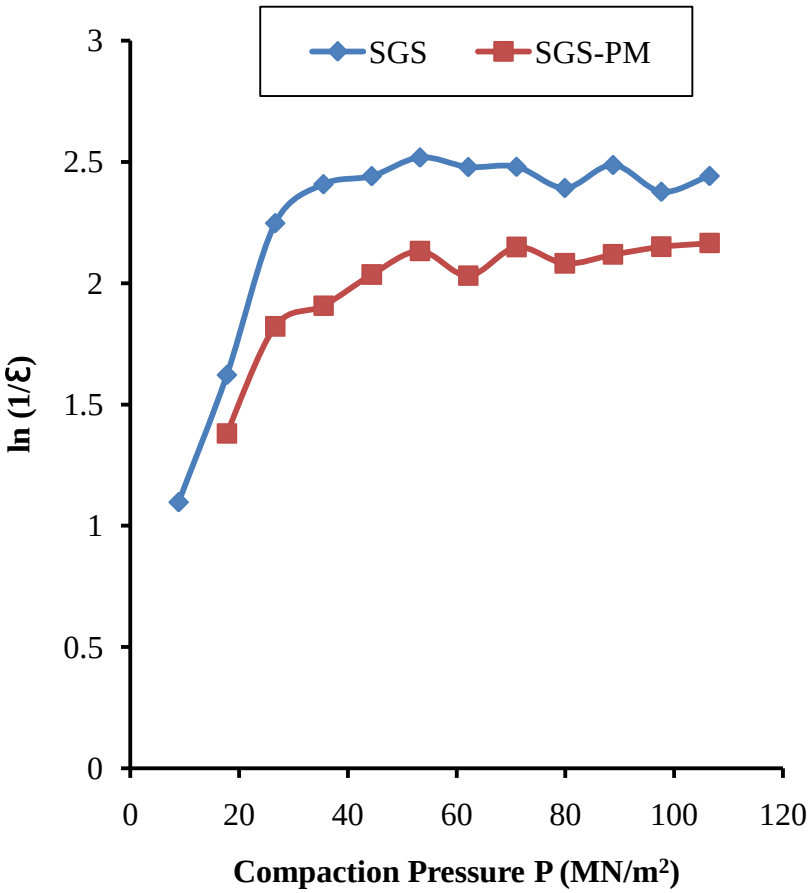

Figure 4.21: Heckel plot of SGS and SGS-PM showing the relationship between compaction pressure P (MN/m^2) and porosity (ln (1/□))

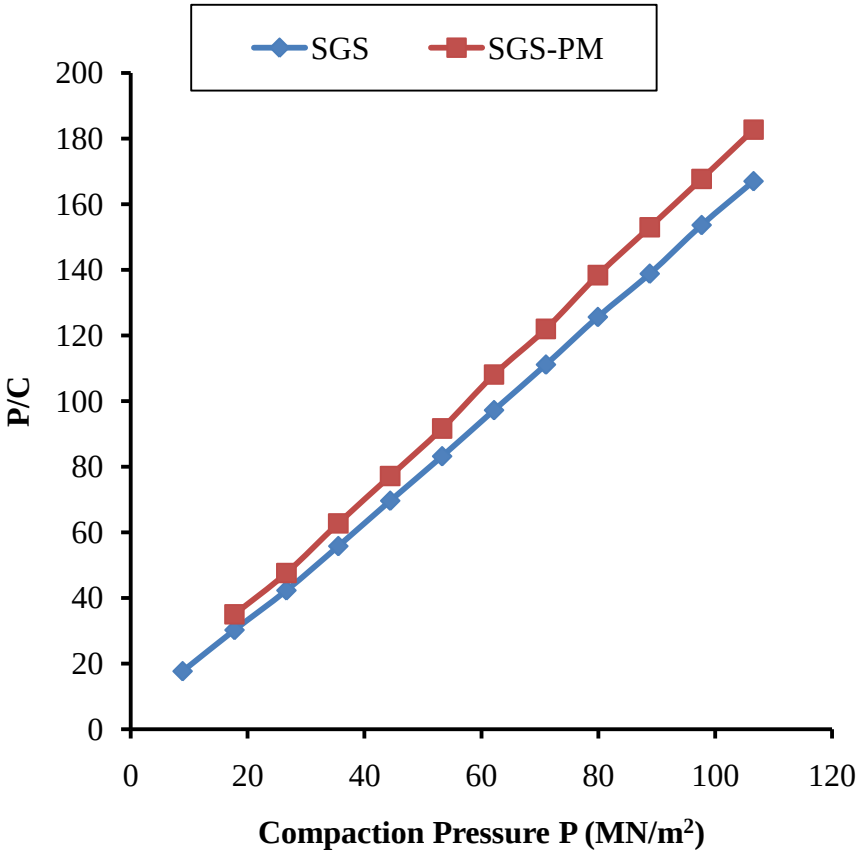

Figure 4.22: Kawakita plot for SGS and SGS-PM showing the relationship between compaction pressure P (MN/m^2) and P/C

The compressibility plot of SGS and SGS-PM is presented as Figure 4.23. The porosity of the material was found to decrease as the compression pressure was increasing and a greater degree of reduction in porosity was observed with SGS compared to SGS-PM.

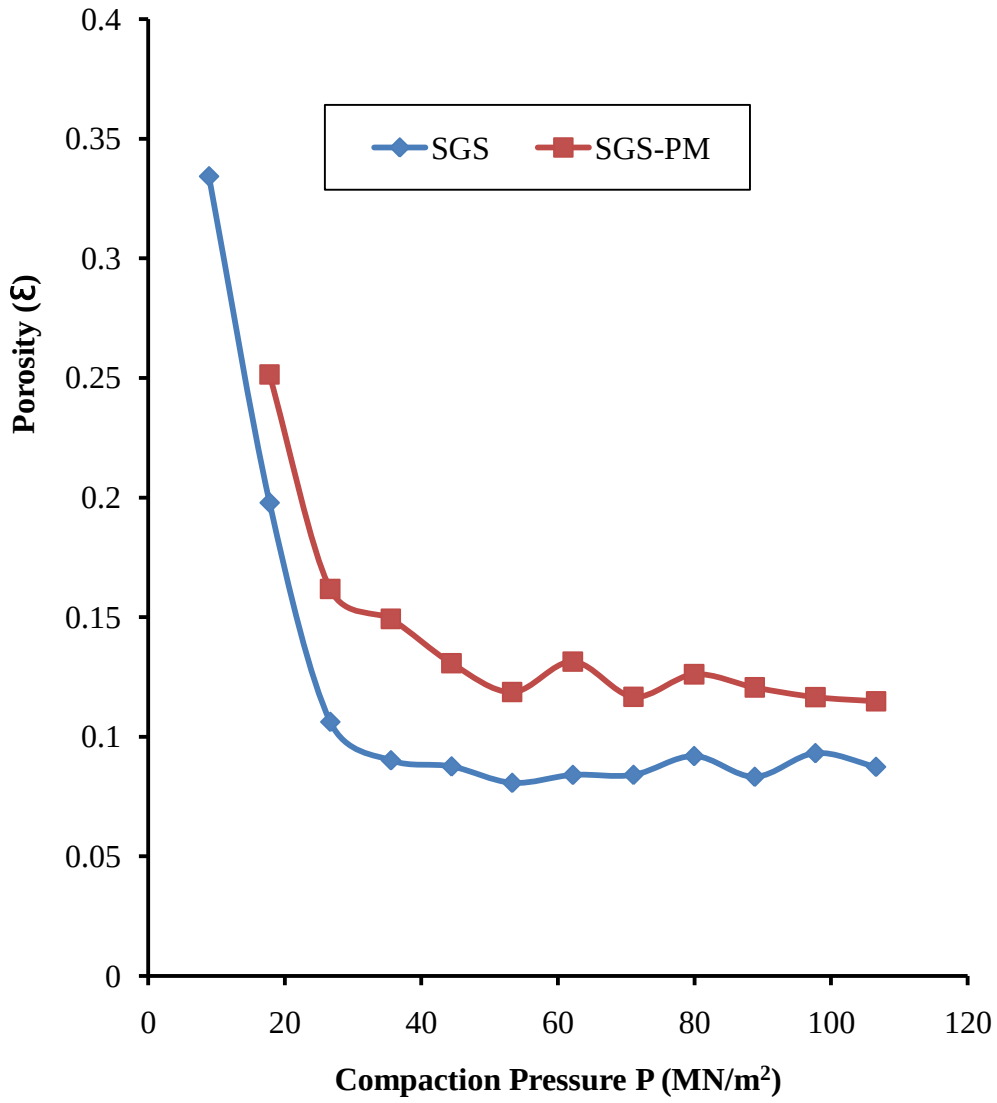

Figure 4.23: Compressibility plot for SGS and SGS-PM showing the relationship between compression pressure P (MN/m^2) and porosity (□)

The compactibility plot of SGS and SGS-PM is displayed as Figure 4.24. The tensile strength of the compacts of SGS and SGS-PM was found to increase as the porosity of the compact increased. SGS produced compacts of higher tensile strength when compared to SGS-PM at the same porosity.

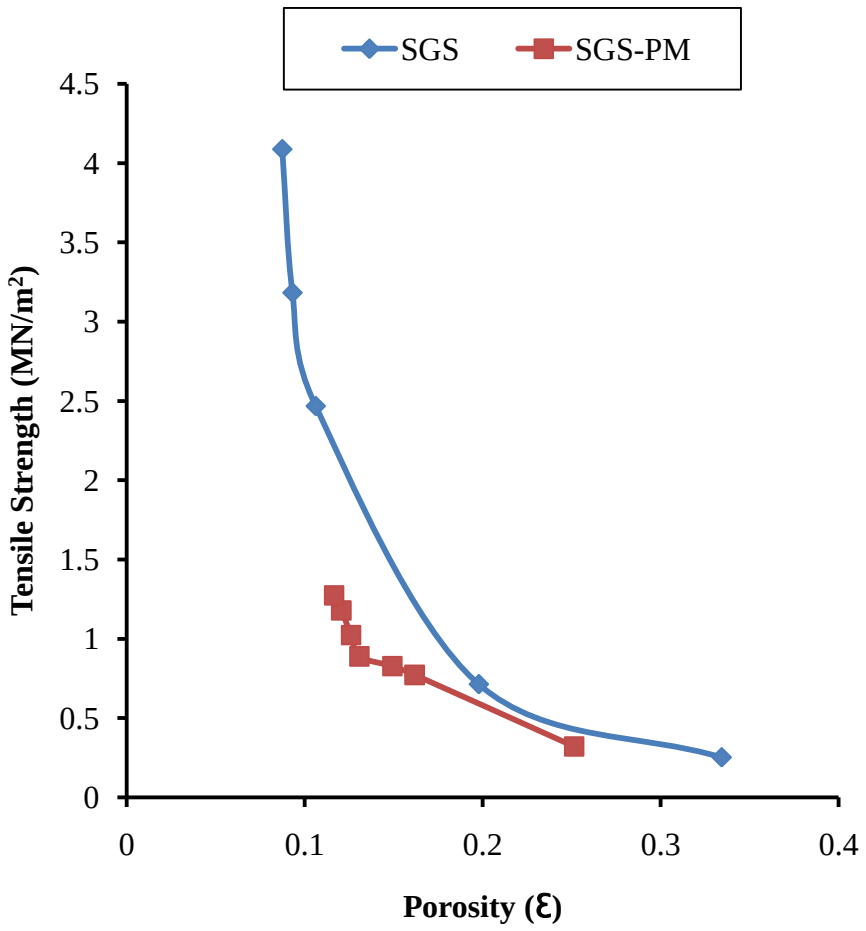

Figure 4.24: Compactability plot for SGS and SGS-PM showing the relationship between porosity (□) and tensile strength (MN/m^2)

Tabletability plot of SGS and SGS-PM is presented as Figure 4.25. The tensile strength of the compacts was found to increase with increase in compression pressure and compacts with superior tensile strength were obtained with SGS compared to SGS-PM at the same compression pressure.

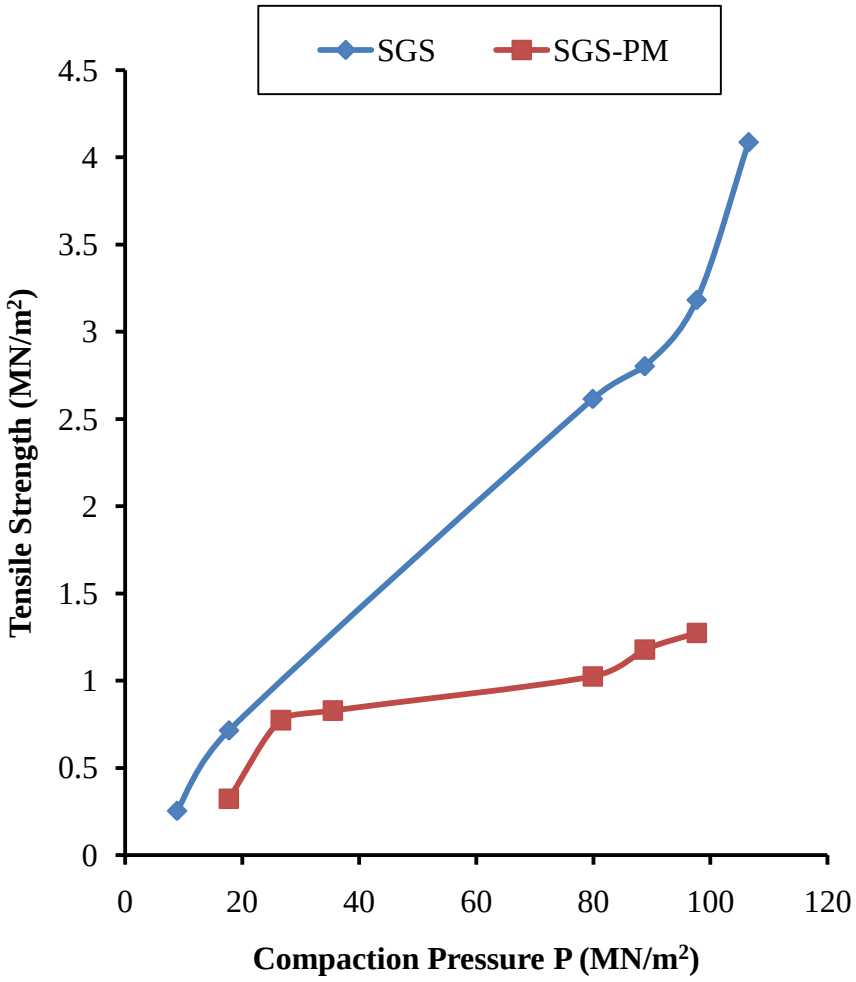

Figure 4.25: Tabletability plot for SGS and SGS-PM showing the relationship between compression pressure P (MPa) and tensile strength (MN/m^2)

4.5 Tablet Properties

The properties of tablets produced using StarGelaSil (SGS), Prosolv® (PSV) and StarLac® (SLC) as the sole excipient is given in Table 4.11. The difference in weight uniformity and thickness was not significant at $p < 0.05$ for all three batches. Significant differences were observed for crushing strength, tensile strength, friability, and disintegration time. The tensile strength of SGS was relatively higher than SLC but lower than PSV and this was reflected in the friability of the tablets. Tablets of SGS disintegrated in less than 30 s (0.32 min) compared to PSV (0.99 min) and SLC (0.62 min).

Table 4.11: Physical properties of tablets prepared using SGS, PSV and SLC

	Parameters								
Batch	**Weight (mg)**	**Thickness (mm)**	**CS (N)**	**TS (MN/m^2)**	**BI**	**FR (%)**	**DT (min)**	**$T_{50\%}$ (min)**	**$T_{90\%}$ (min)**
I	399.7 (4.22)	3.43 (0.03)	79.38 (7.7)	1.23 (0.12)	0.015	0.57 (0.07)	0.32 (0.04)	4.00	32.00
II	395.95 (12.47)	3.27 (0.09)	117.17 (11.34)	1.90 (0.13	0.016	0.30 (0.07)	0.99 (0.2)	20.00	> 60.00
III	402.15 (7.6)	3.39 (0.03)	63.57 (8.85)	0.99 (0.13)	0.015	8.63 (1.79)	0.62 (0.24)	4.00	30.00

Key:-

I - SGS II - PSV III - SLC

TS – Tensile strength

BI – Bonding index

FR – Friability

DT – Disintegration time

$T_{50\%}$ - Time taken to release 50 % of the drug

$T_{90\%}$ - Time taken to release 90 % of the drug

The dissolution plot of the three excipients is displayed as Figure 4.26. The time taken for 50 % and 90 % of the drug to be released by all three excipients was extrapolated from the plot and recorded in Table 4.11. Drug-release profile of SGS was comparable to SLC but performed better than PSV in terms of the time taken for 50 % and 90 % of the drug to be released.

The similarity factor ($f2$) was calculated to measure the degree of similarity between the drug-release profiles of the three excipients. The similarity factor ($f2$) obtained for SGS and PSV was 17 while that for SGS and SLC was 53. This indicates a high degree of dissimilarity between the release profiles of SGS and PSV and a high degree of similarity between the release profiles of SGS and SLC. The similarity factor fits result between 0 and 100. It is 100 when the test andreference profiles are identical and tends towards 0 asthe dissimilarity increases.

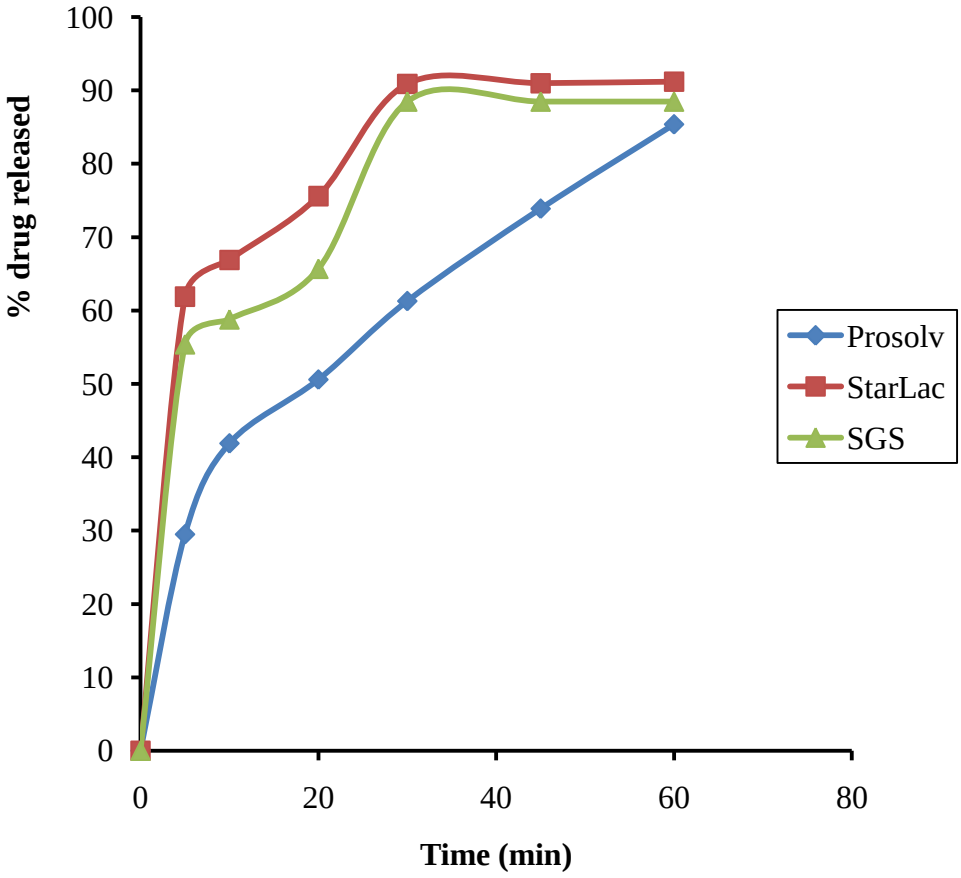

Figure 4.26: Dissolution plot of SGS, PSV and SLC showing the relationship between the amount of drug released (%) and time (min)

CHAPTER FIVE

5.0 DISCUSSION

5.1 Selection of an optimized composition using DoE

The concept of quality by design (QbD) (Yu, 2008; Pawar *et al.*, 2012; Larsen *et al.*, 2014) was applied in this study to optimize the composition of the co-processed excipient, *StarGelaSil* (SGS). The mixture design model (Simple Centroid) of DoE was chosen as the experimental design because the product under investigation (co-processed excipient) is made up of several components/ingredients. Mixture design experiments accounts for the dependence of response on proportionality of ingredients (Cornell, 1990; Anderson and Whitcomb, 2002). This implies therefore that the functionality of the co-processed excipient under investigation is derivable directly from the relative proportions of the individual components that constitute the co-processed excipient.

The Simple Centroid (SC) mixture design specifically studied the effects of the individual components (Cassava starch, Gelatin and Colloidal silicon dioxide) and their interactions at varying concentrations on the predefined responses of tensile strength and disintegration time. It was used to optimize both responses using a higher order polynomial model. The summary statistics obtained with *ANOVA* specifies the special quartic model as the best fitting model for both responses as confirmed by the *p* values documented in Table 4.2. The requirements for accepting a model includes a goodness of fit statistic defined by the coefficient of determination (R^2) and significance of the model at $p<0.05$ (Camargo, 2011; Kurmi *et al.*, 2014; Larsen *et al.*, 2014)). These two criteria were met for both responses as shown in Table 4.2. The suitability of the model chosen to fit the data collected on tensile strength and disintegration time of the tablets

increased as the coefficient of determination (R^2) tends to 1. Hence, the model selected was appropriate in correlating the relationship between the effect of the individual excipients in the varying mixtures on the tablet properties evaluated (Camargo, 2011). Thus, about 99.8 % and 99.9 % of the experimental variances for tensile strength and disintegration time, respectively, were explained by the special quartic model.

The calculated *p* values given in Table 4.3 shows that all the terms included in the model were significant at $p<0.05$ for tensile strength while all the terms except (AC) were significant at $p<0.05$ for disintegration time. This clearly indicates that all the model terms that were significant in the equation exerted an effect whether positive or negative on the final response. The effect of the factors/components on tensile strength followed the order: B>C>A with gelatin (B) having a major positive influence on tensile strength compared to the other two components. Similarly, the effect of the components on disintegration followed the order: B>A>C. Again, gelatin (B) played a prominent role in deciding the outcome of disintegration. The coefficient sign indicates whether the effect on the response is positive or negative. A positive (+) coefficient will increase or enhance the outcome of the response while a negative (-) coefficient will decrease or reduce the outcome of the response. Based on this definition, the presence of gelatin in the co-processed mixture enhanced the tensile strength and increased the disintegration time. Increasing the concentration of gelatin in the co-processed mixture will further increase the tensile strength and prolong disintegration time. In order to tailor the response of the co-processed excipient, the concentration of gelatin can be controlled to deliver the desired response.

The effect of gelatin on tensile strength and disintegration time may not be unrelated to its use as a binder in tablet formulations (Kozlov and Burdygina, 1983; Young *et al*., 2005). Gelatin acts as an adhesive that promotes cohesion between particles thereby

promoting stronger bond formation between particles which reflects as increase in tensile strength of the compact (Zubair *et al.*, 1988; Odeku and Itiola, 2003). The reasonable explanation for the increase in disintegration time as a result of gelatin is due primarily to the formation of a gel-like layer when tablets containing gelatin is immersed in water. This phenomenon is likely to retard the uptake of water by the tablet thereby increasing disintegration time. Table 4.3 also reveals that the interaction of cassava starch and gelatin (AB) demonstrated the most significant positive effect on tensile strength compared to the other interactions in that order: AB>BC>AC. The interaction of cassava starch and colloidal silicon dioxide had the least significant negative effect on tensile strength. This invariably means that the combination of cassava starch and colloidal silicon dioxide will lower the tensile strength. Conversely, the two way interaction of cassava starch and gelatin lowered the disintegration time while the interaction between cassava starch and colloidal silicon dioxide was not significant at $p<0.05$ on disintegration time. This means that the interaction of cassava starch and colloidal silicon dioxide did not influence the disintegration time either positively or negatively.

The regression model was used to generate contour plots for both responses to analyse the effect of each component on response. In a contour plot, the response surface is viewed as a two – dimensional plane where all the points that have the same response are connected to produce contour lines of constant responses (Raghavarao *et al.*, 2010). Contour plots have been used for establishing desirable response values and mixture blends (Anderson and Whitcomb, 2002; Raghavarao *et al.*, 2010). The contour plots for tensile strength and disintegration time displayed as Fig. 4.1 and 4.3 respectively reveals that both responses increases in magnitude as the concentration of gelatin in the mixture is increasing. This is a confirmation of what was observed in the predicted mathematical

model for both responses where gelatin played a dominant role in enhancing the tensile strength and disintegration. As the coloured regions of the plot progress from blue to orange, there is a corresponding increase in the values of tensile strength and disintegration which is consistent with rising concentrations of gelatin. The plots also shows that the values of tensile strength and disintegration time diminishes as the content of cassava starch in the mixture increases confirming the negative effect of cassava starch on tensile strength and a corresponding positive effect on disintegration time. However, the trend observed with colloidal silicon dioxide was such that the tensile strength increased at both extremes of its range of concentration in the mixture.

The optimized contour response plot (overlay plot) displayed as Figure 4.5 highlights the region with factor combinations where a desired range of the response occurred. In this case, it was used to identify the factor settings that maximize response. The yellow-coloured regions in the plot represent an area of the design space that meets the criteria set during optimization. The greyed areas on the overlay plot have not met the selection criteria and therefore they fall outside the range of the design space. On the basis of the selection criteria set for factors and responses during optimization, seven (7) possible outcomes were obtained (Table 4.4). These outcomes were ranked on the basis of the desirability value assigned to each outcome. As the value tends to 1, the more desirable is that combination in fulfilling the criteria set for maximizing response. The first three outcomes as presented in Table 4.4 were chosen and validated to confirm the prediction of the model. Based on the validation results (Table 4.5), the first possible outcome having cassava starch (90 %), gelatin (7.5 %) and colloidal silicon dioxide (2.5 %) (SGS-A) was chosen as the optimized composition of the co-processed excipient.

As a follow-up to its emergence as the choice blend, the flow properties of SGS-A was investigated by measuring the angle of repose and determining the Carr's index (CI) and

Hausner's ratio (HR) from the bulk and tapped densities' indices. The results reported in Table 4.6 revealed that SGS-A had superior flow characteristics in terms of CI and HR. The dilution potential studies carried out on all three possible combinations revealed that SGS-A had a better dilution capacity compared to SGS-B and SGS-C. This may be attributed to the content of gelatin in this mixture which was relatively higher compared to the other two mixtures. As mentioned earlier, the higher concentration of gelatin may have contributed to improved bonding capacity in the presence of a poorly compressible drug. Similarly, the results of the dynamic vapour sorption test that was carried out to determine the degree of hygroscopicity of each blend revealed that SGS-A had the least moisture sorption capacity compared to others. In this instance, the content of cassava starch may have been responsible for the degree of moisture absorbed by each combination. Starch is hygroscopic in nature (Assen *et al.*, 2011) and absorbs water when equilibrated under normal atmospheric condition until the amount present is 10–17 % (Murikipudi *et al.*, 2011; Emeje and Rodrigues, 2012; Odeku, 2013). The content of cassava starch in SGS-A was relatively less compared to SGS-B and SGS-C and this was reflected in its degree of hygroscopicity.

5.2 Solid state characterization

The aim of solid state characterization was to define the solid state properties of materials. It gives an insight into how the material will perform during formulation because there is a correlation between the solid state properties of a material and its functionality during product development (Sainio, 2011). During production process, the excipient's properties in the solid state, as well as those of the active principle, are reflected in the various parameters such as compressibility, flowability, uniformity, lubrication, mixing and weight of the pharmaceutical dosage form (Camargo, 2011). Hence, the characterization of the solid state and the surface parametersistherefore

fundamental to assess and guaranteethe behaviour of the excipient in the formulation andproduction phases.

5.2.1 Optical microscopy

Optical microscopy was used to measure particle size, particle size distribution and the degree of birefringence occurring in SGS after processing. Optical images of SGS and CS revealed spherical shaped particles which were further confirmed by SEM. When viewed under polarized light, CS and SGS granules showed a dark birefringence cross (‘Maltese cross’) which is characteristic of crystalline substances. This indicates that gelatinization did not occur during co-processing thereby maintaining the original structure of the cassava starch granules in the co-processed excipient. During gelatinization, the amorphous growth rings of starch take in water by capillary action leading to a rapid expansion in size. This disrupts the coupled semi-crystalline lamellae that is cross-linked through the amorphous backbone thereby reducing the granule’s crystallinity and causing it to lose its birefringence (Waigh *et al.*, 2000). Particle size increased as a result of co-processing as observed in the D_{10}, D_{50}, and D_{90} values presented in Table 4.8. These parameters represent the diameters corresponding to 10, 50 and 90 % of cumulative undersize particles respectively. Maximum particle size obtained for SGS was 110.9 μ as against 25 μ for CS which translates to a four-fold increase in particle size. The presence of gelatin in the co-processed matrix fused the starch particles together resulting in an increase in the size of the co-processed particle. Particle size is critical in determining the flow properties of a material as larger sized particles tends to flow faster due to reduced cohesion between particles and interparticulate friction (Bodhmage, 2006; Zhou and Qiu, 2010; Adeoye and Alebiowu, 2014a). This is most likely to have contributed to the enhanced flow properties exhibited by SGS.

5.2.2 Hot stage microscopy

HSM images of SGS did not reveal any melting event or phase transition occurring during heating at a constant rate from 25 – 300 °C. However, degradation of SGS was observed at temperatures above 250 °C, confirming the thermal stability of SGS. This is characteristic of materials that are largely amorphous in nature. Starch belongs to the class of materials that possesses a greater degree of amorphous portion although it is semi-crystalline in nature (Waigh *et al.*, 2000). They are far from being perfect crystals. At best they consist of crystalline and amorphous regions and the degree of crystallinity is in the range 17–51 % depending on their origin and the methods used by different authors producing an average of about 35 % (Tester *et al.*, 2004).

5.2.3 Scanning electron microscopy

Scanning electron micrographs (SEM) (Plate IV) depicting surface morphologies of SGS in comparison to SGS-PM, CS, GEL and CSD reveals a mixture of spherical and polygonal shaped particles. The surface of SGS appeared rough due to the homogeneous distribution of CSD on its surface and possibly within the core of the matrix. This is consistent with a similar study carried out by Kittipongpatana and Kittipongpatana (2012). Particle morphology of SGS-PM showed some dispersion of the flaky CSD on the surface of aggregated spherical-shaped CS granules. Most of CSD particles, however, remained as isolated agglomerates. The SEM image of GEL (Plate IV: D) appeared irregular in shape which may have contributed to the alteration of the spherical shaped particles of CS. These characteristics show that processing of CS with GEL and CSD had a major effect on particle morphology and surface properties.

5.2.4 Confocal laser scanning microscopy

Confocal laser scanning microscopy (CLSM) has been used to visualize the distribution of polymers embedded in a mixture (Lamprecht *et al.*, 2000; Van De Velde *et al.*, 2003). It allows for the visualisation of individual components in a complex mixture of biopolymers. The distribution of FITC-labelled gelatin in the co-processed excipient was observed using CLSM in combination with computational image analysis. There was a homogeneous distribution of gelatin in the co-processed matrix as portrayed by the CLSM images (Plate V). This validates the uniformity of mixing that occurred during the processing of the three excipients.

5.2.5 Circular dichroism spectroscopy

Circular Dichroism (CD) spectroscopy was conducted to monitor conformational changes taking place in gelatin during its solubilisation stage or as a result of interaction with the other excipients during co-processing. This technique is suitable for estimating the secondary structures of proteins and polypeptides in solution (Gopal *et al.*, 2012). Gelatin is a protein produced by acid and alkaline processing of collagen and is characterized by a three-chain structure in which individual helical chains are stranded in a super helix about a common molecular axis (Gopal *et al.*, 2012). The triple helical structure of gelatin can be quantified by using CD measurements. In the present study, the CD spectra of gelatin showed two peaks, a negative peak at 205 nm suggesting a random coil conformation, and a positive peak at 222 nm characteristic of the triple-helical conformation of gelatin. There was a slight shift in the positions of the two peaks as observed in the CD spectra of SGS and F-SGS (Fig. 4.20) indicating some degree of alteration occurring probably during solubilisation. The secondary structure of proteins i.e. gelatin, is sensitive to environmental changes like temperature and pH which may lead to denaturation of the protein if the conditions are not controlled. Maintaining the

triple helical conformation of gelatin or collagen-based biomaterials during preparation is important in eliciting the desired biomedical functions of both (Gopal *et al.*, 2012). However, this may not apply to this study because gelatin was employed as an excipient.

5.2.6 Differential scanning calorimetry

Differential scanning calorimetry (DSC) has been employed in a wide range of pharmaceutical applications ranging from the characterization of materials to the evaluation of drug excipient interactions via the appearance, shift, or disappearance of endothermic or exothermic peaks (Daraghmeh *et al.*, 2010). DSC has equally been used to investigate drug-excipient compatibility and thermal stability. The DSC curves of CS, SGS-PM and SGS revealed glass transition events taking place at temperatures above 250 °C. Glass transition temperature (*Tg*) is the onset of transition from a disordered solid to a liquid, characterized by a change in heat capacity where no heat is absorbed or evolved. There exists a linear relationship between the amorphous content of a material and glass transition (Lappalainen and Pitk, 2006). No melting endotherm was detected in all three materials confirming their amorphous nature (Fig. 4.10). Melting endotherms have been associated with crystalline materials.

There was no disappearance in the melting endotherm of ibuprofen (IBU) when mixed with SGS as exhibited in the overlay DSC curve (Fig. 4.11). This shows the compatibility of IBU with SGS. The difference in intensity of the peaks observed in the two thermograms can be attributed to the concentration of ibuprofen in the mixture. The intensity of the peak is influenced by the concentration of the material. Intensity increases with an increase in concentration.

5.2.7 Powder X-ray diffraction

X-ray diffraction is one of the most important characterization tools used in solid state chemistry and materials science. It has been used in two main areas, for the fingerprint characterization of crystalline materials and the determination of their structure. The PXRD diffractogram of SGS and CS (Fig. 4.12) did not show any sharp, distinct diffraction peaks but only broad maxima which are consistent with semi-crystalline material having significant amorphous content. This has been described in literature as a halo pattern (Sharma *et al.*, 2015). Contrastingly, PXRD diffraction patterns of GEL and CSD remained at baseline level because they were not able to deflect the X-rays to any detectable degree, confirming their non-crystalline status. Crystalline solids are known to reflect X-ray beams at certain angles of incidence which appears as sharp, distinct diffraction peaks (Shah*et al*., 2006). The diffraction pattern of SGS was superimposed on that of SGS-PM suggesting that no chemical change or interaction occurred as a result of co-processing (Fig. 4.13). The peak positions of IBU persisted in the diffraction pattern of IBU + SGS, confirming their compatibility. Similarly, the broad peak occurring between 10 ° and 20 ° of the SGS diffraction pattern was reflected in its mixture with Ibuprofen. This also signifies compatibility. No new peak was observed in the diffraction pattern of IBU + SGS, confirming the absence of a new molecule.

5.2.8 Fourier transform infrared spectroscopy

FT-IR spectroscopy was used to determine if there was any significant molecular interaction between CS, GEL and CSD that could lead to incompatibility. FT-IR spectroscopy is used to deduce the functional groups that are present and absent in a molecule (Silverstein and Webster, 1998). Functional groups in a molecule absorb infrared photons of characteristic energies which can be reflected as a plot of photon

energy versus intensity of absorption called the infrared spectrum. The infrared spectrum reveals vibrations of atoms in molecules. The beauty of the spectrum is the close and accessible relationship between infrared bands and molecular structure. When two or more substances are mixed, physical blends versus chemical reaction are reflected by changes in characteristic bands. The FT-IR spectrum of SGS did not reveal any chemical reaction occurring during co-processing because the characteristic absorption bands observed in the IR spectrum of CS, GEL and CSD were maintained in the spectrum of the co-processed mixture. There was no evidence of covalent bonding due to the close association of the three components during co-processing.The improved functionality observed in SGS could be attributed to physical modification occurring in its particle structure(El-Barghouthi *et al.*, 2008). This was confirmed by the superimposition of the IR spectrum of SGS-PM on the spectrum of SGS. Both spectra revealed no changes in the band positions and intensity of peaks. This finding is consistent with studies carried out byKittipongpatana and Kittipongpatana (2012)where no chemical reaction occurred between starch and silicon dioxide during co-processing by co-precipitation. Drug-excipient compatibility was also confirmed by FT-IR analysis from the overlay plot (Fig. 4.17) showing the individual spectrum of IBU, SGS and IBU+SGS. No new functional group or molecule was formed as a result of chemical interaction between the IBU and SGS. The principal IR bands for each spectrum were reflected in the final spectrum of the mixture. This confirms the suitability of SGS as an excipient in the formulation of Ibuprofen tablets by direct compression.

5.2.9 Dynamic vapour sorption

The physical and chemical properties of pharmaceutical solids are critically dependent on the presence of moisture, for example, flow, compaction, dissolution, stability, storage, processing into formulations, and final product packing (Airaksinen *et al.*, 2005; Murikipudi *et al.*, 2011). The interaction of moisture with pharmaceutical solids is highly crucial to an understanding of water-based processes, for example, manufacturing processes or prediction of solid dosage form stability and shelf life (Nokhodchi, 2005). Both the active pharmaceutical ingredient (API) and excipients in the formulation have different moisture sorption properties that can result in unexpected processing-induced phase transitions and they can affect solid-state phase transitions in the final dosage forms (Airaksinen *et al.*, 2005). Phase transformations in formulations can lead to instability in physicochemical, biopharmaceutical, and processing properties of products. The moisture sorption isotherms displayed as Figs. 4.18 and 4.19 characterize the amount of moisture adsorbed at different equilibrium concentrations in the gas phase. Comparing the moisture sorption profiles of CS and SGS, there was no significant difference in the amount of moisture adsorbed at maximum RH (80 %). This indicates that co-processing of cassava starch with gelatin and colloidal silicon dioxide did not modify its degree of hygroscopicity. This finding is consistent with a study carried out by Kittipongpatana and Kittipongpatana (2012) where the co-precipitation of rice starch with colloidal silicon dioxide in the presence of NaOH had no significant effect on the moisture sorption profile of the developed co-processed excipient. Similarly, the work of Daraghmeh *et al* (2015) confirms the superiority of amorphous materials over crystalline substances in the degree of moisture absorption. Starch has been categorized as a hygroscopic material (Assen *et al.*, 2011; Murikipudi *et al.*, 2011) attributable to its amorphous nature. In contrast to crystalline materials, amorphous

materials have a high capacity for moisture sorption i.e. the amount of water sorbed is greater than what could be accounted for only by surface adsorption (Airaksinen *et al.*, 2005; Daraghmeh *et al.*, 2015). Water molecules have a strong affinity for starch due to the combination of an abundance of hydroxyl groups and a relatively open conformation of the anhydroglucose units that comprise starch. The crystalline regions in starch granules are composed of partially crystalline amylopectin and the amorphous regions of linear amylose and branching points of amylopectin. At low RH, water is bound directly to the available anhydroglucose units throughout the starch grain. When RH is increased, polymer–polymer hydrogen bonds break down, which allows water to begin binding to other water molecules already bound to anhydroglucose units. As the moisture content increases, the sorbed moisture causes a subsequent swelling of the biopolymer, the degree of crystallinity decreases, and there is an increasing availability of the polar groups to the water molecules. Finally, at high RH, water directly bound to one hydroxyl group per anhydroglucose unit as well as water can also bind to other water molecules such as free water (Airaksinen *et al.*, 2005). In spite of the high degree of hygroscopicity exhibited by SGS, the amount of moisture adsorbed did not exceed 14 % as specified by the USP/NF (2009). The stability of any formulation incorporating SGS as an excipient is not likely to be impaired as a result of the presence of moisture in its internal structure. The moisture sorption profile of SGS in comparison with PSV and SLC was ranked in the following order: SGS > PSV > SLC. SLC adsorbed the least amount of moisture due to the high content of lactose (85 %) which is crystalline in nature. A greater percentage of pharmaceutical polymer excipients, such as starches, cellulose derivatives, proteins, and synthetic hydrogels, are amorphous to a large extent (Chen, 2009) accounting for the observation seen in SGS and PSV.

5.3 Physicomechanical Properties

A comprehensive understanding of the material properties of an excipient is essential to the successful development, scale-up, and manufacturing of solid dosage forms (Zhou and Qiu, 2010). The robustness of the direct compression is determined to a large extent by the physicomechanical properties of the excipients utilized in the process (Nachaegari and Bansal, 2004; Saha and Shahiwala, 2009). Some of these properties include flow and compressibility. Powder flow plays a critical role in direct compression tableting. Good flowability of powder is needed for content uniformity and less weight variation in the final tablets. The powder blend of API and excipient(s) must flow uniformly into the tablet dies to obtain a uniform product (Bodhmage, 2006). Flow indicators like angle of repose, Carr's index (CI) and Hausner's ratio (HR) were used in this study to assess powder flow. Measured angle of repose for SGS revealed an improvement in flow as compared to CS and SGS-PM. As a rule of the thumb, angle of repose less than 30 ° is an indication of good flow and it is a function of the cohesiveness of the powder. There was a decrease in interparticulate friction due to increase in particle size as a result of co-processing which reduced the cohesiveness of the powder thereby enhancing the flow of SGS. Similar observations were seen with PSV and SLC. The spherical shaped particles of SGS may also have contributed to its enhanced flow due to a reduction in the number of contact points between particles. Perfectly spherical particles have the least possible number of contacts and are usually the most readily flowable (Bodhmage, 2006; Zhou and Qiu, 2010). Generally, co-processing was found to improve the flow of powder by lowering the angle of repose (Kittipongpatana and Kittipongpatana, 2012; Adeoye and Alebiowu, 2014a; Daraghmeh *et al.*, 2015). Flowability issues are generally attributed to the cohesive nature of fine powders or to the mechanical interlocking of powders with irregular shapes. The flow

indices of HR and CI (Table 4.9) also revealed an improvement in the flow properties of SGS as compared to CS and SGS-PM. Carr's index (CI) is a measure of powder bridge strength and stability, and Hausner's ratio (HR) is a measure of the interparticulate friction and consolidation (Kilicarslan *et al.*, 2009). Generally, lower values of these parameters are indicative of excellent flow. The true density gives an insight into the packing behaviour of the powder in tableting conditions and higher values have been associated with crystalline materials (Camargo, 2011; Tuomela *et al.*, 2015). According to Khomane *et al* (2013), higher true density was as a result of closer molecular packing and this translates to greater bonding strength observed in tableting. Due to the loose packing of chains within the molecular structure of SGS, a lower value of true density was obtained in comparison to PSV and SLC. The difference observed in the true density values of SGS and CS has been attributed to the deposition of colloidal silicon dioxide in the particle structure of SGS which made the material much lighter than the parent CS (Camargo, 2011). The obtained values of true density were consistent with the values reported (Klevan, 2011).

5.4 Compaction Studies

Powder compaction is the process of significant powder consolidation under applied pressure, leading to sufficient bonding and formation of tablets. Under the influence of applied pressure, powders may either consolidate by plastic deformation, elastic deformation or by fragmentation of particles (Joiris *et al*., 1998; Zhou and Qiu, 2010; Mahmoodi, 2012). Fragmentation increases the number of surfaces available for bonding, while plastic deformation brings particles in close proximity to each other thereby increasing the area available for bonding. Hence, these two particle deformation mechanisms are bond producing and have a positive effect on tablet strength. Elastic deformation can lead to bond separation after removal of the applied pressure as the tablet

recovers in height (Klevan, 2011). With respect to mechanical properties, a combination of plastic deformation and brittle fracture is desirable and necessary because they are both irreversible and promote tableting (Egart *et al.*, 2014). The yield pressure, P_Y, as obtained from the linear portion of the Heckel plot (Table 4.10) is an index of plasticity and represents the pressure at which the material begins to form a coherent compact by apparent plastic deformation. Higher values tending towards 200 MN/m^2 are characteristic of brittle materials while values ≤ 80 MN/m^2 have been associated with plastic materials. SGS deformed at a higher pressure compared to SGS-PM and this has been attributed to the deposition of silicon dioxidein the internal structure. Camargo (2011) observed that silicification could increase brittleness in the powder bed due to particle rearrangement and deaggregation of fumed silica aggregates. The presence of gelatin in the particle structure of cassava starch may also have contributed to the brittle behaviour of SGS as gelatin is known to deform by brittle fracture under applied pressure. Based on the standards suggested by Roberts and Rowe (1987) for the mechanical classification of pharmaceutical powders, SGS can be regarded as a brittle material. The D_0 values for SGS and SGS-PM were comparable and this corresponds to the degree of densification occurring due to slippage and particle rearrangement at the early stages of compression. The total degree of densification occurring at low pressures represented by D_A was higher for SGS than SGS-PM. SGS had a higher tendency for fragmentation as evidenced by the D_B parameter which was higher than that of SGS-PM. These observed Heckel parameters may be due to the contribution of silicification in modifying the surface properties of SGS (Camargo, 2011). Heckel analysis was originally developed for metals but later extended to pharmaceutical powders (Alderborn and Nyström, 1996). Hence, a lot of caution must be taken when using this equation to characterize the densification behaviour of powders with several deformation mechanisms.

Due to the non-log-linearity encountered with Heckel analysis, Kawakita equation was adopted to linearize the compression data. The Kawakita parameters *a*, *b*, *ab*, and *1/b* were calculated from the intercept and slope of the plot as seen in Table 4.10. The parameter, *a*, which represents the compressibility, was higher for SGS than SGS-PM indicating that co-processing of cassava starch with the other excipients improved its compressibility. This can be attributed to an increased tendency for volume reduction under applied pressure corresponding to a reduction in porosity due to an alteration in surface properties of the co-processed excipient. Particle shape may also have contributed to the improved compressibility by ensuring a more rapid densification of the powder bed during compression. This finding is in agreement with a study conducted by Daraghmeh *et al* (2010) where the co-processing of chitin with mannitol improved the compressibility. The parameter, *1/b*, is an inverse measure of the amount of plastic deformation occurring during the compression process and defines the pressure required to reduce the powder bed by 50 %. SGS demonstrated a more rapid onset of plastic deformation compared to its physical mixture and is probably due to the low degree of interparticulate interactions that opposes volume reduction thereby promoting the ease of compression (Camargo, 2011). The relatively high value of *ab* for SGS, which is a measure of the extent of particle rearrangement, is an indication of the high degree of packing occurring at the onset of compression. This implies that co-processing reduces the surface micro-irregularities of cassava starch and facilitates particle rearrangement during the densification process of compaction (Daraghmeh *et al.,* 2010). As a result, co-processing of cassava starch with gelatin and colloidal silicon dioxide has positively improved the compression characteristics of starch as shown by Kawakita analysis.

The transformation of powders into tablets by compaction involves a two-stage process namely compression and consolidation. During consolidation stage, interparticulate bond formation takes place. The degree of interparticulate bonding (bonding area) and bond strength (bonding strength per unit area) determines the final quality of the tablets. The extent of bonding area can be obtained from the compressibility plots (porosity vs compression pressure), whereas the bonding strength per unit bonding area is obtained from the compactibility plot (porosity vs tensile strength). Collectively both parameters contribute to the quality of the tablets given by tabletability (Upadhyay *et al.*, 2013). Compressibility has been defined as the ability of the powder bed to undergo volume reduction under the given pressure and is represented by a plot of tablet porosity against applied pressure (Khomane *et al*., 2013). The lower the porosity at a given pressure, the higher is the compressibility. Higher compressibility implies greater bonding area of the tablet. A decrease in porosity was seen with an increase in compaction pressure for SGS and SGS-PM. Compressibility of SGS remained higher than SGS-PM at all the compaction pressures (Fig. 4.23). Mechanical properties and particulate properties are among other factors that have contributed to the compressibility of a material (Joiris *et al.*, 1998).

Compactibility is the ability of a material to produce tablets with sufficient tensile strength under the effect of densification and is represented by a plot of tablet tensile strength versus porosity (Egart *et al.*, 2014). The tensile strength of SGS and SGS-PM increased with a decrease in porosity and an increase in compaction pressure (Fig. 4.24). SGS showed higher tensile strength, at a given porosity, indicating higher bonding strength in comparison to SGS-PM. Silicification may have contributed largely to increase in compactibility due to the modification of the particle surface roughness (Hamed*et al.*, 2010; Camargo, 2011).

Compactibility of pharmaceutical powders is mainly governed by the dominant bond mechanisms (intermolecular forces, solid bridges, mechanical interlocking) and the surface area over which these bonds are active. Intermolecular forces constitute the dominant bond mechanism for pharmaceutical materials. These intermolecular forces (van der Waals force, electrostatic force, and hydrogen bonds) are usually weak interactions, hence the surface area (more interactions can be formed) might have a significant effect on the mechanical strength of compacts (Klevan, 2011; Mahmoodi, 2012).

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effectof compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure. Tabletability of SGS remained higher at all measured compaction pressures (Fig. 4.25) in comparison to SGS-PM with maximum tensile strength attained at 100 MPa. The concept of inter-particulate *bonding area* and *bonding strength* otherwise referred to as BABS model has been used to explain tabletability of powders (Sun, 2011). The superior tabletability observed with SGS as compared to SGS-PM can be attributed to the strength of the intermolecular hydrogen bonding holding the particles together as well as increased interfacial adhesion between particles. The findings of Adeoye and Alebiowu (2014a)have shown that compressibility, compactibility and tabletability is enhanced when excipients are co-processed together. Tabletability has been conferred on a material by the interplay between the compaction conditions (pressure and strain rate), mechanical properties, particle properties and chemical nature of the surfaces (Zhou and Qiu, 2010). Tablets of appropriate mechanical strength can only be produced from materials with sufficient tabletability.

5.5 Tablet Properties

In order to validate process and product development of tablets, they are routinely subjected to a series of tests prescribed by compendial and non-compendial standards. Tablets are expected to conform to specifications set by these standards before their quality can accepted or approved for use.

The test for uniformity of weight is a simple way to assess variation in content of drug dose, which makes the test useful as a quality control procedure during tablet production. There was no significant variation in the weights of tablets produced by SGS, PSV and SLC as they were all within the limits specified by the USP/NF (2009). This has been attributed to the uniformity in the flow of powder volumes of their respective formulations into the die cavity during tableting. The flow properties as assessed by angle of repose (Table 4.9) revealed that all three materials had excellent powder flow which ensured uniform filling of the powder mix into the die cavity during tableting.

The mechanical strength of tablets is an important property and it plays a significant role in product development and manufacturing control. Tensile strength and hardness serve as the indicators of the strength of a compact. Pharmaceutical ingredients which bond well together are capable of forming tablets with high tensile strength. The tensile strength of tablets prepared with different excipients ranked in the following order: PSV > SGS > SLC with PSV exhibiting superior tensile strength when compressed at the same pressure. This can be explained by the high bonding capacity of microcrystalline cellulose (MCC) which densify by plastic deformation and promote interparticulate bonding through hydrogen bonding and mechanical interlocking of the irregularly shaped elongated particles of MCC. The presence of silicon dioxide on the surface of MCC may also have contributed to its compressibility as a compressibility-enhancing

agent (Rojas and Kumar, 2011). Therefore, the strength of a tablet depends on the number of bonding sites and the strength of bonding between particles. The nature of this interparticulate bonding attraction is primarily van der Waals forces in pharmaceutical tablets. Other forces that may be implicated in tablet bonding include hydrogen bonding, solid bridges, mechanical interlocking and asperity melting or fusion (Klevan, 2011; Mahmoodi, 2012). Tablets of SGS, most likely, had lesser bonding sites than PSV due to the lower relative densities obtained during Heckel analysis. Relative density (solid fraction) or porosity is a major determinant of tablet hardness (Patel*et al.*, 2006; Zhou and Qiu, 2010; Sun, 2011). The denser the powder bed, the lower the porosity and the higher the strength of tablet. However, this may not apply to all materials and may depend to a large extent on the densification behaviour of the material. Essentially, tablets with sufficient mechanical strength have been produced using co-processed excipients(Hamed, 2009; Hamed*et al.*, 2010; Rojas *et al.*, 2012; Okoye *et al.*, 2014). Elastic recovery arising during the decompression stage of tableting negates the strength of tablets. A parameter referred to as bonding index (BI) has been used to gain more insight on the extent to which elastic recovery affects the bonds formed during compaction stage of tableting. Bonding index has been defined as the ratio between tensile strength and hardness of a tablet (Zhou and Qiu, 2010). It is a measurement of the survival of tablet bonding during decompression. Maximum contacts (bonding) between particles are established at the end of compression. However, some bonding may be lost (broken) during the decompression due to elastic recovery. A large BI indicates strong bonding due to a relatively small fraction of lost bonding. A bonding index exceeding 0.01 is typically desired. There was no significant difference in the bonding index of all three excipients as the values obtained were closely similar.

One of the main objectives of compaction is to obtain tablets that are sufficiently strong to withstand subsequent processing and transportation. Tablet friability is a measure of the ability of tablets to withstand stresses. According to the USP/NF (2009), tablets should show no more than 1 % loss in weight. This test is more rigorous than the crushing strength test since in the friability test compacts are submitted to mechanical stresses simulating wearing due to handling and mechanical shock. All the batches of tablets produced met the requirement except for SLC tablets. The failure of SLC tablets to pass friability test may be attributed to the presence of starch interspersed in the particle structure of lactose leading to the formation of weaker bonds that produced weak tablets.

The ability of a compressed tablet to release the drug is measured by the disintegration test. This is the time it takes for a dosage form to break into primary particles upon exposure to an appropriate medium with mild agitation. Disintegration tests are only indirectly related to drug bioavailability and product performance. For conventional immediate release tablets, disintegration should not exceed 15 min. It is markedly affected by formulation ingredients and processing, hence, it's used as a quality control tool. The study revealed that all the tablets produced passed the disintegration test with SGS tablets disintegrating in less than 30 s. This has been attributed to the amorphous content of starch which facilitates disintegration and the degree of porosity of the tablets formed. The enhanced disintegration time of SGS tablet may not be unrelated to deposition of silicon dioxide on the surface of starch during co-processing which leads to creation of more pore channels that imbibe more water into the matrix of SGS during disintegration (El-Barghouthi *et al.*, 2008; Daraghmeh *et al.*, 2015).

Drug dissolution is the process by which drug molecules are liberated from a dosage form and enter into solution. This is an important step because only drugs in solution

can produce pharmacological action. The effectiveness of a tablet in releasing its drug for systemic absorption is influenced by the rate of disintegration and deaggregation of granules. The drug release profile for SGS, PSV and SLC reveal that more than 80 % of ibuprofen was released after a time period of 60 min. This agrees with the specification for drug release as mentioned under the monograph for Ibuprofen (USP/NF, 2009). The time taken to achieve 50 % drug release was same for SGS and SLC due possibly to the rapid disintegration time observed. Drug release from PSV was slower compared to the other two excipients and this observation can be correlated to the greater tensile strength of its tablets which invariably slows down its disintegration into constituent particles. Mathematical comparisons between the drug release profiles were made using the concept of similarity factor (f_2) as reported in literature (Kumar *et al.*, 2008). This similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of the squared error and is a measurement of the similarity in the percentage drug release between any two curves. $f_2$values greater than 50 (50–100) implies similarities in the drug-release profile of the two curves. On the basis of the values obtained, SGS and SLC had similar drug release profiles compared to SGS and PSV. Due to the high plastic deforming ability of PSV, a stronger interparticulate attraction between the drug and excipient particles may have led to the slow detachment of the drug during dissolution. Contrastingly, the brittle nature of SGS and SLC, coupled with the high level of porosity in both tablet matrixes facilitated the rapid release of ibuprofen due to water uptake by capillary action.

CHAPTER SIX

6.0 SUMMARY, CONTRIBUTION TO KNOWLEDGE, CONCLUSION AND RECOMMENDATIONS FOR FURTHER STUDY

6.1 Summary

Co-processing was employed as a particle engineering technique to improve the functionality of cassava starch in the formulation of ibuprofen tablets by direct compression. This was achieved by co-processing cassava starch with gelatin and colloidal silicon dioxide in optimized ratios to develop a robust excipient with a multifunctional profile.

Design of Experiment (DoE) was applied to optimize the composition of the co-processed excipient by determining the proportion by percentage weight of each of the ingredients used in co-processing. The optimized formula for preparing the coprocessed excipient, *StarGelaSil* (SGS) with a multifunctional profile was found to be Cassava starch (90 %), Gelatin (7.5 %) and Colloidal silicon dioxide (2.5 %) respectively.

Solid-state characterization of StarGelaSil revealed an increase in size of spherically-shaped particles with a rough surface. The birefringent property of cassava starch was not lost as a result of co-processing. The material was found to be largely amorphous in nature, moderately hygroscopic and compatible with the drug of choice for the study.

Flow and compression properties of *StarGelaSil* were enhanced when compared to cassava starch and the physical mixture of the constituent excipients. There was an improvement in the compressibility, tabletability and compactibility (CTC) profile of *StarGelaSil* when compared to the physical mixture of the constituent excipients.

Tablets produced by *StarGelaSil* met the USP/NF (2009) specifications for desirable tablets and compared well with tablets produced by Prosolv® and StarLac®.

6.2 Contribution to Knowledge

- The application of a scientific approach (DoE) to optimize the composition of the co-processed excipient, SGS.
- The study was able to show the distribution of gelatin in the matrix of the co-processed excipient using confocal laser scanning microscopy.
- The development of a three-component multifunctional co-processed excipient containing cassava starch as the parent excipient.

6.3 Conclusion

The aim of this study was to improve the functionality of cassava starch for tablet formulation by direct compression. This was achieved by co-processing cassava starch with optimized quantities of gelatin and colloidal silicon dioxide as determined by Design of Experiment (DoE). The resulting excipient coded "*StarGelaSil*" exhibited superior characteristics required for tableting when compared to its parent excipient (Cassava starch) and the physical mixture, *StarGelaSil-PM* (SGS-PM). Ibuprofen tablets produced using StarGelaSil as the sole excipient were found to have met the USP specifications for desirable tablets and compared well with commercially available co-processed excipients (Prosolv® and StarLac®) in terms of performance. *StarGelaSil*can therefore be put forward as a suitable excipient for tablet formulation by direct compression.

6.4 Recommendations for further study

- Design of Experiment (DoE) can be applied to optimize the co-processing technique.
- Further characterization studies at molecular level can be done to gain more insights into the basis for improved functionality as a result of co-processing.
- Other compaction models like Walker, Rhyskewitch and Modified Heckel analysis can be employed to characterize the compaction behaviour of SGS.

- Formulation studies can be carried out using other poorly compressible drug models.

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APPENDICES

Table A1.1: Dilution potential data

Mass fraction of excipient	Tensile strength (MPa)		
	SGS-A	SGS-B	SGS-C
0.2	0.854 (0.019)	0.798 (0.035)	1.004 (0.014)
0.4	1.422 (0.02)	1.344 (0.03)	1.319 (0.024)
0.5	1.552 (0.026)	1.477 (0.057)	1.338 (0.028)
0.6	1.591 (0.033)	1.545 (0.08)	1.524 (0.065)
0.8	1.676 (0.05)	1.743 (0.058)	1.775 (0.052)
1	2.523 (0.032)	2.271 (0.017)	1.956 (0.036)

Table A1.2: Particle size analysis for CS

Size (µm)	cum	freq	% freq	cum %
5.0 - 6.9	7	7	1.105845	1.10584518
7.0 - 8.9	72	65	10.26856	11.3744076
9.0 - 10.9	210	138	21.80095	33.1753555
11 - 12.9	376	166	26.22433	59.399684
13 - 14.9	486	110	17.37757	76.7772512
15 - 16.9	573	87	13.74408	90.521327
17 - 18.9	612	39	6.161137	96.6824645
19 - 20.9	628	16	2.527646	99.2101106
21 -22.9	631	3	0.473934	99.6840442
23 - 24.9	632	1	0.157978	99.8420221
25	633	1	0.157978	100

Table A1.3: Particle size analysis for SGS

Size (μm)	cum	freq	%	cum %
0 - 19.9	114	114	22.00772	22.00772
20 - 39.9	381	267	51.5444	73.55212
40 - 59.9	470	89	17.18147	90.73359
60 - 79.9	503	33	6.370656	97.10425
80 - 99.9	515	12	2.316602	99.42085
≥ 100	518	3	0.579151	100

Table A1.4: Compaction data for SGS

Pressure (MPa)	Porosity (□)	Tensile strength (MPa)	ln (1/ε)	P/C
8.88	0.3342	0.252641552	1.0965064	17.61787681
17.76	0.19779	0.713914556	1.6214274	30.18174511
26.64	0.10618	2.467786219	2.2474516	42.24674817
35.52	0.09011	2.765093864	2.4080056	55.74643741
44.4	0.08755	3.4266132	2.4414752	69.5771528
53.28	0.0807	3.216811872	2.5183191	83.13443584
62.16	0.08401	3.177727674	2.4789367	97.18854068
71.04	0.08403	2.984285363	2.4798042	111.075576
79.92	0.09189	2.615389754	2.3924222	125.579242
88.8	0.08322	2.803014632	2.4872221	138.7702989
97.68	0.09311	3.182788166	2.3770012	153.5963007
106.56	0.08737	4.087859977	2.4421732	166.9629284

Table A1.5: Compaction data for SGS-PM

Pressure (MPa)	Porosity (□)	Tensile strength (MPa)	ln (1/ε)	P/C
17.76	0.2513461	0.322712621	1.38131356	35.0101104
26.64	0.1617648	0.773425786	1.82200412	47.5746869
35.52	0.1492546	0.828730513	1.90694757	62.7312668
44.4	0.1306985	0.889953592	2.03556631	77.1261991
53.28	0.1186275	0.941130366	2.13250145	91.6262252
62.16	0.1313902	0.936212513	2.03087946	108.043926
71.04	0.1166918	0.956103513	2.14862223	121.974071
79.92	0.1260747	1.024737713	2.08173390	138.366741
88.8	0.1205869	1.179276454	2.1181926	152.969834
97.68	0.116547	1.27399027	2.15010307	167.696332
106.56	0.1148088	1.179196319	2.16495002	182.6828931

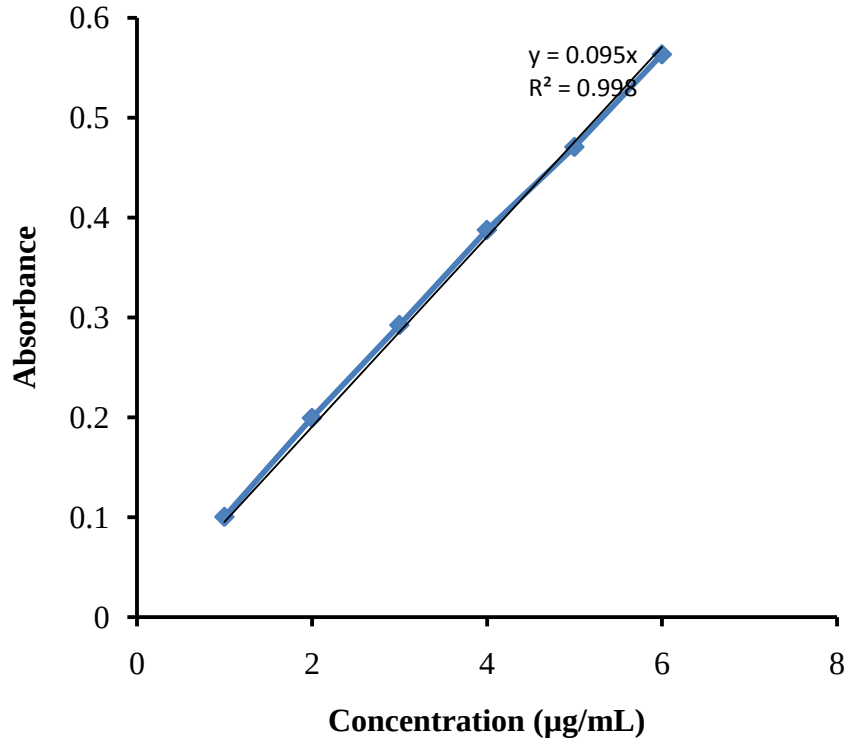

Figure A1.6: Calibration curve of ibuprofen

Table A1.7: Dissolution data for SGS

		SGS	
Time (min)	**Absorbance**	**Conc (µg/mL)**	**% drug released**
5	1.1534	121.4105263	55.18660287
10	1.2286	129.3263158	58.784689
20	1.3699	144.2	65.54545455
30	1.8466	194.3789474	88.35406699
45	1.8472	194.4421053	88.38277512
60	1.8476	194.4842105	88.40191388

Table A1.8: Dissolution data for SLC

		SLC	
Time (min)	**Absorbance**	**Conc (µg/mL)**	**% drug released**
5	1.3266	132.0105263	60.00478469
10	1.4235	142.5894737	64.81339713
20	1.6044	163.0526316	74.11483254
30	1.906	199.7894737	90.81339713
45	1.905	198.7368421	90.33492823
60	1.906	201.2842105	91.49282297

Table A1. 9: Dissolution data for PSV

		PSV	
Time (min)	**Absorbance**	**Conc (µg/mL)**	**% drug released**
5	0.6381	67.16842105	30.53110048
10	0.8979	94.51578947	42.96172249
20	1.0886	114.5894737	52.0861244
30	1.2744	134.1473684	60.97607656
45	1.5346	161.5368421	73.42583732
60	1.79	188.4210526	85.64593301