DESIGN AND EVALUATION OF MICROCRYSTALLINE TAPIOCA STARCH AND ITS UTILISATION IN THE FORMULATION OF MICROCRYSTARLAC AND MICROCRYSTARCELLAC FOR DIRECT COMPRESSION

BY

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PhD /Pharm.Sci/02962/2006- 07

A DISSERTATION SUBMITTED TO POST GRADUATE SCHOOL
AHMADU BELLO UNIVERSITY, ZARIA
NIGERIA

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY IN PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY

FACULTY OF PHARMACEUTICAL SCIENCES, AHMADU BELLO UNIVERSITY ZARIA, NIGERIA

SEPTEMBER, 2012

DECLARATION

I hereby declare that this dissertation was written by me as a record of my research work, carried out under the supervision of Dr. (Mrs) A.R Oyi, Dr. A.B Isah, and Prof. M. A Ibrahim. No portion of this dissertation has been presented in any previous work for award of a degree. The works of other investigators have been duly acknowledged and references made accordingly.

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DEDICATION

This research work is duly dedicated to Almighty God for His special grace and mercy extended to me.

ACKNOWLEDGEMENT

I give all glory to Almighty God for giving me the insight at the beginning and for His wisdom that guided me morning, day and night throughout this research work.

My profound gratitude goes to my supervisors, Dr. (Mrs) A.R Oyi, Dr. A.B Isah and Prof. M.A Ibrahim for their inspiration and total commitment towards the completion of this research work.

Dr. Abdulkarim Agunu has been a good friend that stood by me during my M.Sc. and Ph.D, I duly acknowledge him for his agape love.

My appreciation also goes to Mr. Etim Malachy of the Department of Pharmaceutics, University of Ibadan for his help during the period of my compaction studies in Ibadan.

I salute my wife's courage and the sacrifices of my family throughout the research period.

ABSTRACT

Native tapioca starch (NTS) was modified by annealing and enzyme hydrolysis to obtain microcrystalline tapioca starch (MCTS), which was coprocessed with α-lactose monohydrate (LMH) to form Microcrystarlac (MSL). MCTS was also coprocessed with LMH and microcrystalline cellulose (MCC) to yield Microcrystarcellac (MSCL). NTS was extracted from cassava tuber (*Mannihot esculenta Crantz*) using a standard method. The powder suspensions were prepared at a concentration of 40 %w/v in five separate conical flasks. The starch granules were annealed for 1 h to obtain annealed tapioca starch (ATS) which was subsequently hydrolyzed with α-amylase at 60^{o} and pH 7 for 1, 2, 3, 4, and 5 h in a water bath. The reaction was terminated and neutralized with 0.1 N HCl and 0.1 N NaOH respectively. The MCTS was washed, recovered by sedimentation and air dried at room temperature for 72 h. Following characterization, sieve fraction >75-250 μm from granules modified for 3 h was coprocessed with LMH at concentrations of 10 to 50 % w/w as a dried mass relative to MCTS. In another development MCTS was coprocessed with LMH and MCC at concentrations of 10-50 % (MCTS), 45-25 % (α-LMH) , 45-25 % (MCC). Granule size ranges >75 - 250 μm, and >90 - 250 μm were characterized and compacted at a range of compression load 2.5 to 12.5 KN.

The average granule sizes of NTS, ATS, and MCTS were 10 $\pm$ 0.3 μm, 11.5 $\pm$ 0.3 μm, and 13$\pm$ 0.5 μm respectively. Average flow rate, angle of repose and Carr's index were 2 g/s, 43^{o}, 50% respectively for NTS, 2.5 g/s, 35^{o}, 37.5 % for MCTS, and 3 g/s, 32^{o}, 22 % for MSL (granule size range >90 - 250 μm and component ratio, 50:50).

The corresponding values for the direct physical mixture of MCTS and lactose were 0.65 g/s, 40^{o}, 53 %. In terms of flowability and compressibility, MSL exhibited improved functionality over direct physical mixture of the primary excipients. Average flow rate, angle of repose and Carr's index were 2 g/s, 31.6^{o}, 13.4 % for MSCL (granule size range >90 - 250 μm and component ratio of MCTS, α-LMH, and MCC was 20: 40:40). The corresponding values for the direct physical mixture of MCTS, α-LMH and MCC were 0.45 g/s, 47.5^{o}, 52 %. Based on the flow rate and Carr's index, MSCL had improved functionality over direct physical mixtures of the primary excipients. The crushing strength for NTS, ATS and MCTS were: 30 N, 90 N and 100 N after 3 h of annealing and hydrolysis respectively, at compression pressure of 6 metric ton. The onset of plastic deformation P_y (yield value) were: MSCL (22.3 MNm^{-2}) > Cellactose (24.2 MNm^{-2}) > MSL (68 MNm^{-2}) > MCTS (143 MNm^{-2}) = Starlac (143 MNm^{-2}). The degree of plastic deformation occurring during compression (P_k) was in the following order: MSCL (16.3 MNm^{-2}) > MSL (16.4 MNm^{-2}) > Cellactose® (17 MNm^{-2}) > MCTS (17.7 MNm^{-2}) > Starlac® (19.1 MNm^{-2}). The dilution potential obtained for MCTS, MSL, and MSCL compacted with paracetamol (PCM) and ascorbic acid (AA) as active drug (API) were: 40 % AA with MCTS; 45 % PCM with MSL, 30 % AA with MSL; 50 % AA with MSCL, 45 % PCM with MSCL. The crushing strength of MCTS-40 % AA tablets was found to be 58 N; MSL- 45 % PCM, 80 N; MSCL- 45 % PCM, 70 N; MSCL -50 % AA, 68 N. The $T_{90\%}$ of tablet formulations of MCTS, MSL, and MSCL containing PCM and AA ranged from 12-14 min. They compared favourably with Cellactose® and much better than Starlac ®.

MSL and MSCL were rated equal with Cellactose® in PCM tablet formulation and better in functionality than Starlac ®.

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LIST OF ABREVIATIONS

AA	Ascorbic acid
AM	Amylose
AMP	Amylopectin
API	Active Pharmaceutical Ingredient
ATS	Annealed Tapioca Starch
B.P.C	British Pharmaceutical Codex
DT	Disintegration Time
NTS	Native Tapioca Starch
MCTS	Microcrystalline Tapioca Starch
MSL-B_5	Microcrystarlac Batch 5
MSCL-B_2	Microcrystarcellac Batch 2
MCC	Microcrystalline Cellulose
PCM	Paracetamol
α-LMH	Alpha Lactose Monohydrate
LSR	Lubricant Sensitivity Ratio
USP.	United States Pharmacopoeia

CHAPTER ONE

INTRODUCTION

1.1 Pharmaceutical tablet

Tablet is the most popular pharmaceutical dosage form. It is presently the dominating pharmaceutical dosage form, available in various forms and administered orally (Sam and Fokken, 1997). The advantages of this dosage form are manifold: tablets are cost effective to manufacture, convenient to dispense and store, and easy for patient to administer, and they provide a simple means of delivering the drug. Altering the design and content of the formulation to meet biopharmaceutical and pharmacological requirements will subsequently control the release of drug from the tablet. Moreso, tablets provide a supportive environment for drug stability and generally have a relatively long shelf-life.

The formulation of tablets involves different processing steps comprising operations where particles are engineered with the intention of optimizing functional properties such as technical performance during tableting and drug release properties (Sam and Fokken, 1997; Raseuack and Muller, 2002).

The formulation of tablets requires certain qualities of the powder, such as low segregation tendency, good flowability and compactibility. Also, the active ingredient and excipients must be chemically and physically stable during processing and storage (Bodga, 2002).

Tablets are produced by applying pressure to a powder bed in a die, which compresses the powder into a coherent compact. The powder is made up of either primary particle (i.e. as in direct compression) or aggregated primary particles (i.e. granules). When the powder bed is compressed, bonds are formed between the particles or granules, thus conferring a certain mechanical strength to the compact (Duberg and Nystrom, 1986).

The properties of the tablet, such as the mechanical strength, disintegration time and drug release characteristic are affected by both the properties of the constituent materials and manufacturing processes. Excipients, namely, diluents, binders and lubricants are generally needed in a formulation in order to facilitate the manufacturing process and to ensure that the resulting tablets have the desired properties.

Tablets should be sufficiently strong to withstand handling during manufacturing, transportation, usage and should also disintegrate to release the drug in a predictable and reproducible manner. It is thus pertinent to select the appropriate excipients and manufacturing processes when developing a new tablet formulation.

During manufacturing of pharmaceutical tablets, it is common to prepare particles with the aid of a liquid (wet granulation) that is subsequently removed by drying.

In this context the most common particle preparation method is wet granulation in which fine particles (mostly drug and excipient) are aggregated under convective mixing with the aid of an agglomeration liquid. Liquid bridges will be established between fine particles and when the liquid is removed, cohered aggregated particles are formed (Fuhrer, 1977; Israelachvili, 1992). Another particle preparation technique is preparation from a liquid e.g.

spray drying, codrying and crystallization which involve suspension or dissolution of the material in a liquid and removal of the aggregated particles by drying.

Tablets are made by uniaxial compression using eccentric presses or rotary tableting machines. The compaction of pharmaceutical powder results in an anisotropic and heterogeneous tablet with variation in such properties as porosity, density and mechanical strength throughout the tablets (Nystrom *et al*, 1993). When a powder bed in a die is compressed by an external load its volume is reduced and the inter-particulate porosity is decreased. The tablet porosity of most pharmaceutical materials is about 5 to 30 % (Armstrong and Palfrey, 1989; de Boer *et al*, 1986). No matter the level of compaction pressure used, tablets will rarely be non-porous.

Over the past hundred years, tablet manufacturers have developed materials and processes that can produce compressed tablets containing a precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost. The developments in the field of excipients, APIs and tableting machines during the past three decades have made tablet manufacturing a science and transformed tablets to the most commonly used dosage form (Sam and Fokken, 1997; Raseuack and Muller, 2002). The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, tamper proofness compared to capsules, and safety compared to parentral dosage forms have further promoted the use of tablets. The three well-known methods of tabletng are: wet granulation, dry granulation and direct compression (Table 1.1).

In recent years, a great deal of attention has been given to both product and process development. The introduction of new materials, availability of new forms of old materials

and the invention of new machinery have allowed the production of tablets by simplified and reliable methods (Sam and Fokken, 1997). The introduction of spray-dried lactose in 1960 and Avicel® in 1964 has changed tablet manufacturing process and opened avenues for direct compression tableting.

Direct compression is used to define the process by which tablets are compressed directly from the powder blends of active ingredient(s) and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved (Shangraw, 1988). The simplicity of the direct compression process is apparent from a comparison of the steps involved (Table 1.1) in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques (Shangraw, 1989).

It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets (Shangraw, 1989). The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials

Table 1.1: Major steps involved in granulation methods and direct compression.

Direct Compression	Dry Granulation	Wet granulation
Mixing/blending of **API** and Adjuvants. ↓ Compression	Mixing/blending of **API** and Adjuvants. ↓ Compression into slugs ↓ Size reduction of slugs and sieving. ↓ Mixing of granules with pharmaceutical aid(s) ↓ Compression	Mixing/blending of **API** and Adjuvants. ↓ Preparation of binder solution ↓ Mixing of binder solution step 2 with powder mixture ↓ Wet screening of damp mass ↓ Drying of wet granules ↓ Dry screening of granules and blending with pharmaceutical aid(s) ↓ Compression

Adapted from: Gohel and Jogani, (2005).

Wet granulation method impacts good flow and compressibility to powder materials but is very labourious due to multiple number of steps involved and high cost. It cannot be used for formulation of both moisture and heat sensitive API.

Dry granulation methods involve less number of steps compared with wet granulation method. Less cost is also involved, but heavy duty machines are required for compaction and slugging. This method is less effective compared with wet method of granulation but is useful for formulating heat and moisture sensitive API. The tablets formulated with direct compression method have longer half live compared with those produced with dry and wet method.

1.2 Compaction of Pharmaceutical Powders

When external forces are applied to a powdered mass, the bulk volume of the powder is reduced and energy is consumed. During this process, particles are moved into closer proximity to each other, bonds are likely to be formed between particles.

The establishment of bonds is associated with reduction in the energy of the system (Coffin-beach and Hollenbeck, 1983; Rowlings *et al*, 1995).

The term compression is used to describe the process of densification, while the term compaction describes the entire process from densification to bond formation. The mechanical strength of a tablet is normally employed as a measure of the compactibility of that material. Densification takes place by various mechanisms and different types of bonds may be established between particles.

The compaction of a powder can also be defined as its propensity, when held within a confined space, to reduce the volume under an applied pressure (Klevan, 2005). It is generally accepted that the compaction process is partitioned into several distinct stages. Consequently, it is difficult or impossible to use one simple monovariate equation to cover the entire densification region (Sonnergaard, 2001).

During the initial stage of compaction, i.e., at low pressure, it is commonly considered that some sliding, rearrangement or fragmentation of the particles may occur, resulting in a closer packing structure and reduced powder bed porosity. At a certain load, the reduced space and the increased interparticular friction will prevent any further interparticular movement. The reduction of the tablet volume is therefore associated with changes in the dimensions of the particles, i.e., fragmentation and deformation. Particles can change their shape temporarily by elastic deformation and permanently by plastic deformation. Particles can also fracture into smaller particles, i.e., particle fragmentation. The particle fragments can then fall into smaller spaces, which will further decrease the volume of the powder bed. These small particles can undergo deformation when pressure is further increased. One single particle may undergo these cycle of events several times during one compression cycle.

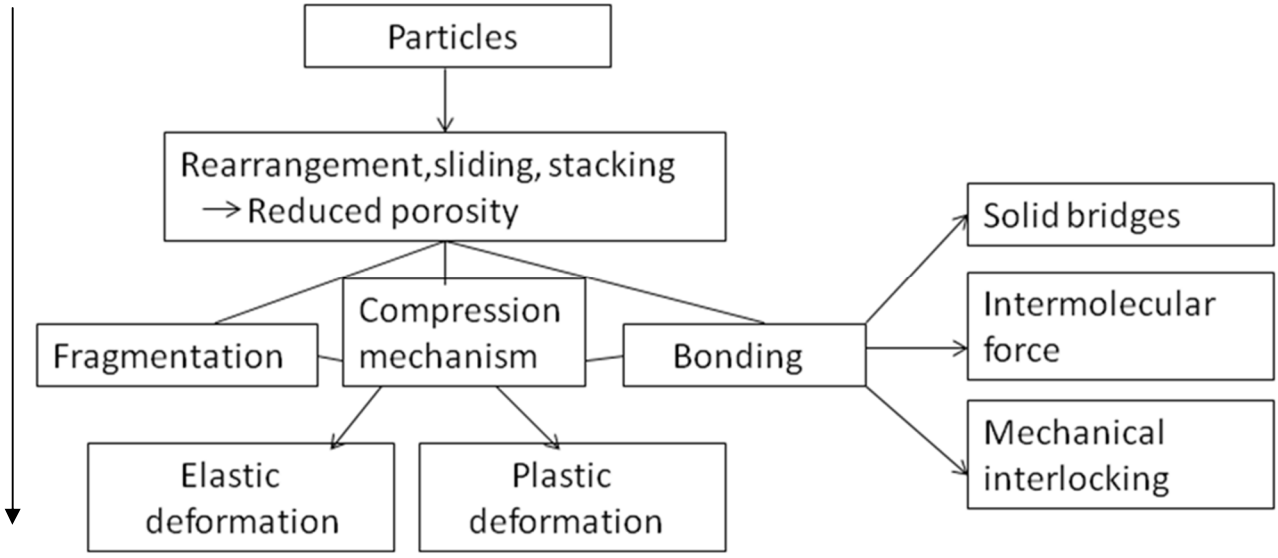


Fig. 1.1: The deformation mechanism of powder particles under compression

(Adapted from: Denny, 2002; Klevan, 2005)

The tensile strength of a pharmaceutical compact is determined by interparticulate bonds and may be described simply in terms of number of bonds and respective bonding force (Denny, 2002; Klevan, 2005). As in Figure 1.1, bonds may be solid bridges, interparticulate forces and/or mechanical interlocking. Particle fragmentation and particle deformation are both bond forming compression mechanisms that affect the number and the force of the interparticulate bonds, respectively (Denny, 2002: Klevan, 2005). Since deformation is the most common mechanism, most of the modeling has been focused on this particular property.

Four stages of events take place during compression (Klevan, 2005).

(i). Initial repacking of particles.

(ii). Elastic deformation of particles until elastic limit (yield point) is reached.

(iii). Plastic deformation and or brittle fracture then predominate until all the voids are virtually eliminated.

(iv). Compression of the solid crystal lattice then occurs.

1.3 Compressibility of pharmaceutical powders

The word compressibility is used to describe the volume reduction ability of a material, while the word compatibility describes the ability of such material to form a compact of a specified mechanical strength (Leuenberger, 1982).

1.31 Volume reduction mechanisms

The term compression refers to a reduction in the bulk volume of materials as a result of displacement of the gaseous phase. Stages involved in the bulk volume reduction of powdered solids include: the onset of the compression process, when the powder is filled into the die cavity, and prior to the entrance of the upper punch into the die cavity, the only forces that exist between the particles are those that are related to the packing characteristics of the particles, the density of the particle and the mass of the material that is

filled into the die. The packing characteristics of the powder mass will be determined by the packing characteristics of the individual particles (Duberg and Nystrom, 1986).

When external mechanical forces are applied to a powder mass there is usually a reduction in volume due to closer packing of the powder particles and in most cases, this is the main mechanism of initial volume reduction. Particles with a regular shape appear to undergo rearrangement more easily than those of irregular shape (York, 1978). However as the pressure increases further rearrangement of particles become more difficult and further compression leads to some type of particle deformation. If on removal of the load, the deformation is to a large extent reversible, then the deformation is said to be elastic (Duberg and Nystrom, 1986). All solids undergo elastic deformation when subjected to external forces. With pharmaceutical materials such as acetylsalicylic acid, elastic deformation is the predominant mechanism of compression within the range of maximum force encountered in practice.

In another group of powdered materials, pressures above elastic limit result in deformation not immediately reversible following the removal of the applied force. Bulk volume reduction in these cases results from plastic deformation and\or viscous flow of particles, which are squeezed into the remaining void spaces (Duberg and Nystrom, 1986). This mechanism predominates in materials in which the shear strength is less than the tensile or breaking strength. Plastic deformation creates highest number of clean surfaces. Because plastic deformation is a time dependant process, higher rate of force application will lead to the formation of less new clean surfaces and thus resulting in weaker tablets (Armstrong and Palfrey, 1989). Tablet formation is dependent on the formation of new clean surfaces.

In materials in which the shear strength is greater than the tensile strength, particles may be preferentially fractured, resulting in multiple but weaker bond formation. This is most likely to occur with hard, brittle particles and the phenomenum is called brittle fracture**.** Sucrose is a typical example of materials that behave in this manner. Brittle fracture creates clean surfaces that are brought in intimate contact by applied force.

The deformation characteristics of a material depend on its lattice structure. Small particles could deform plastically through a process known as microsquashing. In this case, the proportion of fine powders in any sample may be significant. Asperities sheared off highly irregular larger particles could also behave in this form; hence particle shape is an important factor in the design of a suitable directly compressible excipient.

1.3.2 Characterization of volume reduction mechanisms

The mechanical properties of a material have some influence on its volume reduction behavior. Both deformation and fragmentation can occur at different stages of densification process (Duberg and Nytrom, 1986). However one mechanism often predominates. These properties can be obtained by measuring the hardness and Young's modulus of a material in order to assess its plasticity and elasticity (Roberts and Rowe, 1987a). Measurements of elasticity and brittleness have been extrapolated to corresponding values for a tablet of zero porosity to obtain mechanical properties (Mashandi and Newton, 1987). Brittleness of a material has also been assessed by establishing the brittle fracture index (Hiestand and

Smith, 1984). Mathematical equation such as the Heckel, Kawakita and Cooper-Eaton equations have been developed based on porosity measured in order to obtain quantitative value of densification of a powder material (Paronen and Illka, 1996, Heckel, 196la, b). The usefulness of these equations will be determined by the porosity and pressure range studied. The reciprocal of the linear part of the Heckel plot is very useful in establishing the porosity of a powder material during compression and decompression (Heckel, 1961a, b). The value obtained is termed the yield pressure of the material (Hersey and Rees, 1971). The value obtained from in -die measurement during one compression cycle reflect both plastic and elastic deformation (Paronen1986; Duberg and Nystrom,1986) while the value obtained from out-of-die measurements based on the porosity of the tablets after ejection is a reflection of the extent of plastic deformation due to elastic expansion. The yield pressure obtained in-die is generally lower compare to out-of-die due to a low degree of elastic deformation (Paronen, 1986). The reflective difference in porosity or weight during compression can also be used to determine the extent of elastic deformation (Duberg and Nystrom, 1986; Armstrong and Haines-Nutt, 1972).

Heckel plots have been found valuable as a means of comparing materials with differing densification behavior as long as experimental conditions are constant (Duberg and Nystrom, 1986, York, 1979). There are many other relevant methods for characterizing the densification behavior of a powder material in the literature. These include: gas adsorption (Hardman and Lilley, 1973; Alderbon *et al.*, 1985a), mercury porosimetry techniques (Vromans *et al.*, 1980), and scanning electron microcopy (de Boer *et al.*, 1978; Krycer *et al.*, 1982).

1.3.3 Bonding mechanisms

Several works aimed at establishing bonding types adhering particles together in a tablet of dry powder compacted by direct compression confirmed distance attraction forces, solid bridges, and mechanical interlocking (Fuhrer, 1977). Distance attraction forces are a group of forces namely: van der -Waals forces, hydrogen bonds and electrostatic forces. These forces act between surfaces that are separated by some distance e.g. van der-Waals forces occur at a range of distances up to 100 to 1000 Å (Israelachvili, 1992). Hydrogen bonds will occur through electrostatic attraction both intra- and inter- molecularly (Israelachvili, 1992). Microcystalline cellulose is a very good example of a material where hydrogen bonds are responsible for the tablet strength (Reier and Shangraw, 1966).

Electrostatic forces are the result of triboelectric charging during mixing of powders and compaction. These forces though worthy of being mentioned are neutralized relatively and are therefore of no significance in pharmaceutical tablets (Nystrom *et al*., 1993). Solid bridges are formed as a result of particle-to-particle contact. Because of their structures, solid bridges are regarded as relatively strong bonds. Sodium chloride is a good example of material that bonds with solid bridges and the tablets formed have extended disintegration time (Fuhrer, 1977). Amorphous materials are more likely to bond with solids bridges (Sebhatu *et al*., 1997)

The term mechanical interlocking describes the locking and twisting of particles in a tablet.

This mechanism is mostly favoured by particle irregularities and roughness

(Fuhrer, 1977).

1.3.4 Mechanical strength of tablets

The mechanical strength of a tablet can be characterized by the force necessary to break the tablet. The response of a tablet to the applied force can be interpreted on the basis of fracture mechanics or bond summation concept. The main focus is on the propagation of cracks in the tablet during the strength testing (Davies and Newton, 1996).

The several methods used for measuring the strength of tablets include: the breaking strength, axial tensile strength, bending tests and diametral compression. The result obtained varies with the method. This could be attributed to the heterogeneity, anisotropic nature of the tablets and variations in the stress conditions induced by the test (Newton *et al*., 1992).

The diametral compression test is the most common strength test for pharmaceutical tablets and its value is used to calculate the radial tensile strength of a tablet (Fell and Newton, 1970a). During the test, the fracture occurs through a predetermined diametral cross section of the tablet. As a result, the radial tensile strength is likely to reflect the average strength of the tablet rather than the strength of the weakest plane in the tablet.

Axial tensile measurement is another method for determining the strength of a tablet. Here, the force necessary to break the tablet is obtained by pulling the tablet in the direction parallel to the applied force during the tablet compaction. This force is used to calculate the axial tensile strength (Newton *et al*., 1992).

1.3.5 Pore structure of tablets

The pore structure of tablets can be expressed simply in terms of pore size distribution and porosity. This can be influenced by the mode of densification and the compaction pressure. Increase in compaction pressure will bring the particles closer together reducing the tablet porosity. This will in turn affect tablet properties such as the strength and disintegration.

Pores are classified according to size into three categories; micropores (pore diameter

smaller than 2 nm), mesopores (pore diameter 2 – 50 µm) and macropores (pore diameter larger than 50 µm) (Sing et al. 1985). With nitrogen gas adsorption, depending on the equipment used, pore diameter range of 0.3 – 300 µm, i.e. mesopores and macropores, are determined. Low-pressure mercury porosimetry determines macropores (pore diameter 14 – 200 µm), and high-pressure porosimetry mesopores and macropores (pore diameter 3– 14 µm), depending on the equipment.

The porosity of tablets made of plastic materials increases with increased compression speed (Armstrong and Palfrey, 1989). This is attributed to lack of enough room for plastic deformation as the compression speed increases. Moreso, decrease in particle size of the powder has been shown to increase the tablet porosity (de Boer *et al*., 1986).

Some methods employed for assessing the pore size distribution of a tablet include: gas adsorption (WesterMark *et al*., 1998), and mercury porosimetry (WesterMarck *et al*., 1998). They are complementary in that mercury porosimetry is used to measure large pores while gas adsorption is used to measure smaller pores.

1.3.5.1Tablet porosity

The thickness and diameter of a tablet are measured by micrometer screw gauge. The volume of the tablet could be computed from the tablet's geometry. The porosity (ε) can be evaluated based on the volume of the tablet and the true density of the bulk powders.

The tablet porosity can be computed according to the following equation:

$$\varepsilon_{tablet} = 1 - [(M_{tablet} / \rho) / V_{tablet})] \quad - \quad - \quad - \quad - \quad (1)$$

Where, M_{tablet} is the tablet mass (g), ρ is the true density of the applied preblend of the starting materials (powders and composite particles) (g/cm^3), and V_{tablet} is the tablet volume (cm^3).

$$\rho = \frac{V_T - (V_p + V_L + V_s + V_{MCC})}{V_T} \times 100 \quad - \quad - \quad - \quad - \quad (2)$$

Where V_T is the apparent volume of the tablet, V_p is the true volume of e.g., paracetamol, V_L is the true volume of e.g., Lactose, V_s is the true volume of e.g., tapioca starch, and V_{MCC} is the true volume of e.g., MCC.

The tablet height (thickness), applied to calculate the cross sectional area (SA) and the tablet volume, can be determined/calculated.

1.4 Brittle fracture index (BFI)

The brittle fracture index (BFI), is a measure of lamination tendency of tablets.

It has been discovered that the mechanical properties of compressed tablets can be characterized in terms of their bond strength and their brittleness which can be measured by their tensile strength (T) and their brittle fracture index value (BFI) respectively (Itiola, and Pilpel, 1986; 1991).

The BFI was devised by Hiestand *et al*. (1977). It is obtained by comparing the tensile strength of tablets with hole at their centre, which acts as a built-in stress concentrator "defect" with the tensile strength of tablets without a hole. The BFI is defined as:

$$BFI = [\, T / T_o - 1 \,] \qquad - \quad - \quad - \quad - \qquad (3)$$

Where T is the tensile strength of the tablets without a hole and T_o is the apparent tensile strength of the tablet when hole is present – both at the same packing fraction. The BFI is a measure of localized stress relief within the tablet (at the edge of the hole) by plastic deformation. A low value of BFI indicates the ability of the material to relieve localized stresses while a value approaching unity (0 - 1) indicates a tendency of the material to laminate or cap.

1.5 Disintegration of tablets

There is a relationship between pore structure and bonding structure within a tablet and the disintegration time of the tablet. A high porosity and the presence of large pores will facilitate rapid water penetration into the tablet resulting in rupture of bonds and disintegration of the tablet (Shangraw, *et al*., 1980).

Factors such as the viscosity of the penetrating liquid and average pore size are known to influence the penetration of water into tablets (Groves and Alkan, 1979). Also the disintegration medium might weaken the bonds thereby facilitating the disintegration of tablets (Ferrari *et al*., 1996).

The conventional tablet formulations are associated with inherent problem of inadequate disintegration properties. As a result of this, disintegrants with high swelling capacity are added to such tablet formulation in order to facilitate rupturing of bonds during disintegration (Shangraw, *et al*., 1980).

Effectiveness of any disintegrant will depend on tablet porosity. Tablets produced from non-porous granules will have extended disintegration time or will not disintegrate, thereby delaying the release of drug. Moreso, tablets with low porosity have been shown to be most effective for the action of a good disintegrant due to the fact that swelling of the disintegrant particles exert more pressure on the surrounding (Shangraw *et al*., 1980; Ferrari *et al*., 1995).

1.6 Dissolution of drugs

Dissolution test has emerged in the pharmaceutical field as a very important tool to characterize drug product performance (Gray, *et al*., 2009). It is well known that the bioavailability of drug is influenced by their dissolution characteristics (Ford, *et al*.,1989; Marshall *et al*., 1991; Morita *et al*., 1998). The comparison of dissolution profiles has extensive application throughout the product development process and can be used to: develop *in-vitro in-vivo* correlation, establish final dissolution specifications for pharmaceutical dosage forms and also establish their similarity (O'Hara *et al*., 1998).

1.6.1 Dissolution kinetics (Kitazawa equation)

The dissolution rate constant (k_D) was determined by Kitazawa using the following equation:

$$\ln W^{\infty} / (W^{\infty} - W_t) = k_D t \quad - \quad - \quad - \quad - \quad (4)$$

Where, W^{∞} is the amount of drug released in solution at infinite time, W_t is the amount of dissolved drug at time 't', and k_D is the rate constant (Kitazawa *et al*., 1977).

The use of a dissolution kinetic method can cleanly demonstrate the difference between the dissolution profiles of pharmaceutical drugs.

1.7 Directly compressible excipients

An ideal direct compression excipient must possess adequate flowability, excellent compressibility and extremely good compact hardness. The compressional characteristics of direct compression materials can be predicted using compression parameters such as the Heckel, Kawakita and Cooper-Eaton equations.

1.7.1 Basic physicomechanical properties and binding functionality of direct compression excipients

An ideal direct compression excipient will perform as binder because of its plastic deformation under pressure e.g. MCC.

The choice of direct compression excipient for formulation is very critical, as such, it must fulfill certain requirements such as good flow and binding functionalities, a well designed particle size distribution, compatibility with drugs and other excipients, and ability to carry high amounts of active ingredients (Bolhius *et al*. 1996).

The compressibility under pressure, which is predominantly determined by material properties such as surface energy and deformation, is also very important for direct compression excipients. The compressibility of a powder mass could be obtained from the relationship between porosity and applied pressure (Bolhius *et al*. 1996).

1.7.2 Ideal requirements of directly compressible adjuvants

1.7.2.1 Flowability

The directly compressible adjuvant should be free flowing. Flowability is required in case of high speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of ±5%. Many common tablet manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and incorrect filling (Smewing, 2002).

1.7.2.2 Compressibility

Compressibility is required for satisfactory tabletting, i.e., the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible diluent should have good compressibility, i.e., linear relationship between compaction pressure and volume reduction (Khan and Rhodes 1973; Shangraw, 1989).

1.7.2.3 Dilution potential

Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipient. A directly compressible adjuvant should have high dilution potential so that the final dosage

form has a minimum possible weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient.

1.7.2.4 Adjuvant and active ingredient equivalent particle size range

A directly compressible adjuvant should have a particle size equivalent to the active ingredients present in the formulation (Jivraj *et al,* 2000). The particle size distribution should be consistent from batch to batch and reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient(s) in order to avoid segregation.

1.7.2.5 Inert filler-binder

Filler-binders should not accelerate the chemical and/or physical degradation of the API(s) or excipients (Jivraj *et al,* 2000), should not interfere with the biological availability of active ingredient(s) (Armstrong, 1997), and should be compatible with all the adjuvants present in the formulation and should be physiologically inert (Shangraw, 1988).

1.7.2.6 Other requirements of directly compressible excipients

A directly compressible adjuvant should be capable of being reworked without loss of flow or compressibility on recompression, the adjuvant should exhibit satisfactory tableting characteristics.

The adjuvant should remain unchanged chemically and physically. The directly compressible adjuvant should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat.

It should not interfere with the disintegration or dissolution of the active ingredient. It should be colourless and tasteless. It should be relatively cost effective and available in desired time. It should accept colourants uniformly. It should show batch-to-batch reproducibility of physical and physicomechanical properties. It should possess proper mouth feel, which is defined as the feel or the sensation in the mouth, produced when the excipient is used in chewable tablets (Armstrong, 1997).

1.7.3 Advantages of direct compression

1. The prime advantage of direct compression over wet granulation is economic, since direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets.

2. Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects such as change of form of API and excipients.

3. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations (Shangraw, 1988). This is

extremely important because the official compendium now requires dissolution specifications in most solid dosage forms (Banker, 1994).

Disintegration or dissolution is the rate-limiting step in absorption sequence of tablets of poorly soluble API's prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

4. The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less. Materials are "in process" for a shorter period of time, resulting in less chance for contamination or cross contamination, and making it easier to meet the requirements of current good manufacturing practices (Rubinstein, 1998).

Due to fewer unit operations, the validation and documentation requirements are reduced. Due to the absence of water in granulation, the chance for microbial growth is minimal in tablets prepared by direct compression (Ibrahim and Olurinola, 1991).

1.7.4 Limitations of direct compression

Direct compression is more prone to segregation due to the difference in density of the API and excipients (Rubinstein, 1998). The dry state of the material during mixing may induce static charge and lead to segregation. This may lead to the problems like excessive weight variation and non-content uniformity. Directly compressible excipients are specialty products produced by potential spray drying, codrying, fluid bed drying or co-crystallization. Hence,

the products are relatively costly than the respective raw materials. Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may be difficult to swallow.

All the spray-dried directly compressible adjuvant show poor reworkability since on preparation of tablets the original spherical nature of the excipient particles is lost. API that has poor flow properties and/or low bulk density is difficult to process by direct compression. Lubricants have more adverse effects on the filler, which exhibit almost no fracture or shear on compression (e.g., Starch Rx 1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimizing the length of blending time to as little as 2-5 min (Shangraw, 1988). There is a lack of awareness in some situations that the excipient behave differently, depending upon the vendor so much so that substitution from one source to that of another is not encouraged (Banker, 1994). Hence, there is a need for greater quality control in purchasing of raw material to assure batch uniformity.

1.7.5 Methods of preparation of directly compressible excipients

Direct compression excipient can be prepared by various methods. These include: coprocessing, chemical modification, physical modification, grinding and/or sieving, crystallization, spray drying, and granulation/agglomeration. Coprocessing is one of the most widely explored and commercially utilized methods for the preparation of directly compressible adjuvants.

1.8 Fundamental powder properties

1.8.1 Particle (true) density

Several methods have been used for the determination of particle/true density of the powders and granules. One of these methods is: liquid displacement method using specific gravity bottle with xylene as the displacement fluid. The particle density, D_p is computed using the following equation:

$$D_p = W / [(a + W) – b] \times SG \quad - \quad - \quad - \quad - \quad (5)$$

Where W is the weight of powder, SG is the specific gravity of the solvent, a, is the weight of bottle plus solvent, and b is the weight of bottle plus solvent plus powder.

Other methods of determining particle density include gas adsorption and mercury porosimetry. In mercury porosimetry, gas is evacuated from the sample cell, and mercury is then transferred into the sample cell under vacuum and pressure is applied to force mercury into the sample. During measurement, applied pressure, p and intruded volume of mercury, V, are registered. As a result of analysis, an intrusion-extrusion curve is obtained. Parameters describing the pore structure of the sample can be calculated from the data obtained.

Mercury porosimetry is based on the Washburn equation (Washburn 1921)

$$p \cdot r = -2 \cdot \gamma \cdot \cos\theta, \quad - \quad - \quad - \quad - \quad (6)$$

where r is the radius of the pore where mercury intrudes, γ surface tension of mercury and θ contact angle of the mercury on the surface of a solid sample. Generally used values for surface tension and contact angle of mercury are 480 mNm^{-1} and 140°, respectively.

1.8.2 Bulk and tapped densities

Bulk density can be determined from 50 g weight of the powder or composite and its volume measured with a 250 ml graduated cylinder.

Bulk density D_b is a characteristic of a powder and is given by the mass, M of a powder occupying a known volume, V_b.

$$D_b = M/V_B \quad - \quad - \quad - \quad - \quad (7)$$

Bulk density depends on particle shape. As the particle becomes more spherical in shape, bulk density increases (Banker and Anderson, 1986). The bulk density of a powder bed is always less than the true density (D_T) of its component particles because the powder contains inter-particle pores or voids. Hence, a powder can possess a single true density but have many bulk densities depending on the way it is packed and the porosity of the powder bed. A high bulk density value does not necessarily mean a close-packed low porosity bed due to the fact that bulk density is directly proportional to true density.

That is: $D_b = D_R \,.\, D_T$ - - - -(8)

or $D_R = D_b / D_T$ - - - - (9)

The proportionality constant D_R, is known as the relative density or packing fraction of the powder bed which is a dimensionless quantity. During compression process, the relative density increases to a maximum of unity when all air spaces have been eliminated.

$$\varepsilon = 1 - D_R \quad - - \quad - \quad - \quad (10)$$

Where ε is the fractional voidage or porosity of the powder bed which is usually expressed as percentage and termed the powder porosity (Staniforth, 1988).

The tapped density determination involves tapping cylinder containing 50 g weight of the powder for a minmum of 100 times and the tapped density calculated from the weight and the corresponding volume after tapping.

Tapped density is an important characteristic in solid dosage formulations. This parameter is achieved under the influence of externally applied forces and it depends on a number of factors such as particle size distribution, true density, particle shape and cohesiveness due to surface forces and moisture. Therefore, the tapped density of a material can be used to predict its flow properties and its compressibility (see Carr's index). These two parameters are very important in the overall tabletting process, due to the fact that loose powders are required to be compacted into a desirable solid form having correct mechanical strength, porosity and dissolution characteristics, while in capsule, filling is determined by the flowability.

Both compressibility index (often referred to as Carr's or densification index) and the Hausner ratio are the two most commonly used measures of the relative importance of inter-particulate interactions (Carr, 1965; Hausner, 1967).

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1.8.3 Compressibility index

The ability of a powder bed to undergo volume reduction (densification) is derived from the following equation:

$$C I = 100 (V_o - V_f)/ V_o = 100 (D_o - D_f)/ D_o \quad - \quad - \quad - \quad (11)$$

Where "V" and "D" represent powder volume and density respectively, while subscript "o" denotes the initial or untapped state and '$_f$ ' the final tapped state.

1.8.4 Hausner ratio

The tendency for a powder mixture to form a continuous free flowing powder mass or to segregate is derived using the following equation:

$$H R = V_o / V_f = D_f / D_o \quad - \quad - \quad - \quad - \quad (12)$$

In all free-flowing powders the initial bulk and final tapped densities will be more similar than in poor flowing powders, which yield greater difference between the two values.

The usefulness of the two simple ratios above, both based on the decrease in powder volume during tapping is in their ability to predict flowability. The lower the value (i.e.

number), the more free-flowing the powder, while an increase in the value is indicative of adhesion and higher friction in the powder (Podczeck, 1998). A higher value of Hausner ratio is a pointer to tendency for a powder blend to segregate.

1.8.5 Compact evaluation/characterization of tablets

The stages and mechanisms involved during compaction of pharmaceutical powder materials have become an important concept in the design and development of solid dosage forms.

Many empirical relationships have been proposed to describe the resulting data which may be expressed equivalently in terms of stress-strain, pressure-volume or pressure-density, since the natural strain is equal to the natural log of the ratio of the initial bed height or volume to the current height or volume respectively (Kawakita and Ludde, 1970/71).

Compaction equations relate some measure of stages of consolidation of a powder, such as volume (or relative volume), porosity, density or void ratio with a function of the compaction pressure.

The compaction studies are normally conducted over a range of pressures so as to allow reasonable and obvious plot logarithmically to spread out the data in a distinguishable form. Walker (1923) plotted the relative volume (V) of the applied axial pressure (P_a) as shown in the following equation:

$$V = a_1 - K_1 \, 1nP_a \qquad - \quad - \quad - \quad - \qquad (13)$$

Where ‘a’ and K are constants which can be derived from the slope and intercept of the V’’ versus ‘P’ plots respectively.

Today, many different mathematical expressions of the compaction process have been validated for pharmaceutical systems (Celik, 1992). Several of these include: Heckel (Heckel, 196la, Heckel, 1961b), Kawakita (Kawakita and Ludde, 1970/71) and Cooper-Eaton equations. It is very unlikely that a single compaction equation will fit all the compaction mechanisms. A good compaction curve should be able to indicate changes in the compression mechanism. Therefore, in interpreting compaction curves, it is essential to know which mechanism(s) is/are operating over different region of pressure. The weight of compact and its dimensions (diameter and thickness), can be used to calculate relative density (D_R), porosity (ε), and degree of volume reduction (C), using the following equations.

$$D_R = \rho_A / \rho_T \quad - - - - \quad (14)$$

$$\boldsymbol{\varepsilon} = 1 - D_R \quad - - - - \quad (15)$$

$$C = 1 - \rho_o / \rho_A \quad - - - - \quad (16)$$

Where D_R is the relative density of a powder compact at pressure P, ρ_A is the apparent density of a powder compact at pressures P, ρ_T is the true density of a powder, ε is the porosity, C is the degree of volume reduction of a powder compact at pressure P, and ρ_o is the bulk density of a powder (Zhang *et al*., 2003).

1.8.6 Crushing strength

The crushing strength of a compact can be determined by compressing a compact diametrically on a tablet tester. The radial tensile strength of the compacts can then be calculated from the compact crushing strength and compact thickness in accordance with Fell and Newton's method (Fell and Newton, 1968). The radial tensile strength (T) is given by the equation:

$$T = \frac{2P}{\pi DH} \quad - - - - \quad (17)$$

Where T is the tensile strength (MPa); P is the force required to cause failure in compact (N); D is the diameter of the compact (mm); and H is the thickness of the compact (mm) and π is a constant.

The use of tensile strength allows the dimensions of the compact to be taken into account, which is in contrast to the use of crushing strength. Only the force that led to sample failure in compact was used for the calculation of tensile strength (Zhang *et al*, 2003).

1.8.7 Heckel equation and data analysis

The Heckel analysis is a popular method of determining the volume reduction mechanism under the compression pressure (Celik, 1992; Heckel, 1961a,b). Heckel equation is based on the assumption that powder compression follows first-order kinetics with the inter-particulate pores as the reactants and the densification of the powder as the product

(Heckel, 1961a,b). According to the analysis, the degree of compact densification with increasing compression pressure is directly proportional to the porosity as follows:

$$dD_R / dP = K\varepsilon \quad - \quad - \quad - \quad - \quad (18)$$

Where D_R is the relative density at pressure, P, K is a constant, and ε is the porosity. The relative density is defined as the ratio of the density of the compact at pressure, P, to the density of the compact at zero voids or true density of the material (see equation 14). The porosity (ε) (see equation 15) can also be written as:

$$\varepsilon = (V_p - V) / V_p = 1 - D_R \quad - \quad - \quad - \quad - \quad (19)$$

Where V_p and V are the volume at any applied load and the volume at theoretical zero porosity, respectively.

Thus equation 18 can be expressed as:

$$dD_R/dP = k (l - \rho_R) \quad - \quad - \quad - \quad - \quad (20)$$

And then transformed to:

$$\ln [1/(1- D_R)] = kP + A \quad - \quad - \quad - \quad - \quad (21)$$

Plotting the value of $\ln [1/(1- D_R)]$ against applied pressure, P, yields a linear graph having slope, k and intercept A. The reciprocal of k yields a material-dependent constant known as yield pressure, P_y**,** which is inversely related to the ability of the material to deform plastically under pressure. Low value of P_y indicates a faster onset of plastic deformation (Odeku and

Itiola, 1998). This analysis has been extensively applied to pharmaceutical powders for both single and multi-component systems (Duberg and Nystrom, 1986; Itiola, 1991).

The intercept of the extrapolated linear region A, is a fraction of the original compact volume. It represents two stages of densification - one due to the initial relative density of the powder and the other, due to densification by particle rearrangement. From the value of A, the relative density, D_A, which represents the total degree of densification at zero and low pressures (Paronen and Juslin, 1983; Mitreveji *et al.*, 1996), can be calculated using the equation below (Roberts and Rowe, 1985):

$$A = \ln 1 /(1 - D_A) \quad - \quad - \quad - \quad -(22)$$

$$\text{Thus, } D_A = 1 - e^{-A} \quad - \quad - \quad - \quad (23)$$

The relative density of the powder bed at the point when the applied pressure equals zero is D_o it is used to describe the initial rearrangement phase of densification as a result of die filling. D_o is equal to the ratio of bulk density at zero pressure to the true density of the powder (Roberts and Rowe, 1985). The loose packing of granules or powders at zero pressure tends to yield low D_o values (Itiola and Pilpel, 1986).

The relative density, D_B, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation, although fragmentation can occur concurrently with plastic and elastic deformation of the constituent particles. D_B can be obtained from the equation:

$$D_B = D_A - D_O \quad - \quad - \quad - \quad - (24)$$

The important value of Heckel plots is derived from the ability to identify the predominant form of deformation in a material. Heckel plots have been used:

i) to differentiate materials that consolidate by plastic deformation from those that consolidate by fragmentation.

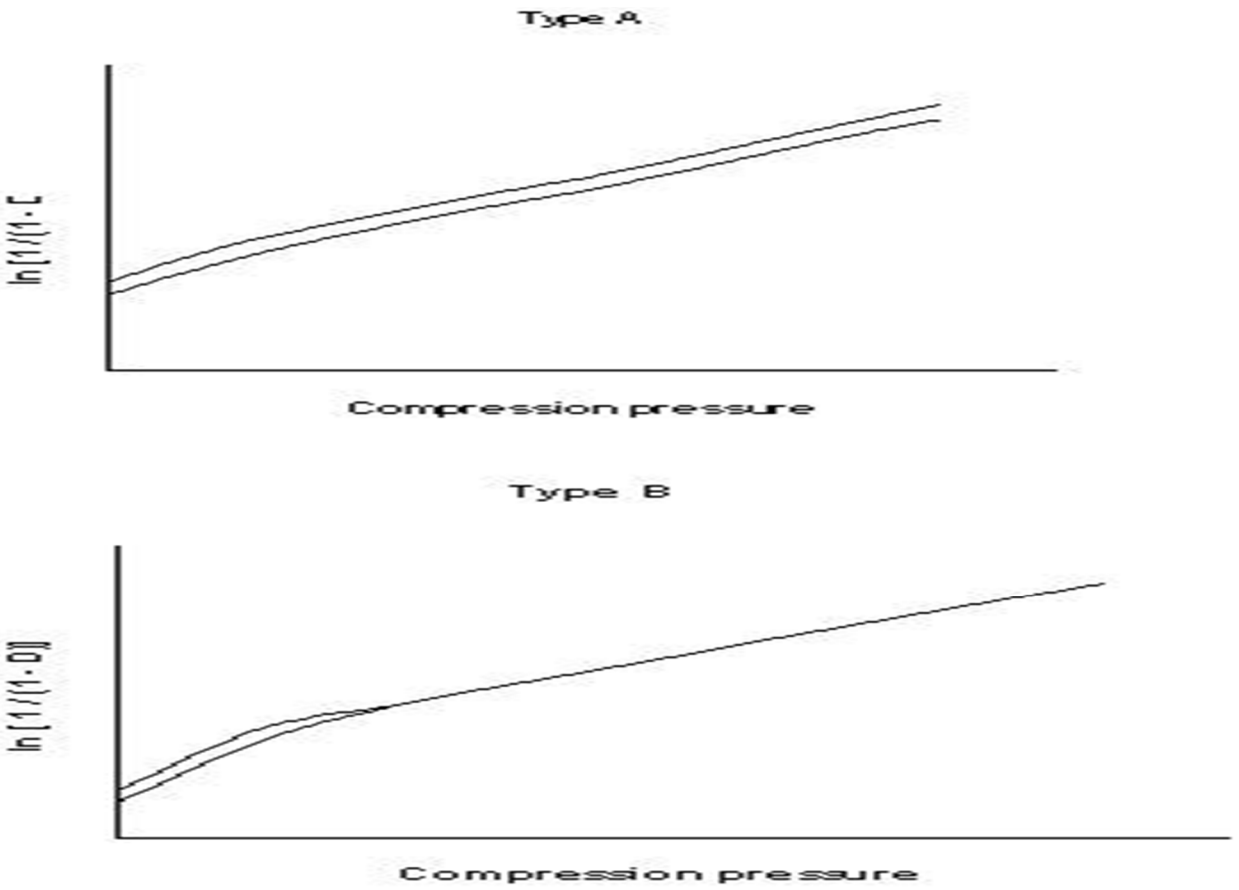
ii) in assessing plasticity.

Thus, a Heckel plot allows for the interpretation of the mechanism of bonding. The slope of the Heckel plot (k) is indicative of the plastic behaviour of the material (Heckel, 1961; Paronen and Illka, 1996). A larger value for the slope is related to a greater amount of plasticity in the material that is comparatively soft and readily undergoes plastic deformation. Conversely, materials with higher mean yield pressure values usually consolidate by fragmentation first, to provide denser packing. While hard, brittle materials are generally more difficult to compress than soft ones.

The consolidation of powder materials has been classified into three types: A, B and C, by Hersey and Rees (1971); and York and Pilpel (1972). The classification is based on Heckel plots and the compaction behaviour of the material.

In type A materials (Fig. 1.2), a linear relationship is observed with the plots remaining parallel as the applied pressure is increased indicating deformation apparently only by plastic deformation. A good example of materials with type A behaviour is sodium chloride. Type A materials are usually soft comparatively and readily deformed plastically.

The type B material (Fig. 1.2) shows an initial curve region followed by a straight line. This characteristic feature is an indication that the particles are fragmenting at the early stages of the compaction process i.e. brittle fracture precedes plastic flow. The type B Heckel plots is a characteristic of harder powder materials with higher yield pressures, which usually undergo volume reduction by fragmentation first to create a denser packing.



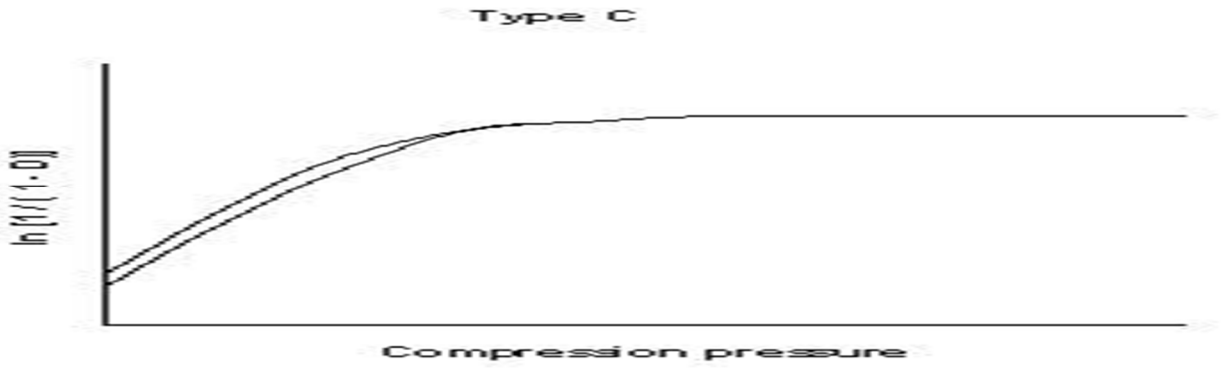


Fig. 1.2: The three different types of Heckel plots (Adapted from: Odeku, 2007).

A good example of powder material exhibiting type B Heckel plot is lactose.

Type C materials (Fig. 1.2) are usually characterized by an initial steep linear region, which become superimposed and flatten out as the applied pressure is increased. This behaviour is ascribed to the absence of rearrangement stage and densification is due to plastic deformation and asperity melting.

Furthermore, type A Heckel plot is characterized by a higher slope than slope type B, which means that the former materials have a lower yield pressure. This is due to the fact that fragmentation with subsequent percolation of fragments is less efficient than void filling by plastic deformation. In the true sense, as the porosity approaches zero, plastic deformation may be the predominant mechanism for all powder materials.

In the type B plots, the two regions are thought to represent the initial repacking stage and subsequent deformation process, while the point of intersection corresponds to the lowest pressure at which a coherent compact tablet is formed.

Furthermore, the crushing strength of tablets can be correlated with the value of the Heckel plot. In most cases, larger k value usually corresponds to harder tablets. This information can be employed in the selection of binder when designing tablet formulations. Heckel plots can be affected by the degree of lubrication, the overall time of compaction and the size of punch/die set. The effects of these variables should be taken into consideration.

1.8.7.1 Influence of elastic deformation of particles on Heckel analysis

Two types of Heckel analysis are in common use to derive an important property called yield strength (yield value). One is the out-of-die, or zero-pressure method, the other is the in-die or at-pressure method. Because particles undergo elastic deformation under pressure, which tends to lower the porosity of the powder bed, the out-of-die method describes powder consolidation and compaction more accurately than the in-die method (Sun and Grant, 2001). However, in-die Heckel analysis has been widely used because of the speed and ease of data collection (Sun and Grant, 2001). Elastic deformation causes positive deviations in the Heckel plot, and therefore leads to a yield strength that is lower than the true value. The lower the elastic modulus of the powder, the greater is the deviation from the true value.

Therefore, the in-die method gives values of yield strength that are significantly lower than true values for most pharmaceutical powders (Sun and Grant, 2001).

1.8.8 Kawakita equation and data analysis

The compaction characteristics of a powder mass can be evaluated by using Kawakita equation. The equation describes the relationship between the degree of volume reduction "C" of the powder column and the applied pressure 'P' (Nicklasson *et al*, 2000). The degree of volume reduction is a parameter equivalent to the engineering strain of the particle bed and is expressed as:

$$C = (V_o - V_p) / V_o = abP/ (1 + bP) \quad - \quad - \quad - \quad (25)$$

The Kawakita equation can be rearranged to give:

$$P/C = P/ a + 1/ab \quad - \quad - \quad - \quad - \quad (26)$$

Where C is the degree of volume reduction, V_o is the initial volume of the powder bed and V_p is the final volume after compression, 'a' and 'b' are constants which can be derived from the slope and intercept of the P/C versus P plot respectively. V_o is computed from the equation:

$$V_o = W/B_d \quad - \quad - \quad - \quad - \quad (27)$$

Where W is the weight of loose powder e.g., 500 mg, D_b is the bulk density of the powder.

The constant 'a' gives the value of the minimum porosity of the bed prior to compression while 'b', which is termed the coefficient of compression, is related to the plasticity of the

material. The value of 1/a yields the initial relative density of the material, D_I indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and Chain, 1995). The reciprocal of b yields a pressure term, P_K, which is the compression pressure, required to reduce the powder bed by 50 % (Shivanand and Sprockel, 1992). The value of P_k gives an inverse measurement of plastic deformation during compaction process. The lower the value of P_K, the higher the degree of plastic deformation occurring during compression (Odeku and Itiola, 1998).

The Kawakita equation appeared to be applicable to materials in powder form only (Celik, 1992). The equation should be adjusted by substituting the initial compaction volume with an initial bulk volume in order to have a better fit to the equation. It is now generally accepted that the Kawakita equation is best applied to powders of high porosity and low pressures (Denny, 2002). This equation has been applied successfully to tapping and densification by vibration. Here, the pressure term is replaced by the number of taps or time in the case of machine vibration (Kawakita and Ludde, 1970/71).

Odeku and Itiola (1998) have used both the Heckel and Kawakita plots to evaluate the compression characteristics of paracetamol tablet formulations. Both plots have limitation and exhibit linearity for materials at high and low pressures respectively (Celik, 1992). Researchers have shown that Heckel and Kawakita plots gave different results for the plasticity of the formulations investigared (Odeku and Itiola, 1998) The difference between the value of P_Y and P_K for the different binders studied is likely to be due to the fact that the P_Y value (yield value obtained from the slope of Heckel plot) relate to the onset of plastic deformation during compression, while the P_K value seems to relate to the amount of plastic

deformation occurring during the compaction process (Odeku and Itiola, 1998). Plastic deformation is essentially a time dependent process, as such, the more the time allowed for plastic deformation to establish (i.e. increase in dwell time), the more the difference between the values of P_Y and P_K obtained.

It is important to note that difference between P_Y and P_K would be more for materials that deform mainly by plastic flow than for those that deformation is mainly by fragmentation (Robert and Rowe, 1986).

Heckel plots showing decrease in slope at higher pressure indicates a decrease in the rate of densification as void spaces between particles decrease. Paronen and Juslin (1983) described the importance of the yield pressure, P_Y as an important indicator for granule compressibility and tendency of the material to deform either by plastic flow or fragmentation. In general, a low P_Y value (steep slope) reflects low resistance to pressure, good densification and easy compression. A low P_Y value does not necessarily mean that the compact has acceptable tensile strength (Hyunjo *et al*, 1998).

Heckel plots allow for the interpretation of the mechanism of bonding. Heckel (1961), describes the decrease in porosity with pressure by first-order kinetics in which the powder bed represents the reactant while the densification is the product.

1.9 Statement of research problem

Most pharmaceutical excipients have problems of poor flow, compressibility and disintegration. The introduction of wet and dry granulation did not proffer satisfactory

solution. The labour, time and cost of production using either of these methods in the present global economic depression has made tablets to be unaffordable to average patient in Nigeria.

Total dependence on importation of excipients causes fluctuation in prices of drugs and hence affects overall cost of health care.

There is narrow pipeline of chemical excipients as a result of high cost of research and production, thus necessitating new line of excipient formulation as alternative.

1.10 Justification

- There is growing popularity of the direct compression process and a demand for an ideal filler-binder that can substitute two or more excipients.
- Tabletting machinery's increasing speed capabilities and requirements to maintain good compressibility and low weight variation even at short dwell times require excipient with high functionality.
- Shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose upon wet granulation, high moisture sensitivity and poor die filling as a result of poor flow (Tobyn, *et al,* 1998) has placed a high demand for new range of excipients that can help to overcome these shortcomings.
- The growing performance expectations of excipients to address issues such as disintegration, dissolution and bioavailability also placed a demand for newer excipients with high functional properties.

- Availability of tapioca starch with standardized production lines, low cost of production is a hope in Africa to develop pharmaceutical raw materials.
- The fact that production of α-amylase does not require sophisticated production line, resulting in low cost of production is an added advantage for new process of excipient production.
- The continued popularity of solid dosage form and an increasing preference for the direct compression process create a significant opportunity for the development of high functionality excipients.
- There is no chemical change involved in the process. The final composite excipient is 100 % safe, while the process is cost effective.

1.11 Hypotheses

- Annealing tapioca starch and subsequent hydrolysis with α-amylase will improve its flow property and compressibility.
- Coprocessed or tailored excipient will have improved flowability, compressibility and compactibility, and high dilution potential (capacity), over individual and direct mixture of the primary powders.

1.12 Aim and objectives

1.12.1 Aim

The aim of this research is to develop a directly compressible spherical free flowing and high functionality composite excipient from two existing diluents by the method of particle engineering called 'coprocessing'.

1.12.2 Objectives

The objectives of this research are as follow:

i. to extract tapioca starch from cassava tubers and characterize it for:
   - Powder and compact properties

ii. to modify tapioca starch physically at molecular level to obtain a free flowing highly crystalline tapioca starch by annealing and subsequently subjecting it to enzyme hydrolysis with α-amylase

iii. to characterize the annealed enzyme hydrolyzed tapioca starch /microcrystalline tapioca starch (MCTS) for:
   - Powder and compact properties (compressibility and compactibility)
   - Mode of deformation (Heckel and Kawakita plots)
   - Lubricant sensitivity
   - Dilution potential

iv. to develop a directly compressible highly functional 2- component composite excipient comprising of MCTS and α-lactose monohydrate (α-LMH) using a simple co-drying method of coprocessing.

v. to develop a directly compressible highly functional 3- component composite excipient comprising of MCTS, α-lactose monohydrate (α-LMH), and microcrystalline cellulose (MCC) using a simple co-drying method of coprocessing.

vi. to evaluate the multi-component composite excipients for:

- Powder and compact properties (compressibility and compactibility)
- Mode of deformation (Heckel and Kawakita plots)
- Lubricant sensitivity
- Dilution potential

vii. to characterize the multi-component composite excipients with active pharmaceutical ingredient (API) for:

- Powder and compact properties

viii. to compare the best multi-component composite excipients with Starlac® and Cellactose® (commercially available coprocessed directly compressible filler-binders).

CHAPTER TWO

LITERATURE REVIEW

2.1 Coprocessed excipients for solid dosage forms

In recent times, tablet manufacturing has been improved by the introduction of the direct compression process and high-speed machines. These two developments have increased the demand on the functionality of excipients in terms of flow and compression. Particle engineering of individual excipient and excipient combinations using coprocessing by virtue of sub-particle modifications has provided an attractive tool for developing high-functionality excipients that are suited to modern tablet manufacturing processes.

Tablets and capsules are the most preferred dosage forms by pharmaceutical scientists and clinicians and patients because they can be accurately dosed and provide good patient compliance, they are easy for companies to manufacture, and can be produced at a relatively low cost. This popularity of tablet coupled with an increased understanding of the physics of compression and of manufacturing process variables have turned the manufacture of tablets into a science in its own right (Shangraw and Demarest, 1993). Tablets are manufactured primarily by either granulation compression or direct compression. The latter involves the compression of a dry blend of powders that comprises drugs and various excipients. The simplicity and cost effectiveness of the direct - compression process have positioned direct compression as an attractive alternative to traditional granulation technologies (Odeku and Itiola, 1998; Shangraw and Demarest, 1993).

Since the tabletting process was introduced in the early 1840s numerous changes have taken place, apart from changes in tablet manufacturing, including the establishment of stringent regulatory requirements for the materials that should be used, the establishment of stability requirements, and the development of high performance tabletting machines that can produce 100,000 - 200,000 tablets/h (Shangraw, 1990). Interestingly, such developments have affected the manufacturing process negatively because the number of materials that can fulfill such regulatory and performance requirements has decreased substantially (Shangraw, 1990).

The direct compression process is highly influenced by powder characteristics such as flowability, compressibility and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physico-mechanical properties required for the development of a robust direct compression manufacturing process, which can be scaled up from laboratory to production scale smoothly. Most formulations (70 - 80 %) contain excipients at a higher concentration than the active drug (York, 1992). Consequently, the excipients contribute significantly to a formulation's functionality and processability.

2.2 The need for new excipients

Increasing regulatory pressure on purity, safety and standardization of the excipient has catalyzed the formation of an international body, the International pharmaceutical excipients council (IPEC).

IPEC is a tripartile council with representatives from the United States, Europe and Japan and has made efforts to harmonize requirements for purity and functionality testing (Blecher, 1993).

For the past three decades, not a single new chemical excipient has been introduced into the market. The primary reason for this lack of new chemical excipients is the relatively high cost involved in excipient discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities. Other factors driving the search for new excipients are:

- The lack of excipients that address the needs of a specific patient such as those with diabetes, hypertension and lactose and sorbitol sensitivity.
- The ability to modulate the solubility, permeability, or stability of drug molecules.
- The growing performance expectations of excipients to address issues such as disintegration, dissolution and bioavailability (Tobyn, *et al.,* 1998).

The continued popularity of solid dosage forms, a narrow pipeline of new chemical excipients, and an increasing preference for the direct compression process creates a significant opportunity for the development of high functionality excipients.

2.3 Sources of new excipients

Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials and new combinations of existing materials (Moreton, 1996). Any new chemical excipient being developed as an excipient must undergo

various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is lengthy and costly. In addition, the excipient must undergo a phase of generic development (Bansal and Nachaegari, 2002), The high risk and significant investment involved are not justified in view of the meager returns from the new excipients. Developing new grades of existing excipients has been the most successful strategy for the development of new excipient in the past three decades (Shangraw and Wallace, 1981), a process that has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, croscamellose and crospovidone (Shangraw, 1997).

However, functionality can be improved only to a certain extent because of the limited range of possible modification. New combinations of existing excipients are an interesting option for improving excipient functionality because all formulations contain multiple excipients. Many possible combinations of existing excipients can be used to achieve the desired set of performance characteristics. However, the development of such combinations is a complex process because one excipient may interfere with the existing functionality of another excipient. Over the years, the development of single-bodied excipient combinations at subparticle level, call coprocessed excipients, has gained importance (Moreton, 1996).

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2.4 Particle engineering as source of new excipients

Particle engineering is a broad-based concept that involves the manipulation of particle parameters such as shape, size, size distribution, and simultaneous minor changes that occur at the molecular level such as polytypic and polymorphic changes. All these parameters are

translated into bulk level changes such as: flow properties, compressibility, moisture sensitivity, and machineability.

Solid substances are characterized by three levels of solid state: the molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo - polymorphism and the amorphous state.

Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level is composed of an ensemble of particles and properties such as flowability, compressibility and dilution potential, which are critical factors in the performance of excipients. The interdependency among the levels provides the scientific framework for the development of new grades of existing excipients and new combinations of existing excipients (Bansal and Nachaegari, 2002).

The fundamental solid - state properties of the particles such as morphology, particle size, shape, surface area, porosity and density influence excipient functionalities such as flowability, compactability, dilution potential, disintegration and lubricant sensitivity. Hence, the creation of a new excipient must begin with a particle design that is suited to deliver the desired functionalities (Reimerdies and Aufmuth, 1992). Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters. It is also possible to engineer particles without affecting the preceding molecular level. Table 2.1 shows how particle engineering can help achieve the desired excipient functionalities (York, 1992). Avicel PH 101 and 102

(Microcrystalline cellulose) and spray dried lactose are examples in which such an approach has been successfully applied.

Table 2.1: Various properties influencing excipient functionality

Particle property	Excipient functionality
Enlargement of particle size	Flowability, compressibility
Restricting particle size distribution	Segregation potential
Enlargement of particle porosity	Compressibility, solubility
Surface roughness	Flowability, segregation potential.

(Extracted from York, 1992)

However, particle engineering of a single excipient can provide only a limited quantum of functionality improvement.

A much broader platform for the manipulation of excipient functionality is provided by coprocessing or particle engineering of two or more existing excipients. Coprocessing is based on novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients (Reimerders, 1993). The availability of a large number of excipients for coprocessing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements.

Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another excipient using a process such as co-drying (e.g. spray drying, flash drying or drum drying).

They are simple physical mixtures of two or more existing excipients mixed at the particle level. Coprocessing was first 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 galactomanan (Modliszewski and Ballard, 1996).

2.4.1 Coprocessing of excipients

The actual process of developing a coprocessed excipient involves the following steps:

- Identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements.
- Selecting the proportion of various excipients
- Assessing the particle size required for coprocessing. This is especially important when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.
- Selecting a suitable process of drying such as spray drying or flash drying
- Optimizing the process (because even this can contribute to functionality variations).

Coprocessing of two or more components was applied to produce composite particles or coprocessed excipient. The composite particles or coprocessed multi-component-based

excipients are introduced to achieve better powder characteristics and tabletting proprieties than a single substance or the physical mixture.

2.4.2 Characteristics of candidate material to be considered in coprocessing

Material science plays a significant role in altering the physicomechanical characteristics of a material, especially with regard to its compression and flow behaviour. Coprocessing excipients offers an interesting tool to alter these physicomechanical properties. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials.

In the truest sense, materials cannot be classified in one category absolutely. Pharmaceutical materials exhibit all three types of behavior, with one type being the predominant response. This makes it difficult to demarcate which property is good for compressibility. Coprocessing is generally conducted with one excipient that is plastic and another that is brittle. Maarschalk and Bolhius (1999), reported coprocessing performed with a large amount of brittle material and a small amount of plastic material as exemplified by cellactose (Meggle Corp.) in which 75 % is lactose (brittle material) and 25 % is cellulose (plastic material) (Maarschalk and Bolhius, 1999).

This particular combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and reduced tendency

of capping and lamination (Casahoursat *et al.,* 1988). However, examples of the other extremes also exist (e.g. silicified microcrystalline cellulose has a large amount of MCC [plastic material] and a small amount of silicon dioxide [brittle material]). These two situations exemplified the fact that coprocessing is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics.

A combination of plastic and brittle materials is necessary for optimum tabletting performance. Hence, coprocessing these two kinds of materials produces a synergistic effect in terms of compressibility by selectively overcoming their disadvantages. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture.

2.4.3 Advantages and disadvantages of the coprocessed excipients

2.4.3.1 Advantages

Several authors have reported the advantages and possible limitations of the properties of coprocessed excipients such as silicified microcrystalline cellulose (SMCC), Cellactose®, and Ludipress®. However, few authors have evaluated the possible location of coprocessed ingredients in the excipient matrix and the mechanisms involved therein. The primary attribute associated with these excipients is that no chemical change exists during coprocessing, and all the reflected changes show up in the physical properties of the excipient particles (Casahoursat *et al.,* 1988; Maarschalk and Bolhius, 1999).

a). Absence of chemical change

Many detailed studies of an excipient's chemical properties after coprocessing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X -ray diffraction analysis, solid-state nuclear magnetic resonance (NMR), and IR spectroscopy have detected no chemical changes and indicated a similarity to the physicochemical properties of MCC (Tobyn, *et al*., 1998). This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

b). Improved flow properties

Controlled optimal particle size and particle size distribution ensures superior flow properties of coprocessed excipients without the need to add glidants. The volumetric flow properties of SMCC were studied in comparison with MCC. The particle-size range of these excipients was found to be similar to those of the parent excipients, but the flow of coprocessed excipients was better than the flow of the simple physical mixture. A comparison of the flow properties of Cellactose® with the direct physical mixture of cellulose and lactose was also performed. The angle of repose and the Hausner ratio were measured, and Cellactose was found to have better flow characteristics than the physical mixture of cellulose and lactose (York, 1992). The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.

c). Improved compressibility

Coprocessed excipients have been used mainly in direct compression tableting because, in this process, there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler-binder. The pressure-hardness relationship of coprocessed excipients when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such as Cellactose® (Belda and Mielck, 1996), SMCC (Sherwood and Becker, 1988; Alien, 1996) and Ludipress (Schmidt and Rubensdorfer, 1994), have been reported to be superior to the simple physical mixtures of their constituent excipients. SMCC was used as an ingredient in a formulation and subjected to compaction on an instrumented tableting machine. The compression force was recorded, and a graph of the tensile strength versus the compression force was used as a comparative parameter.

SMCC retained its compaction properties even at high compression forces, yielding tablets of good hardness. MCC, however, lost its compaction properties. Although direct compression seems to be the method of choice for pharmaceutical manufacturing, wet granulation is still preferred because it has the potential advantages of increasing flow properties and compressibility, and it achieves a better content uniformity in case of low dose drugs (Staniforth and Chatrath, 1996).

d). Better dilution potential

Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients (Flores *et al*., 2000).

e). Low fill weight variation

In general, materials for direct compression tend to show high fill-weight variations as a result of poor flow properties, but coprocessed excipients, when compared with simple mixtures or parent materials, have been shown to have lower fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near-optimal size distribution, causing better flow properties. Fill-weight variation tends to be more prominent with high speed compression machines. Fill-weight variation was studied with various machine speeds for SMCC and MCC, and SMCC showed less fill-weight variation than MCC (Sherwood and Becker, 1988).

f). Reduced lubricant sensitivity

Most coprocessed products consist of a relatively large amount of brittle materials such as α-lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material (Maarschalk and Bolhius, 1999). The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

g). Miscellaneous advantages

Co processed excipients offer the following additional advantages.

- Pharmaceutical manufacturers have option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.
- Improved organoleptic properties such as those in Avicel CE-15® which is a coprocessed excipient of MCC, and guar gum were shown to have distinctive advantages in chewable tablets in terms of grittiness and tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability.
- Although coprocessing adds some cost, the overall product cost decreases because of improved functionality (Prosolv Tech., 2001), and fewer test requirements compared with individual excipients (Reimerdes, 1993).

- Because they can retain functional advantages while selectively reducing disadvantages, coprocessed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations.
- Coprocessed excipients can be used as proprietary combinations and in house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights.
- With the absence of a chemical change during processing, coprocessed excipients can be generally be regarded as safe (GRAS) if the parent excipients are also GRAS certified by the regulatory agencies (Moreton, 1996).

Hence, these excipients do not require additional toxicological studies. Excipient mixtures or coprocessed excipient have yet to find their way into official monographs, which is one of the major obstacles to their success in the market place. The mixture of excipients was presented as a topic to the national formulary and was assigned a priority on the basis of the use of the mixture in marketed dosage forms in which processing has provided added functional value to the excipient mixture (Bolhius and Chowhan., 1996).

- Although spray crystallized dextrose-maltose (EMDEX) and compressible sugars are coprocessed, they are commonly considered as single components and are listed as such in the USP-NF (Moreton, 1996).

2.4.3.2 Disadvantages

Coprocessed excipients also have some limitations as a result of the fixed ratio of its constituents. These shortcomings are mainly two, and they are:

1. Particle size of the coprocessed filler-binder and API must be within the same range to avoid segregation.
2. Dilution capacity of a coprocessed filler-binder is not necessarily fixed for all API's.

2.4.4 Commercial Status

Many coprocessed excipients have been launched in the market in the past few years, and few of them are commercially available. Tables 2.2 feature some of the marketed coprocessed excipients along with their manufacturers and benefits.

Table 2.2: Examples of marketed coprocessed filler-binders

Coprocessed excipients	Trade	Manufacturer	Added advantage
85% α-Lactose MH + 15%	Starlac	Roquette (France)	Good flow
75% Lactose, 25% cellulose,	Cellactose	Meggle GmbH & Co KG Germany	Highly compressible, good mouth feel, better tabletting at low cost
25%Microcrystalline cellulose, 75% lactose	Microcelac	Meggle GmbH & Co KG Germany	Capable of formulating high dose, small tablets with poorly compressible API.
98 % MCC, 2 % silicon dioxide	Prosolv	Penwest Pharmaceuticals	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability.
70 % MCC, 30 % guar gum	Avicel CE-15	FMC Corporation, U.S.A.	Less grittiness, reduced tooth packing, minimal chalkiness, creamer mouth feel, improved overall palatability.
95% β-lactose + 5% Lactitol	Pharrnatose	DMV Vegliel Netherlands.	High compressibility, low lubricant sensitivity.

NB. Adapted from: Bolhuis, G. K., and Chowhan, Z. T.(1996)

2.5 Starch

Most starch types consist of granules in which two types of glucose polymers occur, namely amylose (15 – 35 wt % on dry substance) and amylopectin (65 – 85 wt % on dry substance). Amylose consists of substantially linear molecules having an average degree of

polymerization (DP) of 1000 – 5000 (depending on the starch type). Amylopectin consists of very large, highly branched molecules having an average degree of polymerization of about 2,000,000 (WIPO, WO /1997/031627).

Most of the starch types occur in plants as semi-crystalline granules, which are practically insoluble in cold water. The starch granules have a diameter varying between 1 – 100 micrometers. Starch granules usually consist partly of amorphous regions (about 20 – 30 wt % of the granules). The crystalline material consists substantially of radially oriented, linearly juxtaposed chain portions of amylopectin molecules. The crystalline regions are also designated as micelles or as crystallites. These crystallites are relatively very small, namely about only 0.02 µm on average. The amorphous regions contain both amylose and amylopectin. During the action of acid/or enzymes on starch granules in aqueous medium below the gelatinization temperature, substantially the amorphous portion of the starch granules is affected by hydrolysis and dissolution (etched away). Because of their compact crystalline structure, the crystallites are practically not affected. During continued action of acid/or enzymes on the starch granules, the granular structure is more and more weakened, while the content of crystalline material increases. After the desired degree of action, the resulting starch product, preferably after neutralization, separation, and washing, can be dried to a powder of microcrystalline starch. The microcrystalline starch can be reduced to the desired particle size by mechanical treatment (e.g. by homogenizing or grinding) before or after drying (WIPO, WO /1997/031627).

The microcrystalline starch products according to the invention mentioned above have improved properties with respect to the binding force and the breaking strength. It has in

fact been found that microcrystalline starch possesses improved properties as tableting excipient if the starch product obtained by action of acid/or enzymes on starch granules is first dehydrated by means of a water – miscible organic solvent (such as isopropanol) and the resulting dehydrated microcrystalline starch is then dried at room temperature. The obtained microcrystalline starch powder has an increased specific surface area and with respect to binding force and breaking force, have improved properties as tableting excipient. The starch granules treated by means of acids and/or enzymes separated from the medium, have a dry substance content of e.g., 10 to 40 % w. To enable the processing of the microcrystalline starch products in that formulation, the dry substance must be enriched to about 85 to 95 % w. It has been found that the method of dehydrating influences the properties of the dehydrated microcrystalline starches. The microcrystalline starch products for use as tableting excipient have a relatively high specific surface area, preferably about 1 m^2/g. Tablets manufactured using starch hydrolysis products often show a sufficiently short disintegration time (WIPO, WO/1997/031627).

2.5.1 Hydrolysis of starch

Table 2.3 shows some physicochemical properties of various starches used in pharmaceuticals. The amylase/amylopectin ratio and the temperature of gelatinization displayed in the table will assist in the process of enzyme/or acid hydrolysis.

2.5.1.1 Acid hydrolysis

This involves making a slurry or suspension of 36 %w/w starch and treating it with 6 N HCl at a predetermined temperature (such as 48 ^{o}C) and time (such as 6, 12, 18 and 24 h). The reaction medium is maintained at pH 7-8 in a water bath and the reaction terminated by neutralizing with 0.1N NaOH, and thereafter washed with 3 times with freshly distilled water. The microcrystalline starch is recovered by vacuum filtration.

2.5.1.2 Enzyme hydrolysis

This involves making starch powder suspensions in concentration of 40 %w/v in separate flasks. The suspensions are first subjected to annealing by maintaining the temperature at 60 ^{o}C for a period of 30-60 min after which it is treated with α-amylase at temperature between 58 ^{o}C and 60 ^{o}C (below gelatinization) and pH 6.5-7.5 for predetermined time in a water bath. The reaction could be terminated and neutralize with 0.1 N HCl and 0.1 N NaOH respectively. The microcrystalline starch could then be recovered by sedimentation using vacuum filtration and air drying at room temperature.

The physicochemical properties of some starches are illustrated in Table 2.3.

Table: 2.3 Physical properties of some starches

Granule size (µm)	Granule shape Gelatinization Temp.^{o}C	Amylose/Amylopectin	
Maize 5-15-25	Round polygonal	26/74	62/74
Rice 3-8	Polygonal clusters	17/83	61/78
Wheat 2-10, 20-35	Round elliptical	25/75	52/64
Potato 15-100	Egg like with striations	24/76	54/69
Cassava 5-20-35	Round oval	17/83	65/80
Yam 10-70	Round oval	21/79	65/76

Adapted from: Jaiyeoba and Opakunle (1988).

2.5.2 Pharmaceutical uses of starch

The use of starch has been well established in the formulation of solid dosage forms e.g tablets, where starch satisfies most criteria as an excipient. In designing and formulation of drug product, compatibility of the excipient must be considered dequately in order to have a stable and acceptable product. Considering the above requirement, the factors that favour starch as one of the excipients suitable for drug product formulation include:

i Relative inertness

ii Adequate physicochemical nature

iii Abundance and cheap

In the last three decades starch has functioned as diluent, disintegrant, binder, lubricant and adsorbent (Opakunle and Jaiyeoba, 1988).

2.5.2.1 Starch as diluent

Inclusion of an inert diluent is vital in the formulation of low dose drugs in order to obtain the minimal bulk volume required to form a compressed tablet of convenient size. Researches have produced diverse grades of starches from various sources, which play significant role as bulking agents in tablets. These starches are available as finely divided powders with poor flowing characteristic. In order to employ starch as a bulking agent, it is necessary to improve the flow property and to impact compression characteristic to the starch granules. Several attempts have been made to modify starches to obtain free flowing and directly compressible materials with some success (Manudhane *et al,* 1969). One of the outstanding achievements of researches in production of directly compressible starch is the production of Starch Rx, 1500 which was obtained by treating corn starch with hypochlorite (Short and Varbanak, 1969; Manudhane *et al,* 1969). This is a modified maize starch introduced for the use of pharmaceutical industries. The Starch Rx,1500 was characterized by free flowing, direct compression properties and disintegrant properties with improved dissolution characteristic (Manudane *et al,* 1969).

2.5.2.2 Starch as disintegrant

Starches obtained from different sources have been investigated for disintegrant properties and they have yielded acceptable results.

The basic function of a disintegrant is to oppose the functions of the binder and the physical forces holding both primary and secondary particles due to compression (Lachman *et al,* 1976).

Disintegrants act by aiding the release of drug from the compact tablet thereby allowing for its rapid dissolution. For example, starch granules will absorb water and swell, by this process, it breaks a tablet into granules and particles. Various investigations have shown that starch has the unique physical characteristics to perform the function of a disintegrant.

A five percent (5 %) concentration of starch could be sufficient for a disintegration effect but concentrations up to 10 or 15 % will yield a more rapid disintegration. The various starches in Table 2.4 have been investigated and found to have good disintegrant properties with little variations. The efficacy of various starches used as disintegrant varies, and the variations can be associated with the amylase-amylopection ratio, granule size, moisture absorption properties and differences in fat content (Frazer and Ganderton, 1971).

Table 2.4 : Sources of starches used as disintegrant

Potato	Banana	Maize	Yam	Arrow root
Wheat	Cassava	Maranta		
Rice	Cocoyam	Mariyo	Waxy	
Corn	Barley			

Adapted from: Jaiyeoba. and Opakunle (1988).

2.5.2.3 Starch as lubricant

Lubricants used in tablet formulations are in three categories:

i) the true lubricants

ii) antiadherents (reduce die wall friction)

iii) glidants (improve the flow rate of granules).

Starches have been proven to be useful as glidant, while the metallic stearates have been found to be useful in eliminating die wall friction. It is possible for a lubricant to belong to more than one category.

Investigation of the glidant properties of potato, cassava and yam starches revealed that cassava starch has excellent glidant properties and improved the flow of chloroquine phosphate granules better than those of potato and yam starches (Lachman *et al,* 1976).

2.5.2.4 Tapioca starch

Cassava tuber yields 32 %w/w by weight of starch from peeled tuber (Opakunle and Jaiyeoba, 1988). Cassava plants grow abundantly in many parts of Nigeria. The tubers are used in different forms as staple food in the entire country and a general analysis of its composition is displayed on Table 2.5.

Table 2.5: Composition of peeled cassava tuber *(Mannihot esculenta Crantz)*

Content	Percent (% w/w)
Moisture	65.0
Starch	32.0
Protein	1.0
Fat	0.4
Fibre	0.8
Ash	0.4

Adapted from: Jaiyeoba. and Opakunle, (1988).

2.6 Physical methods of modifying starches at molecular level

The molecular arrangement in a starch granule can be altered by various physical treatments. Annealing and heat-moisture treatment (HMT) are two common physical means by which the treated starch can acquire modified properties without rupturing the granule.

2.6.1 Heat-moisture treatment

Heat-moisture treatment (HMT) is carried out at limited moisture contents (18, 21, 24, and 27 %) but at an elevated temperature below gelling point (Eliasson and Gudmundsson, 1996). These physical treatments can change certain properties of starch.

In previous works, Collado and Corke (1999) applied HMT to sweet potato starch and found that the starch paste became short and shear – stable and the starch gel exhibited marked increase in hardness and adhesiveness, whereas, annealing potato starch increased susceptibility to amylase (Wang *et al.,* 1997).

2.6.2. Annealing

Annealing is generally carried out by heating starch granules with a large quantity of water (40 % w/v) at a temperature below the starch gelling point, over a predetermined period of time after which the heating is terminated and the suspension is subjected to centrifugation. The supernatant is discarded, while the starch is collected and air dried.

2.6.2.1 Impact of annealing on granular swelling

Annealing has been shown to reduce granular swelling in potato (Debon and Tester, 2000; Nakazawa and Wang, 2004), corn (Nakazawa and Wang 2004; Qi *et al.,* 2005) and cassava starches (Nakazawa and Wang, 2004). The decrease in granular swelling has been attributed to the interplay of the following factors:

(1) increased crystalline perfection and decreased hydration (Tester *et al.,* 1998; Waduge *et al.,* 2006),

(2) amylose-amylose and/or amylopectin - amylopectin interaction (Jacobs *et al.,*1998b),

(3) increased intragranular binding forces and reinforcement of the granule (Hizukuri,1996; Jacobs *et al.,* 1995), and

2.6.2.2 Impact of annealing on x-ray diffraction pattern and crystallinity

Gough and Pybus (1971) were the first to study X-ray diffraction patterns of annealed starches. Muhrbeck and Wischmann (1998) reported that the effect of annealing is more pronounced in B-type starches than on A-type starches. Annealing of potato (Hoover and Vasanthan, 1994a; Jacobs *et al*., 1998a; Vermeylen *et al.,* 2006), cassava (Tukomane *et al.,* 2007) and maize starches showed no effect on their polymorphic pattern (Ozcan and Jackson, 2003; Qi *et al.,* 2005). X-ray crystallinity has been shown to increase on annealing in normal maize starches (Ozcan and Jackson, 2003). Tukomane *et al.,* (2007) showed that

annealing of tapioca starch close to the onset temperature of gelatinization combined with the addition of α-amylase were found to increase the relative crystallinity of the starch by removal of the amorphous region without changing the X-ray pattern.

2.6.2.3 Effect of annealing on granule morphology

It was surprising to find that there is a dearth of information (especially for tuber and root starches) on the effect of annealing on granule morphology. Several authors (Jacobs *et al.,* 1998c; Stute, 1992; Waduge *et al.,* 2006) found no changes in granule morphology on annealing of wheat, oat, lentil, barley (certain cultivars) and potato starches. However, Kiseleva *et al.* (2005) observed that the lens shaped granules of high amylose and waxy wheat starches were slightly deformed on annealing. Wang *et al.* (1997) postulated that annealing could create pores or fissures.

2.6.2.4 Effect of annealing on starch structure

The following changes have been shown to occur on annealing:

- Decrease in B-type crystallinity in high amylose barley (Waduge *el al.,* 2006) and sweet potato (Genkina, *et al.,* 2004c) starches,

- Increase in granule stability (Hoover and Vasanthan, 1994a; Jacobs *et al.,* 1995).
- Crystallite growth and perfection/optimization (Tester and Debon, 2000; Tester *et al.,* 1998).
- Twisting of unordered ends of double helices (Tester *et al.,* 1998, 1999).
- Starch chain interactions within the amorphous and crystalline domains of the granule (Hoover and Vasanthan, 1994a; Jacobs and Delcour, 1998; Stute, 1992).
- Increase in order within the amorphous domain without increase in crystallinity (Jacobs and Delcour, 1998; Tester and Debon, 2000) formation of double helices and compartmentalization of amylose-amylose (AM-AM) amylopectin-amylopectin (AMP-AMP) and AM-AMP helices (Atichokudomchai *et al*., 2002; Jacobs *et at.,* 1998a, 1998b; Knutson, 1990; Tester *et al,* 2000).
- Extra reinforcing of the -D-(16) linkages (Jacobs *et l.,* 1998a),
- Polymer chain realignment within granules and partial crystallite melting (Stute, 1992),
- Mobility differences in amorphous or crystalline regions (Stute, 1992) and an increase in the glassy nature (more rigid and less mobile) of the amorphous material (Tester and Debon, 2000).

However, annealing has been shown to have no influence on the wide angle X-ray diffraction pattern of maize (Muhrbeck and Wischmann, 1998; Qi *et al*., 2005; Waduge *et at.,* 2006), cassava (Tukomane *et al,* 2007) and potato (Stute, 1992) starches.

2.6.3 Modification of starch granules at molecular level by enzyme hydrolysis

Tukomane *et al.* (2007) on using scanning electron micrographs to study the morphological changes and the mode of enzyme attack during enzyme hydrolysis, found that, α–amylase preferentially attacked the interior of the starch granule, leaving a deep round hole on the starch granule surface. It was revealed by X–ray diffraction that both annealing and amylolysis did not alter the A–type diffraction pattern. The % relative crystallinity of enzyme–hydrolyzed starch was raised with increasing hydrolysis time and with decreasing amylose content. High performance size exclusion chromatography (HPSEC) detected the decrease in degree of polymerization (DP) of the amylose fraction after prolonged hydrolysis of the starch (Tukomane *et al.*, 2007). They found that the increased relative crystallinity of starch resulted in increased compressibility (when compacted at 4 KN), crushing strength and disintegration time and decreased tablet friability.

2.7 Fabricated composite particles

Vasinee *et al.* (2004) fabricated composite particles of rice starch (RS) and MCC by spray drying technique for use as a direct compression excipient. The composite particles produced were evaluated for their powder and compression properties. The spherical composite particles between RS and MCC in the ratio of 7:3 (RS:MCC) were then evaluated for powder properties and compressibility in comparison with some marketed directly compressible diluents. Compressibility of RS:MCC–7:3 was greater than commercial spray dried RS

(Eratab®), coprocessed lactose and cellulose (Cellactose®) and agglomerated lactose (Tablettose®), but, as expected, lower than the compressibility of MCC (Vivapur® 101), (Vasinee *et al*., 2004). Flowability index of RS:MCC–7: 3 was found to be slightly lower than Eratab® but higher than Vivapur® 101, Cellactose® and Tablettose®. Tablets of RS:MCC–7:3 exhibited low friability and good self–disintegrating property (Vasinee *et al*., 2004).

2.8 Microcrystalline cellulose (MCC)

MCC is a well known tablet diluent and disintegrant. Its major advantages over other excipients are that it can be directly compressed into self-binding tablets which disintegrate rapidly when placed in water.

MCC is purified partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. After purification by filtration and spray-drying, porous microcrystals are obtained. MCC is a white, crystalline powder composed of agglomerated porous microfibres (Shangraw *et al.,* 1987).

Apart from its use in direct compression, MCC is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. In the pharmaceutical market, MCC is available under the brand names: Avicel®, Emcocel®, Vivacel®, Vivapur® etc. MCC products exhibit capping tendencies at high compression speeds. Dittgen (1993) reported no correlation between the crystallinity and tableting properties of MCC obtained from various suppliers (Hewenten® 40 and 12; Vivacel® 101 and 102; Avicel® PH 101 and 200; and Sanag® PH 101 L and 102 L). The author also reported difficulty in obtaining satisfactory

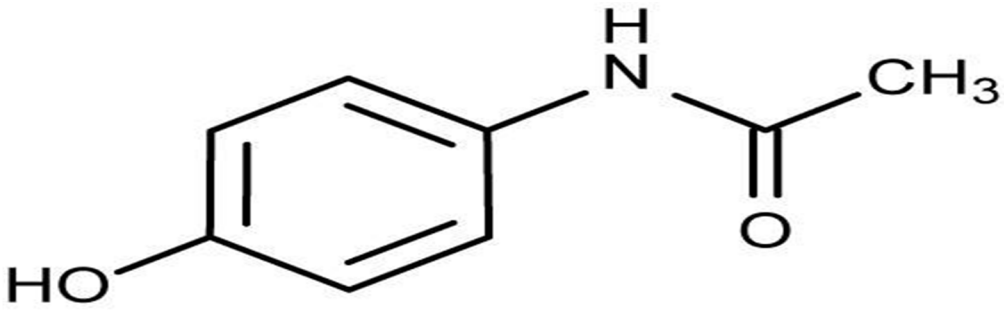
tablets by direct compression using Sanag® PH 101 L and PH 102 L and attributed this behaviour to higher bulk volume and poor compressibility (Dittgen, 1993). Lahdenpaa *et al.* (1997) demonstrated that tablets containing higher percentage of Avicel PH 101 exhibited higher crushing strength and longer disintegration time, while tablets containing Avicel® PH 102 and PH 200 showed lower crushing strength, shorter disintegration time and small weight variation (Lahdenpaa *et al* 1997). Avicel PH 102 exhibited better fluidity because of its more granular form (Bolhius and Lerk, 1973). Larger particles of MCC (PH 102, PH 302 and SMCC 90) had better flowability and lubricity but lower compressibility. Denser particles of MCC (PH 301 and PH 302) showed improved flowability, reduced lubricity and reduced compressibility (Hwang and Peck, 2001). Obae *et al.* (1999) reported increase in the tensile strength of tablets with increase in ratio of length to diameter of particles. Celous® KR 801 with higher percentage of rod shaped particles than Avicel® PH 101 yielded tablets which gave significantly higher tensile strength (Obae *et al.*, 1999). Hardness of MCC tablets was decreased with an increase in percentage of magnesium stearate while the disintegration time was unaffected by addition of lubricant (Mitreveji *et al.,* 1996). The physical and tableting properties of Emcocel® were similar to those of Avicel® (Pesonen and Paronen, 1986). Parenon (1986) reported that Avicel® PH 101 undergoes plastic deformation. Tsai, *et al.,* (1998) prepared co-dried mixture of MCC and cyclodextrin and demonstrated that the coprocessed MCC-cyclodextrin exhibited significant improvement in flowability and compressibility than the physical blend of the primary excipients. Garr (1992), demonstrated that incorporating l% polyethylene glycol to a mixture of 25% DCP (Dicalcium phosphate) and 75% MCC gave intact compacts at relatively low compaction force.

Levis and Deasy (2001) evaluated coprocessed MCC-sodium lauryl sulphate prepared by an ultrasonic homogenization process followed by spray drying. The author concluded that the coprocessed excipients were inferior compared with MCC in the tableting of paracetamol, resulting largely from poor flow.

MCC is commercially available in several grades, which range in average particle size from 20 to 200 micron. It is water-insoluble but has the ability to draw fluid into a tablet by capillary action. The tablets then swell on contact with water and the MCC thus acts as a disintegrating agent. The material has sufficient self-lubricating qualities that allowed a lower level of lubricant as compared to other excipients.

MCC is used as binder/diluent in wet granulation and direct compression formulations in amount of 5-30% of the formulation or more, depending on the requirement of the formulation.

2.9 Paracetamol (synonym: acetaminophen)



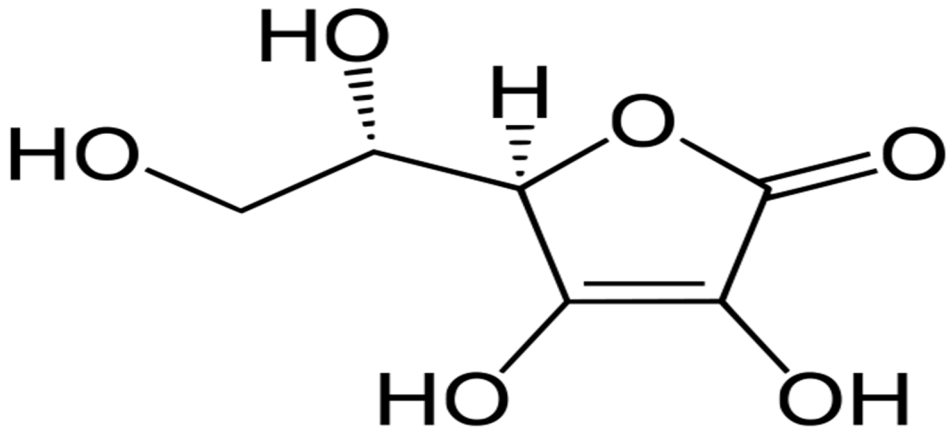
Paracetamol is *p*-acetaminophenol. ($C_8H_9NO_2$ = 152.1) B.P.C, 1973.

Soluble at 20°, in 70 parts of water, in 7 parts of alcohol, in 13 parts of acetone, in 40 parts of glycerol, and 9 parts of propylene glycol; soluble in solutions of alkali hydroxides. It occurs as odourless white crystals or crystalline powder and contains not less than 98.0 and not more than the equivalent of 101.0 percent of $C_8H_9NO_2$, calculated with reference to the dried substance. The loss on drying under the prescribed conditions is not more than 0.5 percent. It has a melting–point of 169° to 172° C. The wavelength of maximum absorption is 243 nm in 0.1 N HCl (B.P.C, 1973). It absorbs insignificant amounts of moisture at 25° C at relative

humidities up to about 90 percent. It should be stored in airtight containers, protected from light.

Paracetamol has analgesic and antipyretic effects similar to, but weaker than, those of aspirin, it has no anti-inflammatory properties. The use of paracetamol include: treatment of pain, such as headache, toothache, rheumatism, and neuralgia. It could be formulated into tablets, each containing 500 mg (B.P); elixir, paediatric (B.P.C). Acetaminophen is poorly compactible.

2.10 Ascorbic Acid (B.P.C., 1973)



Ascorbic acid ($C_6H_8O_6$) is the enolic form of 3–oxo–L glucofuranolactone and may be prepared synthetically or extracted from vegetable sources such as black currants, rose hips, citrus fruits and the ripe fruit of *Capsicum annum* L**. (**Fam**.** Solanaceae) (B.P.C, 1973)**.** It occurs as almost odourless, colourless crystals or white or very pale yellow crystalline powder and contains not less than 99.0 percent of $C_6H_8O_6$. It is soluble at 20^o, in 3.5 parts of water, in 25 parts of alcohol, and in 10 parts of methyl alcohol; insoluble in ether and in light petroleum.

It melts with decomposition at about 190^{o}. A five percent solution in water has a pH of 2.2 to 2.5. The wavelength of maximum absorption is 265 nm in 0.1 N HCl (B.P.C, 1973)**.** It is unstable, especially in alkaline solution, readily undergoing oxidation even by atmospheric oxygen, the change being accelerated by light and heat; it exhibits maximum stability in solution at about pH 5.4. The first stage in the oxidation is reversible and results in the formation of dehydroascorbic acid (B.P.C, 1973). It should be stored in airtight containers, free from contact with metal and protected from light.

Ascorbic acid is essential for the formation of collagen and intercellular material, and hence for the development of cartilage, bone and teeth, and for the healing of wounds. It is also essential for the conversion of folic acid to folinic acid. It facilitates the absorption of iron from the gut; 5 milligrams of ascorbic acid being required for each milligram of iron. It also influences the formation of haemoglobin and erythrocyte maturation. Ascorbic acid is used primarily for the prophylaxis and treatment of scurvy.

Ascorbic acid is poorly compactible due to its brittleness and its strong cohesive properties. It is highly hygroscopic in nature.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

Microcrystalline cellulose (Avicel PH101,Yashica Pharma. Ltd. Maharashtra India), A7595.

α -lactose monohydrate, B.P., (Veghel, Netherland).

Cassava tuber (*Mannihot esculenta Crantz*) obtained from University of Agriculture Abeokuta, Nigeria.

All other chemicals were of analytical grade:

Isopropanol (Mopson Pharm. Ltd, Nigeria),

α-amlylase (NOVO, Nordisk, Denmark),

Hydrochloric acid (Aldrich laborchemikalien GmbH, Germany)

Sodium hydroxide pellets GRG (Avondale laboratories Ltd. Banbury, Oxen, England),

Xylene (BDH Chemical Ltd. Poole, England)

Paracetamol powder (Tianjin Zhong Xin Pharmaceutical Group of Company, Tianjin, China).

Ascorbic Acid powder (BDH Chemical Ltd. Poole, England).

Starlac® (Roquette, France).

Cellactose® (Meggle GmbH & Co KG Germany).

3.2 Method

3.2.1 Extraction of tapioca starch

A modified method of Radley (1976) was adopted. Cassava tubers were washed and peeled to remove the outer skin with the aid of a handy stainless steel knife. The peeled tubers were washed with freshly distilled water and manually rasped to a pulp on a stationary grater. The rasp is a sheet of metal plate perforated with nails, clamped around a stainless steel bucket with the protrusions facing outwards. Water was applied in small quantities continuously to the rasper. The process was continued until the whole tubers were turned into a fine pulp in which most but not all of the starch granules were released. The pulp was then transfered on to nylon fastened/clamped around a stainless steel bucket. A small spray of water was applied to assist the separation of starch granules from their fibrous matrix and to keep the screen mesh clean while water was added, the mass was stirred manually to aid the release of the granules. Starch granules carried with water passed through the sieve into the bucket. The starch milk was then allowed to stand for a period of 8 h. The supernatant liquid was decanted and the sediments was centrifuged to remove the free water, after which a cake was obtained with thin layer of protein at the top. The protein was scrapped off and the starch cake was then crumbled into small lumps (1 – 3 cm) and spread out in thin layers on stainless trays and air dried for 120 h (Radley, 1976; Grace, 1977).

3.2.2 Annealing of tapioca starch

The method of Knutson (1990) was adopted. The fine particle fraction of starch grains (< 75 µm) obtained through sieving was utilized. One hundred gram (100 g) of the starch granules were suspended in freshly distilled 250 ml water (40 % w/w) and heated on a digital water bath (Model HH-S, Mc Donald Sci. Int. U.S.A), at a constant temperature of 60 ^{o}C (below temperature of gelatinization, for tapioca starch which is 75 to 85 ^{o}C) for various periods of time: 1, 2, 3, 4, 5, and 6 h. At the end of each specified time, each sample was centrifuged, excess water removed and the starch granules air dried for 24 h and later dried in an oven at 60 ^{o}C until a constant weight was obtained. The percentage recovery was determined from the weight recovered. The starch granules were subsequently used for further work.

3.2.3 Enzyme hydrolysis of tapioca starch

The method reported by Tokumane *et al*. (2007) was adopted with modification.

Two hundred and forty grams (240 g) of tapioca starch granules were weighed into five places and each placed in a 1000 ml capacity conical flask. Six hundred millilitres (600 ml) of freshly distilled water was added to the content of the flask to make a suspension (40 %w/w). The pH of the medium was adjusted to between 6.5 and 7.0 with 0.1 N NaOH. All the flasks were placed on a digitalized water bath and the starches were annealed at 60 ^{o}C for 30 min. Each flask was dosed with 0.5 ml of α-amylase (0.1 % v/w dry solid) at 60 ^{o}C on water bath and was allowed to stand for hydrolysis to take place at various periods of specified time: 60, 120, 180, 240, and 300 min). At the end of the first 60 min., the enzyme reaction in

one of the flasks was terminated by adjusting the pH to 2.0 with 0.1 N HCl after which the pH was raised to 6.5 with 0.1 N NaOH. The medium was filtered through a Buckner funnel and the residue washed 3 times, with distilled water and finally dehydrated by adding enough isopropanol (99 %). The resulting dehydrated products were air dried. These steps were repeated for the remaining hydrolyzed starches at the expiration of experimental periods.

3.2.4 Preparation of composite excipient

3.2.4.1 Preparation of two component composite filler-binder by codrying method

A modified method of Tsai *et al.* (1998) was adopted for coprocessing the two powder materials to yield 2-component composite granules.

The slurry form of annealed enzyme hydrolyzed tapioca starch (MCTS) was coprocessed with α-lactose monohydrate (α-LMH) both of particle size fraction of less than 75 µm. The slurry was made by suspending the MCTS in 100 ml solution of isopropanol and freshly distilled water in a ratio of 2:1 respectively. MCTS slurry was blended with α – LMH, at concentrations of 10 – 50 %w/w as a dried mass relative to MCTS as shown in Table 3.1. The composite slurry was stirred vigorously with a stirrer (plastic stirrer having 3 cm width and 25 cm length) until a semi-solid mass was formed. The composite mass was then wet granulated through a 1500 µm sieve and dried at 60 ^{o}C to a constant weight. Codried granules were pulverized using pestle and mortar and sized by passing through mesh size 500 µm, and the fraction

between > 75 – 250 µm was reserved. The powder and tabletting properties of the codried products were evaluated and compared to those of corresponding components and physical mixtures.

Table 3.1: Working formula for preparation of a novel two component composite excipient "microcrystarlac" (MSL)

	Batches and Composition of Materials (%w/w)				
Material	1	2	3	4	5
MCTS (g)	90	80	70	60	50
Lactose (g) (α – L-MH)	10	20	30	40	50

3.2.4.2 Preparation of three component composite filler-binder by codrying method

A modified method of Tsai *et al.* (1998) was also adopted for coprocessing the three powder materials to yield 3-component composite granules.

The slurry form of annealed enzyme hydrolyzed tapioca starch (MCTS) (sieved fraction, < 75 µm) was coprocessed with α-lactose monohydrate (α-LMH) and microcrystalline cellulose (MCC) both of particle size fraction of less than 75 µm. The slurry was made by suspending the MCTS in 100 ml solution of isopropanol and freshly distilled water in ratio 2:1 respectively. MCTS slurry was blended with α-LMH, and MCC at concentrations indicated in Table 3.2 as a dried mass relative to MCTS. The composite slurry was stirred vigorously with a stirrer (plastic stirrer having 3 cm width and 25 cm length) until a semi-solid mass was formed. The composite mass was then granulated through a 1500 µm and codried at 60 ^{o}C to a constant weight. Codried granules were pulverized and sized by passing through mesh size 500 µm, and the fraction between > 75 – 250 µm was reserved. The powder and tabletting properties of the codried products were evaluated and compared to those of corresponding components and physical mixtures

Table 3.2: Working formula for preparation of a novel three component composite excipient "microcrystarcellac" (MSCL)

Material	Batches and Composition of Materials (%w/w)				
	1	2	3	4	5
MCTS (g)	45	40	35	30	25
Lactose (g) (α – L-MH)	45	40	35	30	25
MCC (g)	10	20	30	40	50

3.2.5 Water content

Ten gram (10 g) of the granule was weighed and dried to a constant weight in an oven at a temperature of 105 ^{o}C. The moisture content (MC) was then calculated using the following equation:

$$MC = (1 - W_t/W_o) \times 100 \quad - \quad - \quad - \quad - \quad (28)$$

Where W_t and W_o represent weight of powder after time 't' and the initial weight before heating respectively.

3.2.6 Microscopic analysis of granule size and shape

The particle size and size distribution of the individual primary powder, annealed starch, annealed enzyme hydrolyzed tapioca starch were determined using light microscope (Nikon AFX-DX, Nikon, Inc., Japan). Each of the samples was covered with glycerin mounted on a slide, and examined by a combination of low and high power objective lenses of x10, and x40, magnification respectively. The photomicrographs were taken, granule sizes were determined through calibration, and shapes were observed.

3.2.7 Granule size distribution by sieving

The U.S.P (2003) standard method of sieve analysis was employed. The nest of sieves used were: 500, 250, 150, 125, 90 and 75 µm respectively arranged in that order (top to bottom). The sieves were arranged on an electric shaker (Ro-Tap, model E, Ohio, U.S.A) and 100 g of the granules was placed on the 500 µm sieve size. The sieves were shaken for 15 min after which the sieves were dismantled, the weight of granules retained by individual sieve was determined and the percentage retained over size

calculated.

3.2.8 Determination of flowability (flow rate)

Three parameters that theoretically describe flowability such as the Hauser ratio, Carr index, and the Kawakita analysis, were used. In addition, the flow rate of 'the powder was determined as the ratio of mass (g) to the time (seconds) using flow-rate meter (Erweka, model GDT, Germany).

Time taken for 50 g of each powder: NTS, ATS, MCTS, MSL, MSCL and physical mixture powders, to flow through the orifice were taken.

3.2.9 Measurement of angle of repose

A clean glass funnel was placed in a ring on a retort stand, so that the tip of the funnel was exactly 10 cm from a piece of paper (920 cm x 25 cm) placed below the funnel assembly.

A neatly cut cardboard was carefully placed on the lower ring (orifice) of the funnel so that it fits tightly but loosely enough to be removed. Fifty gram (50 g) of the granule/powder was transferred into the funnel. The cardboard was removed and the granules allowed free flow through the orifice. The height of the powder heap was measured with a ruler in millimeter (mm), a circle was drawn round the powder heap (that is, the circular base). The radius of the circle was recorded.

The angle of repose **θ** was then determined as the tangent of the height of the cone, 'h' divided by the radius 'r' , (Jones and Pilpel, 1966) as represented by equation 29.

$$\tan \theta = h/r \quad - \quad - \quad - \quad - \quad (29)$$

The measurement was performed in triplicate.

3.2.10 Densities

3.2.10.1 True (particle) density

The true (particle) densities of the primary powders (NTS and MCC), ATS, MSL, MSCL particles were determined by the liquid displacement method using a specific gravity bottle (pycnometer) with xylene as displacement fluids. The particle density, D_p, in each case computed according equation 5.

3.2.10.2 Bulk and tapped density

Bulk density

The bulk and tapped densities were determined by the mothod of Kumer and Kothari (1999). These parameters were determined by weighing 50 g quantity of each granule/powder and pouring qualitatively into a 100 ml measuring cylinder. The volume (V_o) was recorded as the bulk volume. The bottom of the cylinder was raised 10 cm above the slab and made to fall on the platform continuously for 100 taps. The volume (V_t) of the granule was recorded, and this

represents the volume of the granules minus the voids and is called the tapped volume. The bulk and tapped densities were calculated using the following equations:

$$D_b = W/V_o \quad - \quad - \quad - \quad - \quad (30)$$

$$D_t = W/V_t \quad - \quad - \quad - \quad - \quad (31)$$

Where, D_b and D_t, are bulk and tapped density respectively, and W, is the weight of the powder (50 g). The results presented are the mean of three determinations.

3.2.11 Carr's index

The compressibility index of the various powder materials was determined using the Carr's index formula below.

$$\text{Carr's Index (CI)} = (D_t - D_b)/D_b \times 100\ \% \quad - \quad - \quad (32)$$

Where D_b is the poured or bulk density and D_t is the tapped density.

3.2.12 Powder porosity

The powder porosity was also determined with the equation below.

$$\text{Powder porosity } (\varepsilon) = 1 - (D_t / D_T) \quad - \quad - \quad - \quad (33)$$

Where, D_T is the true (or particle) density of a powder.

3.2.13 Preliminary compactibility studies

The preliminary compactibility study was carried out to select promising batches of the following:

(1) the best batch out of the five batches of hydrolysed starch (MCTS) having the best tablet properties to be coprocessed with lactose and MCC,

(2) the best two batches (out of five) of coprocessed filler-binder (2- and, 3-component composites) were selected for compaction studies based on acceptable tablet properties.

The native tapioca starch, annealed tapioca starch, and the microcrystalline tapioca starch at various time of hydrolysis were compressed on a single punch Erweka tabletting machine (Erweka, AR 400, Germany), fitted with 10.5 mm diameter flat faced punch and die. Tablet target weight was 500 mg, and pressure load used ranged from 4 to 7 KN.

The coprocessed filler-binder: MSL and MSCL (5 batches each) were subjected to the same procedure to streamline the batches to just two for effective research and particle restructuring. The batches chosen here were subjected to particle sieving and further employed for compaction studies.

3.2.14 Compaction studies

3.2.14.1 Preparation of compacts

Compacts of 500 mg weight of each of the powders having the following composition were prepared: (1) NTS, (2) MCC, (3) α-LMH, (4) ATS, (5) MCTS, (6) MSL (B_4 and B_5) (Table 3.1) (7) MSCL (B_2 and B_3) (Table 3.2) (8) physical mixture of MCTS and α-LMH and (9) MCTS, α-LMH and MCC. A single punch carver hydraulic hand press (model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A) was used at machine compression force ranging from 2.5 KN to 12.5 KN. Forty compacts were made at each compression level for each individual material. Before compression, the die (10.5 mm diameter) and the flat faced punches were lubricated with a 1 % w/v dispersion of magnesium stearate in ethanol-ether (1:1). The compacts were stored over silica gel for 24 hours (to allow for elastic recovery and hardening and to prevent falsely low yield values) before evaluations. The dimensions (thickness and diameter) and weight uniformity of ten compacts were determined. The relative density, D_R, was calculated as the ratio of density of the compact, D to the particle density, D_T of individual powder or composite (equation 9). The data obtained using 'ejected tablet method (out-of-die)' were used to obtain the Heckel plots.

The weights, W, and dimensions of compact were used to determine the compact density D using the following equation:

$$D = W/ [V_t \times D_T] \quad - \quad - \quad - \quad - \quad (34)$$

Where V_t is the volume of the tablet in cm^3, and D_T is the particle density of the solid material in gcm^{-3}.

3.2.14.2 Compression of composite tablet with a hole at the centre

Tablets (500 mg) were prepared from the composite particles by compressing them for for a cycle and held for 1 min (dwell time). with predetermined loads using a Carver hydraulic hand press (Model C, Carver Inc., Menomonee Fall, Wisconsin, USA). Before each compression, the die (10.5 mm diameter) and the flat-faced Punches were lubricated with a 1 % w/v dispersion of magnesium stearate in ethanol-ether (1:1). Tablets with a hole (1.59 mm diameter) at their centre were made by using an upper punch with a hole through the centre and a lower punch fitted with a pin (Kawakita and Ludde, 1970/71; Itiola, 1991; Itiola, and Pilpel, 1991). After ejection, their weights and dimensions were taken immediately, after which the tablets were stored over silica gel for 24 h to allow for hardening and elastic recovery. Their weights (W) and dimensions were then determined respectively.

3.2.15 Compact analysis

3.2.15.1 Tensile strength

The tensile strength of the normal tablets (T) and apparent tensile strength of those containing hole (T_o) were determined at room temperature by diametral compression (Fell

and Newton, 1968) using an hardness tester (model EH O1, capacity 500 N, India) and by applying the equation:

$$T \text{ (or } T_o) = 2F / (\pi dt) \quad - \quad - \quad - \quad - \quad (35)$$

Where T (or T_o) is the tensile strength of the tablet (MNm^{-2}), F is the load (MN) needed to cause fracture, d is the tablet diameter (m) and t is the tablet thickness (m). Results were taken from tablets which split cleanly into two halves without any lamination. All measurements were made in triplicate, and the results given are the means of several determinations.

The brittle fracture index (BFI) of the tablets was calculated using the equation 3.

3.2.15.2 Thickness of tablets

The thickness of the tablets was measured with the aid of digital vernier caliper. Five tablets were selected randomly and the thickness for each was measured and the mean value determined.

3.2.15.3 Compact density (CD)

The compact density was calculated using equation below:

$$CD = CW(g)/CV\ (h\pi r^2)cm^3 \quad - \quad - \quad - \quad - \quad (36)$$

Where, CW and CV represent compact weight and volume respectively.

3.2.15.4 Friability

The abrasion test was performed in a friabilator (Erweka, TA3R, Germany) operated at 25 r.p.m for 5 min. The weight of 10 tablets was taken before and after the test. The friability was calculated as the percentage weight loss.

3.2.15.5 Heckel's analysis

Heckel plots of ln (1/ 1-D) versus applied pressure 'P' (equation 21, page 28) was plotted for the all the materials compacted. Linear regression analysis was carried out over the compression range of 2.5 to 12.5 KN and other parameters from Heckel plots were evaluated.

3.2.15.6 Kawakita compact analysis

The Kawakita equation (26, page 33) was employed to determine the extent of plastic deformation the material undergoes. Kawakita plot of P/C versus applied pressure (P) was plotted for all the materials compacted.

3.2.15.7 Weight variation limit test

The U.S.P (1988) provides limit for the average weight and comparing individual tablet weight to the average. Twenty tablets were randomly drawn from the samples. The tablets

meet U.S.P weight variation test if not more than two tablets (10 %) are outside the percentage limit and no tablet differs by more than twice the percentage limit. For average weight of 500 mg, maximum percentage difference allowed is 5 % (i.e., $\pm$ 25 mg) by U.S.P (1988).

The weight of 20 tablets was determined collectively and individually on a sensitive balance (Model, XP 300, Denver, U.S.A). The mean weight X, percentage deviation (%), standard deviation, standard error, and percent coefficient of variation (%CV) were calculated using the following equations:

$$S_{10} = \sqrt{\sum(X - X)^2/n-1}$$

$$\% \text{ CV} = \frac{\text{Standard Deviation}}{\text{Calculated mean}} \times 100$$

$$S_m = S_{10}/\sqrt{n}$$

$X \pm 2 S_m$ represent 95 % confidence limits of finding the true mean.

X' represent average or mean of 20 tablets.

S_m represents standard error of the mean.

3.2.16 Disintegration time

Using Erweka disintegration apparatus (Erweka, ZT 3, Germany) three tablets were placed each in a compartment of the disintegration basket which was lowered into a glass beaker (1 L capacity) filled with deionized water to 800 ml mark and in turn was placed in a water bath

maintained at 37 .0 ± 0.5 ^{o}C. The time taken for the disassociated tablet particles to pass through the mesh was recorded as the disintegration time. Average of three readings was taken as the disintegration time.

3.2.17 Determination of dilution capacity

Ascorbic acid and paracetamol were used as model drugs representing both highly water soluble and moisture sensitive, and elastic/poorly water soluble active ingredient respectively.

Model drugs were blended in deferent ratios, ranging from 0 %, 5 %, 10 %, up to 50 % with MCTS, microcrystarlac and microcrystarcellac (Table 3.3).

Formulations were blended by trituration and lubricated with 1 % magnessium stearate. Each batch was compressed for 30 seconds on single punch carver hydraulic hand press (model, C, Carver Inc. Menomonee Falls, Wisconsin, U.S.A) at pressure load of 7.5 KN and target weight of 500 mg. Compacts were allowed to relax for 24 h post compression. Compact dimensions (diameter and thickness) were determined using a digital vernier caliper. Crushing strength was determined using an electronic/digitalized tablet hardness tester (Model EH O1, Capacity 500 N, India).

The relationship between amount in percent (%) of model drug added to the formulation and the tensile strength was investigated. In general, the dilution capacity or potential was expressed as the maximum amount of active pharmaceutical ingredient that can be

compressed with the excipient, while still obtaining tablets of acceptable quality (that is, acceptable crushing strength average of 60 N, friability < 1.0 %, good disintegration time < 15 min, and must meet the requirement of U.S.P weight variation limit test).

Table 3.3: General formula for determination of dilution capacity for MSL and MSCL using ascorbic acid and paracetamol as model drugs

BATCH	MSL / MSCL /MCTS	A A / PCM	
	MG/TAB	MG/TAB	% of Drug
B1	500	00	0
B2	475	25	5
B3	450	50	10
B4	425	75	15
B5	400	100	20
B6	375	125	25
B7	350	150	30
B8	325	175	35
B9	300	200	40
B10	275	225	45
B11	250	250	50

3.2.18 Lubricant sensitivity

Lubricant sensitivity was determined by mixing 0.2 g of magnesium stearate (1 %w/w) with 20 g of MSL and 20 g of MSCL respectively for the period of 5 min.

The granules without lubricant and granules with lubricant were compressed into tablets using Carver hydraulic hand press at 7.5 KN. This procedure was repeated with the same amount of magnessium stearate (1 %w/w) but the mixing time extended to 30 min.

The granules were compacted at the same compression load, crushing strength were determined and the tensile strength computed for compacts made with granules at two different mixing times. Lubricant sensitivity ratio (LSR) was computed using the following equation:

$$LSR = (H_o - H) / H_o \times 100\ \% \quad - \quad - \quad - \quad - \quad (37)$$

Where, LSR, H_o, H represent lubricant sensitivity ratio, hardness of tablet without lubricant, and hardness of tablet with lubricant respectively.

3.2.19 Dissolution of drug

3.2.19.1 In-vitro drug release studies

Drug availability is an important aspect of drug development and formulation. Drug release from the various tablets was determined using the basket method of U.S.P XXIII dissolution apparatus (model, RC-6, Tian Jin, China). The tests were conducted in 1000 ml 0.1 N HCl

medium maintained at 37.0 ± 0.5 ^{o}C at a paddle rotation speed of 50 rpm. Five ml (5 ml) of the menstrum (sample) were taken at the end of the specified (predetermined) time period of 5 , 10, 15, 20, 30, 45 and 60 min. The samples were filtered and analyzed for paracetamol in one experiment and ascorbic acid in another experiment using U.V-vis Spectrophotometer (Jenway, 6310, U.K) at wavelength of 272 and 265 nm maximum absorption respectively. A five milliliter (5 ml) volume of filtered, fresh dissolution medium was added to maintain a constant volume after each sample withdrawal. The results were mean of three reading.

3.2.20 Statistical analysis

Statistical analysis was carried out using the statistical software – GraphPad Prism (version 3).Data obtained from the various experiments were expressed as mean ± SD. Differences between means were determined using the analysis of variance (ANOVA) and statistically significant difference were set at $P < 0.05$

CHAPTER FOUR

RESULTS

4.1 Percentage yield of tapioca starch

Following extraction of tapioca starch from the fresh tubers of cassava (*Mannihot esculenta crantz*) and adequate drying, the percentage yield was calculated to be 31.9 %. This agrees with the result (32 %) reported by Jaiyeoba and Opakunle (1988).

4.2 Physical features of starch granules

The starch granules were mostly round and subspherical in shape with few appearing as half moon. Striations were visible, and hilium appeared mostly as dot at centre with few linear and cleft. The average granule size of NTS was found to be 10 $\pm$ 0.2 μm

(Figure 4.1).

The photomicrographs of NTS at different magnifications are shown in Figures 4.2 and 4.3. The starch granules were in aggregates of 2 to 3.

4.3 Tablet properties of NTS

Average crushing strength for NTS tablets at compression force 6 metric ton was 30 N and it failed the abrasion test by crumbling few seconds into the friability test.

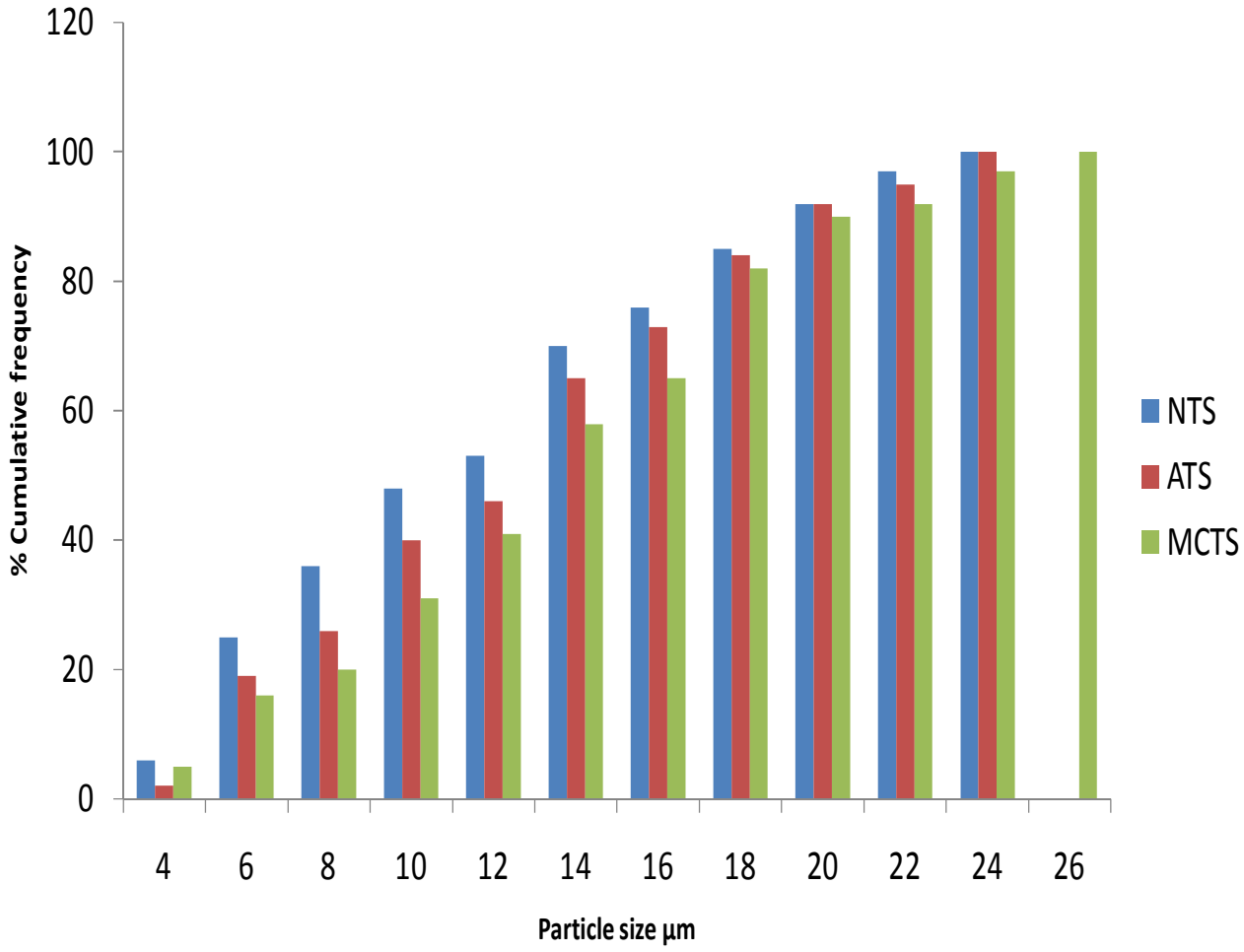


Fig 4.1: Cumulative frequency (%) vs Partcle size (µm) of NTS, ATS, and MCTS .

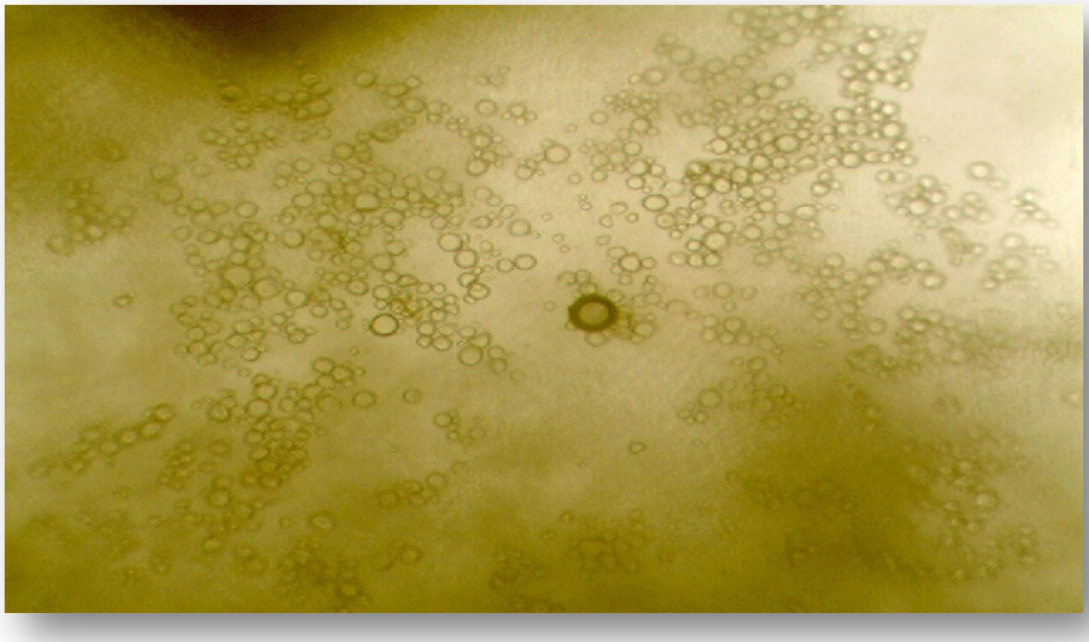


Fig. 4.2: Photomicrograph of NTS granules x 10.

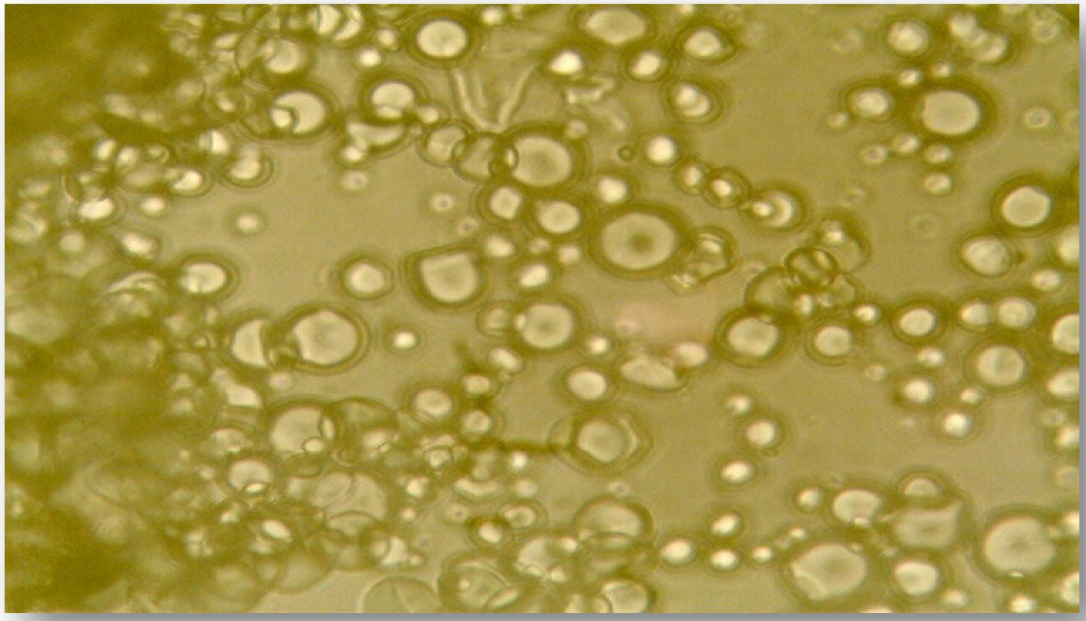


Fig. 4.3: Photomicrograph of NTS granules x 40.

4.4 Effect of annealing on starch granules

The effects of annealing on both granule characteristics and tablet properties were investigated.

4.4.1 Physicochemical characteristics of NTS and ATS

Table 4.1 shows some physicochemical characteristics of the NTS and ATS. There was no colour change observed after annealing. The pH remained neutral and microscopic examination revealed no change in the granules as, most of the granules appeared to be round and subspherical after annealing. The only difference was in swelling property, where

15.5 % and 11.1 % were obtained for NTS and ATS respectively. This revealed a reduction in swelling capacity. The flow rate, angle of repose, compressibility index and Hausner ratio for ATS were 2.60 $\pm$ 0.01 g/s, 32^{o}, 31.2 %, and 1.5 respectively. The corresponding values for NTS were: 2.00 $\pm$ 0.02 g/s, 43^{o}, 32.2 % and 1.5 respectively. There is an improvement in flow property of the starch granules after annealing for 3 h.

4.4.2 Compressibility studies

Four out of six batches of ATS were selected and subjected to compressibility studies using compression force of 4 to 6 metric tons. Table 4.2 shows that ATS-3 h tablets had the best compact quality in terms of tensile strength and friability. The tablet crushing strengths of this batch at compression forces 5 and 6 metric tons were 45 and 90 N respectively. The corresponding values for NTS were 30 and 40 N respectively.

Table 4.1: Physicochemical properties of NTS and ATS

	NTS	**ATS (3 h)**
Organoleptic	Odourless, white and tasteless	Odourless, white and tasteless
Identification	Blue colour with iodine-solution	Blue colour with iodine-solution

		Solution
Organic impurities	No red colour with acidified phloroglucinol	No red colour with acidified phloroglucinol
pH	7.2 - 7.8	7.3
Solubility in water	Practically insoluble	Practically insoluble
Microscopy	Mostly round, sub-spherical	Round, oval, subspherical
Swelling capacity (%)	15.5	1 1.1
Loss on drying (%w/w)	5.5	6.0

Table 4.2: Characteristics of NTS and ATS Tablets at Various Compression Pressures

Material	Comp-action force (KN)	Compression pressure $N/M^2 xl0^5$	Weight of tablet (g)	Thickness of tablet (m) $xl0^{-3}$	Crushing strength (N)	Radial tensile strength $N/M^2 x10^5$	Compact density g/cm^3	Friability	DT (sec) n=3
NTS	6	4.9	0.500	3.30	30 ± 0.5	5.79	1.235	Failed	14 ±1
ATS-1 h	5	4.1	0.500	3.76	30 ± 0.5	4.1	1.120	3.50 ±0.50	20 ± 1
	6	4.9	0.500	3.50	56 ± 5.0	8.2	1.165	5.4 0 ±0.50	20 ±0
ATS-2 h	5	4.1	0.500	3.80	50 ± 5.0	6.7	1.073	3.60 ±0.50	25 ±1
	6	4.9	0.500	3.75	70 ± 5.0	9.5	1.087	2.60 ±0.50	25 ±0
ATS-3 h	5	4.1	0.500	3.80	45 ± 0.5	6.0	1.073	2.96 ±0.50	22 ±1

	6	4.9	0.500	3.67	90 ± 0.5	10.4	1.111	2.50 ±0.50	25 ±1
ATS-4 h	5	4.1	0.500	3.73	55 ± 5.0	7.5	1.093	4.00 ±0.50	20 ±1
	6	4.9	0.500	3.54	80 ± 5.0	11.5	1.152	4.00 ±0.50	20 ±1

Note: compression pressures were 5 and 6 KN, punch diameter, 10.5 mm, and target weight, 500 mg. DT denote disintegration time.

4.5 Enzyme hydrolyzed tapioca starch (MCTS)

The physical features of the starch granules after hydrolysis remained the as shown in Figure 4.4 and Table 4.3 with the exception of increased average size of the MCTS granule from 10.0 $\pm$ 0.2 µm (NTS) to 13.0 $\pm$ 0.5 µm (MCTS). Table 4.4 shows the characteristics of the enzyme hydrolyzed tapioca starch (MCTS) granules at various times of hydrolysis. It can be seen that the flow rates and the compressibility indices obtained were better than those of NTS. Table 4.5 compares the granule properties of ATS with those of NTS, and MCTS-3 h. The result indicated an improvement in flow properties as reflected by flow rate of 2 .0 g/s, 2.6 g/s and 2.5 g/s for NTS, ATS and MCTS-3 h respectively. The corresponding angles of repose were 43^{o}, 32^{o} and 35^{o} respectively. The compressibility as reflected in table 4.5 for NTS, ATS-3 h, and MCTS-3 h were: 32.2 %, 31.2 % and 27.3 % respectively. With annealing and enzyme hydrolysis, flowability and compressibility of NTS were successfully modified.

Table 4.6 shows the tablet properties of MCTS at various periods of hydrolysis. It can be seen that the tablets of MCTS-3 h compressed at 6.5 metric tons gave the best compacts in terms of tensile strength (90 N), friability (1.05 %) and disintegration time (80 sec.). Based on this result, MCTS-3 h was selected to be coprocessed with lactose and MCC in the next stages.

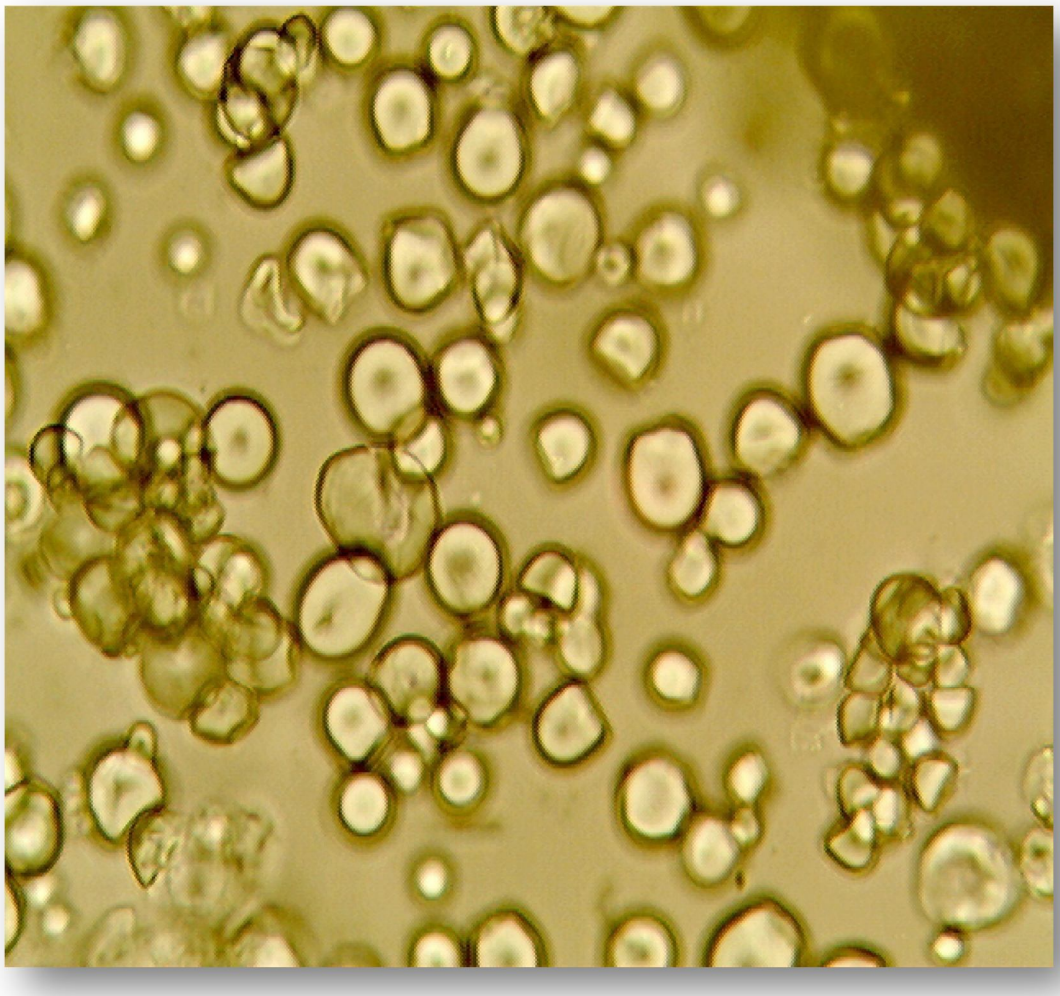


Fig. 4.4: Photomicrograph of MCTS granules x 40

Table 4.3: Comparative structural features of NTS, ATS-3 h, and MCTS -3 h as observed under light microscope (x 40 magnification)

Parameter	NTS	ATS-3 h	(MCTS 3 h)
Shape	Mostly round, sub-spherical, Polyhedral, half moon, oval.	Polyhedral, round, half moon, semicircle, oval, spherical.	Mostly round and half moon, sub-spherical
Striation	Faint in appearance	Faint, mostly concentric.	More visible, concentric
Helium	Mostly dot at centre, few linear and cleft.	Dots at centre, few cleft.	Dots, cleft, linear at mostly centre. Mostly cleft type
Aggregate	Mostly 2 – 3	Mostly of 2	2 – 3

Average granule size	10 0 ± 0.2 µm	11.5 ± 0.5 µm	13 ± 0.5 µm

Table 4.4: Characteristics of MCTS granules at various times of hydrolysis

Material	**Time of hydrolysis (min)**	**Flow rate g/sec n=3**	**Angle of repose n=3** (degree)	**Bulk density g/cm^3 n =3**	**Tapped density g/cm^3 n =3**	**Compr-essibility index %**	**Hausner ratio**

MCTS							
1	60	3.93±0.03	26.0±0.1	0.454±0.012	0.617±0.003	26.4±0.2	1.3±0.0
2	120	3.94±0.02	23.0 ±0.3	0.491±0.011	0.640±0.000	30.4 ±0.2	1.3±0.0
3	180	2.44±0.01	31.0 ±1.2	0.516±0.012	0.712±0.010	27.5 ±0.5	1.4±0.1
4	240	1.74±0.08	36.0 ±1.2	0.517±0.003	0.709±0.003	26.9±0.4	1.4±0.2

Note: Temperature of the reaction medium was 60 ^{o}C at pH 6 – 7.

Table 4.5: Comparison between granule characteristics of NTS, ATS-3 h, and MCTS-3 h

Material	Flow rate g/sec	Angle of repose (degree)	Bulk density g/cm^3	Tapped density g/cm^3	Compres-sibilty index(%)	Hausner ratio
NTS	2.00±0.02	43.0±1.0	0.545±0.05	0.817±0.011	32.2±0.2	1.5±0.0
ATS-3 h	2.60±0.01	32.0±0.0	0.616±0.004	0.895±0.085	31.2±0.0	1.5±0.1
MCTS-3 h	2.50±0.01	31.0±1.2	0.516±0.012	0.712±0.010	27.5±0.5	1.4±0.1

Table 4.6: Tablet properties of MCTS made from hydrolyzed starches at various period of time

Material (h)	Comp-action force (KN)	Comp-ression pressure $N/m^2 \times 10^5$	Weight of tablet (g) n=3	Thickness of tablet (m) $\times 10^{-3}$	Crushing strength (N) n=3	Radial tensile strength (N/m^2) $\times 10^5$	Compact density g/cm^3	Friability %	DT (sec) n =3
MCTS-1 h	5	6.4	0.500	3.65±0.05	20.0±0.4	2.8	1.13±0.01	3.37±0.35	35±2
	6	7.6	0.500	3.61±0.05	55.0±0.5	7.8	1.13±0.01	2.22±0.21	55± 5
	6.5	8.3	0.500	3.35±0.10	60.0±2.5	9.1	1.22±0.10	1.12±0.02	60±5
MCTS-2 h	5	6.4	0.500	3.61±0.06	45.0±1.5	6.4	1.13±0.03	2.11±0.10	77±5
	6	7.6	0.500	3.42±0.04	75.0±2.5	11.2	1.19±0.07	2.15±0.12	82±4
	6.5	8.3	0.500	3.28±0.12	95.0±2.5	14.8	1.24±0.02	3.19±0.15	106±6
MCTS-3 h	5	6.4	0.500	3.66±0.06	40.0±0.2	5.6	1.12±0.00	1.04 ±0.02	72±4
	6	7.6	0.500	3.45±0.05	85.0±1.0	12.6	1.18±0.02	1.04±0.02	75±5

	6.5	8.3	0.500	3.43±0.03	90.0±0.5	13.4	1.19±0.01	1.05±0.02	80±2
MCTS-4 h	5	6.4	0.500	3.73±0.13	20.0±0.2	2.7	1.09±0.03	2.18 ±0.12	20± 1
	6	7.6	0.500	3.43±0.06	60.0±1.5	8.9	1.19±0.03	2.11±0.10	30±2
	6.5	8.3	0.500	3.23±0.03	65.0±1.5	10.3	1.26±0.08	2.11±0.11	36 ±2

Note: Target weight and punch/die diameter were 500 mg, and 10.5 mm respectively .DT denotes disintegration time.

4.6 A novel two component composite MSL

Fig. 4.5 illustrates the granule size distribution as composed in the MSL (MCTS 50 % : LMH 50 %). About 60 % of the granules were greater than 250 µm and all the granules (100 %) were greater than 90 µm. This range of granule size distribution was responsible for the improved flow property over individual and the direct physical mixture of the primary excipients.

The photomicrograph of the coprocessed MSL (50 % MCTS plus 50 % α-LMH) granules is as shown in Figure 4.6. This revealed the homogeneity of the component of the composite excipient. Figure 4.7 and Figure 4.9 show the photograph of the fresh semi-solid mass and flakes of coprocessed microcrystarlac. This process guarantees even distribution of the three primary components within the mass. Whole granules (Fine - 500 µm., size range > 75 to 250 µm and > 90 to 250 µm were obtained from the granulation and employed for both granule characterization and compaction studies.

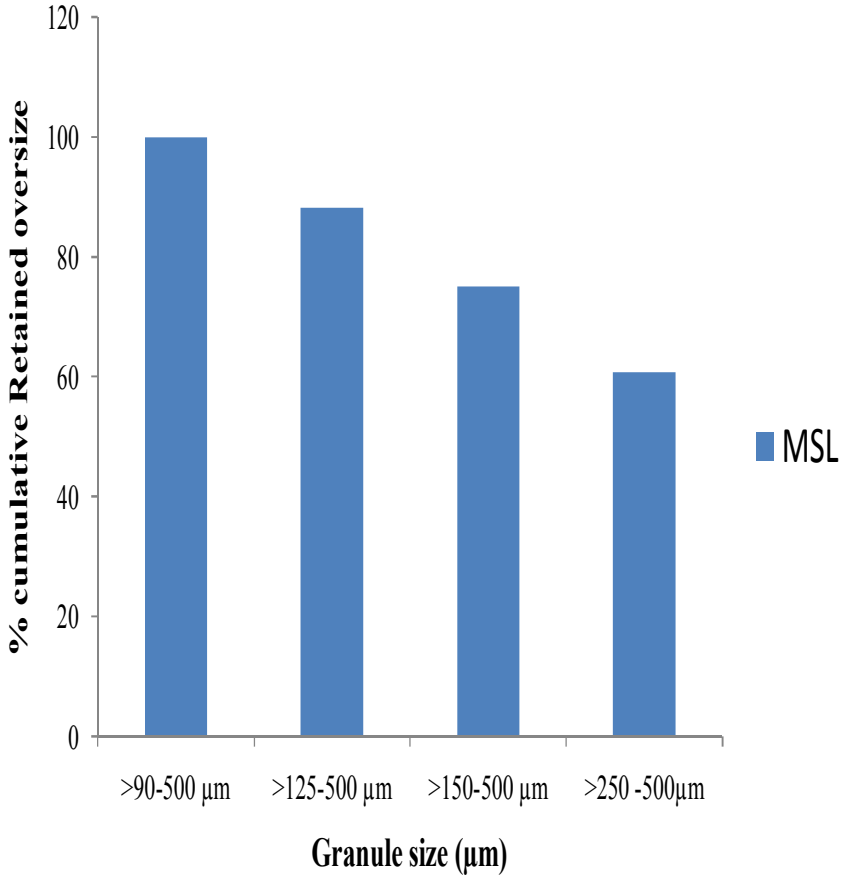


Fig.4.5 : MSL granule distribution (%) cumulative retained oversize versus granule size (µm).

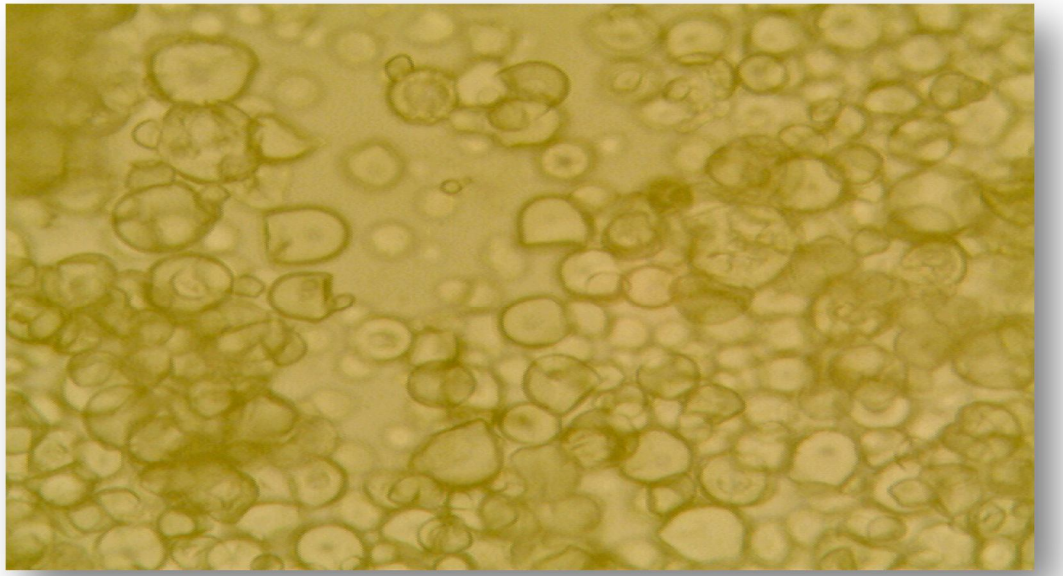


Fig. 4.6: Photomicrograph of MSL- B_5 granules x 40



Fig. 4.7: Photograph of fresh semi-solid mass of MSL B_5 after mixing.



Fig. 4.8: Photograph of moist flakes of MSL B_5 after 6 h of air drying ready for coarse granulation



Fig. 4.9: Photograph of MSL B_5 granules 6 h after coarse granulation through 1.5 mm mesh

The MCTS-3 h was tailored with α-LMH at different proportion according to the method described under section 3.2.4.1 and Table 3.1 to yield a composite filler-binder "MSL". Table 4.7 shows the result of the characteristics of MSL granules, while Table 4.8 shows the tablet properties of the co processed MSL. The composite tablets made with MSL-B_4 (MCTS 60 %: Lactose 40 %) at 5 KN had crushing strength

of 120 N, friability of 0.8 % and disintegration time of 150 sec. while tablets formulated with MSL-B_5 (MCTS 50 % and Lactose 50 %) had crushing strength, friability index value and disintegration time of 130 N, 0.4 % and 210 sec. respectively. Both batches gave acceptable compacts based on the tensile strength and friability. These two batches were selected for further particle restructuring.

Material	Batch	Flow rate (g/sec) n=3	Angle of repose (degree) n=3	Bulk density (g/cm^3) n =3	Tapped density (g/cm^3) n =3	Compr-essibility index (%)	Hausner ratio	Loss on drying (% w/w)
MCTS+ α-LMH (Fine - 500µm)	1	3.00±0.02	36±0.02	0.500 ±0.011	0.682 ±0.022	56.4±0.2	1.4±0.1	4.5±0.05
	2	2.94±0.02	32±0.01	0.517 ±0.012	0.714 ±0.021	38.1±0.1	1.4 ±0.1	4.7±0.0 2
	3	2.51 ±0.01	39±0.03	0.556 ±0.013	0.790 ±0.020	42.1±0.0	1.4 ±0.1	4.9 ±0.02

4	2.80±0.02	43±0.0 3	0.560 ±0.010	0.833 ±0.023	49.0 ±0.5	1.5 ±0.1	4.4 ±0.01
5	2.21±0.01	48±0.02	0.577 ±0.022	0.882 ±0.022	53.0 ±0.5	1.5 ±0.0	4.8 ±0.02

Table 4.7: Characteristics of composite granules of MSL

Key: 1, 2, 3, 4 and 5 represent batches 1 to 5 containing MCTS and α-LMH.

Table 4.8: Tablet properties of various batches of MSL.

Coprocessed Material/ Batch	Comp-action force (KN)	Comp-ression pressure $N/M^2 \times 10^5$	Weight of tablet (g) n=3	Thickness of tablet (m) $\times 10^{-3}$	Crushing strength (N) n=3	Radial tensile strength (N/M^2) $X 10^5$	Compact density g/cm^3	Friability % n=3	DT (sec) n =3
MSL Batch 1	3	2.5	NC	-	-	-	-	-	-
MCTS+LMH	4	3.3	0.492±0.0 05	3.65±0.02	32±0.5	4.5±0.0	1.09±0.02	4.0±0.4	60.0±5.0
(90 %:10 %) w/w	5	4.1	0.498±0.0 02	3.50±0.00	30±0.8	4.4±0.0	1.11±0.01	4.2±0.6	96.0±6.0
MSL Batch 2	3	2.5	0.492±0.006	3.93±0.03	17±0.3	2.2±0.0	1.03±0.01	3.8±0.4	41.0±2.0
MCTS+LMH	4	3.3	0.498±0.004	3.39±0.03	55±0.5	8.3±0.0	1.20±0.00	2.8±0.4	100.0±10.0
(80 %:20 %) w/w	5	4.1	0.497±0.003	3.31±0.01	72±0.9	11.1±0.0	1.23±0.01	1.6±0.1	120.0±11.0
MSL Batch 3	3	2.5	0.498±0.004	3.87±0.05	17±0.2	2.2±0.0	1.05±0.00	3.4±0.2	46.0±5.0
MCTS+LMH	4	3.3	0.498±0.004	3.42±0.03	47±0.3	7.0±0.0	1.19±0.02	1.7±0.1	90.0±5.0
(70 %:30 %) w/w	5	4.1	0.499±0.002	3.30±0.02	65±0.5	10.0±0.0	1.23±0.01	1.2±0.1	120.0±10.0

MSL Batch 4	3	2.5	0.501 ±0.001	3.86 ±0.06	33 ±0.3	4.4 ±0.0	1.06 ±0.02	1.4 ±0.2	40.0 ±2.0
MCTS+LMH	4	3.3	0.502 ±0.001	3.69 ±0.03	107 ±5.2	14.8 ±0.0	1.11 ±0.01	1.1 ±0.1	120.0 ±8.0
(60 %:40%)	5	4.1	0.499 ±0.002	3.27 ±0.02	120 ±5.5	18.7 ±0.0	1.25 ±0.02	0.8 ±0.0	150.0 ±12.0
MSL Batch 5	3	2.5	0.501 ±0.002	3.80 ±0.04	52 ±0.5	7.0 ±0.0	1.09 ±0.02	0.5 ±0.1	60.0 ±3.0
MCTS+LMH	4	3.3	0.507 ±0.005	3.59 ±0.03	127 ±7.0	18.0 ±0.0	1.15 ±0.02	0.3 ±0.0	150.0 ±11.0
(50 %:50 %) w/w	5	4.1	0.504 ±0.002	3.33 ±0.03	>130 ±7.5	20.0 ±0.0	1.23 ±0.02	0.4 ±0.0	210.0 ±15.0

Note: Tablet target and Punch/ die diameter were 500 mg, and 10.5 mm respectively. NC: No compaction. DT represents disintegration time.

4.7 A novel three component composite excipient MSCL

Fig. 4.10 shows the granule size distribution of MSCL (MCTS 40 %: LMH 40 %: MCC 20 %). More than 50 % of the granules were greater than 250 µm and all the granules (100 %) were greater than 90 µm This range of granule size distribution was responsible for the improved flow property over the individual excipients and the direct physical mixture of the primary excipients. Figure 4.11 shows the photomicrograph of MSCL-B_2 (40 % MCTS, 40 % α-L MH, and 20 % MCC). It can be seen that the fibres of MCC are evenly distributed and properly embedded within the structure of the composite excipient. Figure 4.12 also shows the photomicrograph of microcrystarcellac (B_3) containing 35 % of MCTS, 35 % α-L MH, and 30 % MCC. In this case more fibres of MCC are visible due to increase in its percentage and they are well distributed within the starch granules and the lactose. Figure 4.13 shows the photograph of the fresh semi-solid mass of coprocessed MSCL. Figure 4.14 shows the moist flake after six hours of air drying. Table 4.9 shows the result of granules characteristics of MSCL, while Table 4.10 illustrates the tablet properties of the coprocessed MSCL. The composite tablets formulated with MSCL-B_2 (MCTS 40 %: Lactose 40 %: MCC 20 %) at 7.5 KN had crushing strength, friability and disintegration time of 127 N, 0.28 % and 210 sec. respectively, while compact of MSCL-B_3 (MCTS 35 %: Lactose 35 %: MCC 30 %) had corresponding crushing strength, friability and disintegration time of 130 N, 0.19 % and 180 sec. respectively.

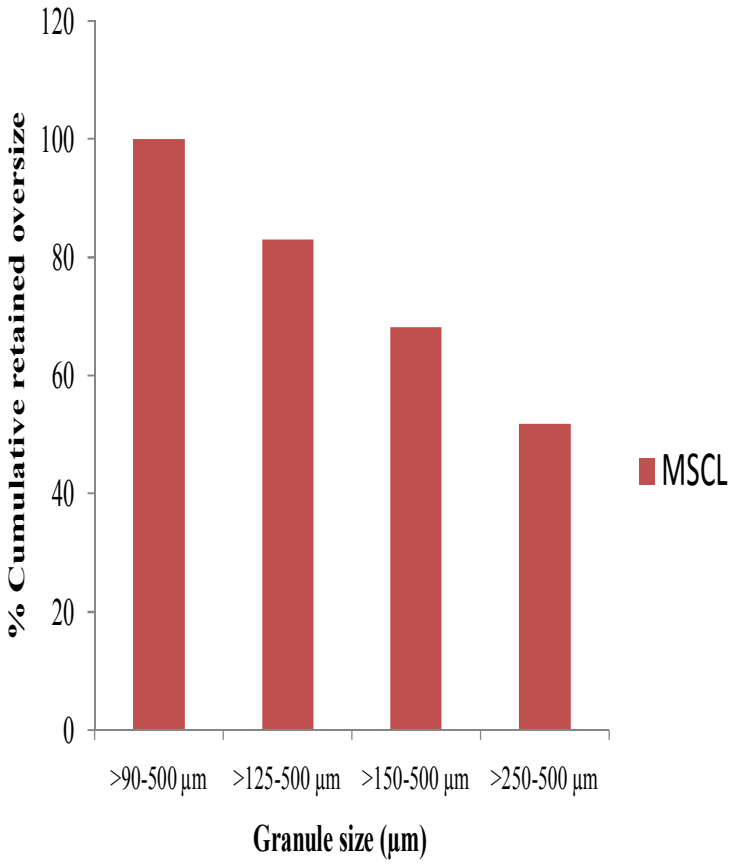


Fig. 4.10: MSCL granule distribution in % cumulative retained oversize versus granule size (µm)

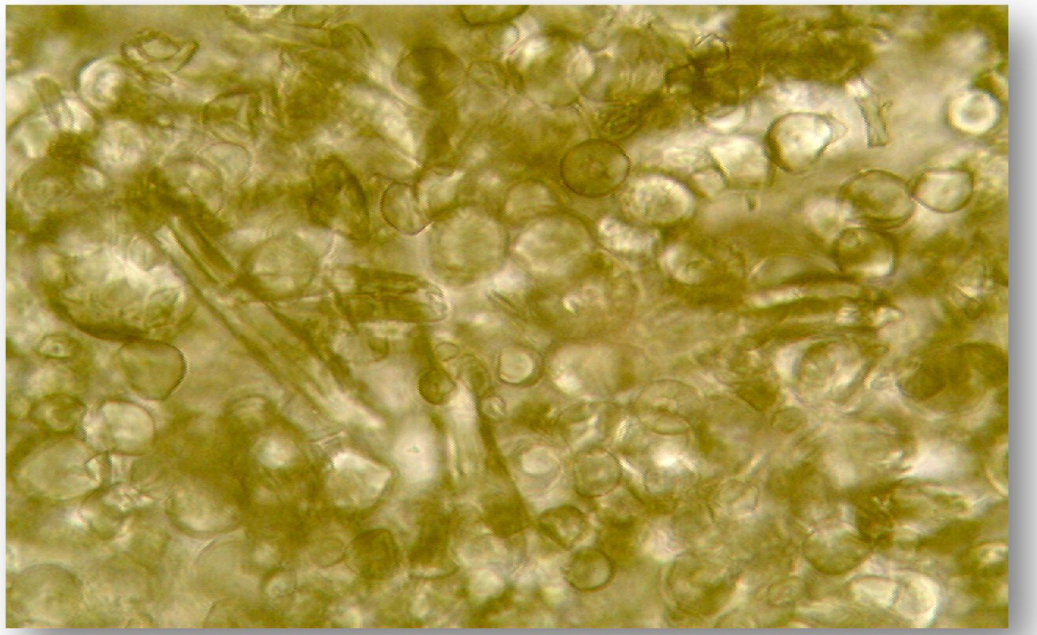


Fig. 4.11: Photomicrograph of MSCL- B_2 granules x 40

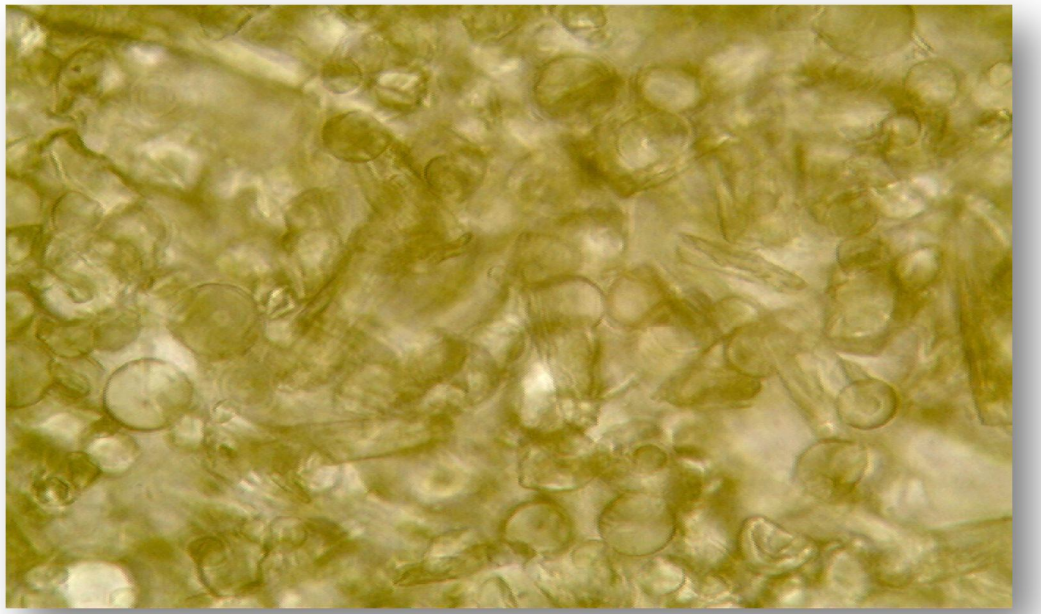


Fig. 4.12: Photomicrograph of MSCL- B_3 granules x 40



Fig. 4.13: Photograph of fresh semi-solid mass of MSCL B_2 after mixing.



Fig. 4.14: Photograph of moist flakes of MSCL B_2 after 6 h of air drying

ready for coarse granulation

Table 4.9: Characteristics of the composite granules of MSCL

Material (Fine - 500µm)	**Batch**	**Flow rate (g/sec) n=3**	**Angle of repose (degree) n=3**	**Bulk density (g/cm^3) n =3**	**Tapped density (g/cm^3) n =3**	**Compr-essibility index (%)**	**Hausner ratio**	**Loss on drying (% w/w)**
MCTS+ Lactose+ MCC	1	2.42 ± 0.02	37± 0.5	0.60± 0.01	0.79 ±0.02	32.0± 0.7	1.3± 0.0	5.4± 0.2
	2	3.13 ± 0.03	28 ± 0.3	0.50 ± 0.01	0.65± 0.01	30.0 ± 0.5	1.3 ± 0.0	5.2 ± 0.1
	3	3.52 ± 0.02	24 ± 0.1	0.45± 0.01	0.63± 0.01	40.0 ± 0.5	1.4 ± 0.1	4.8 ± 0.1

	4	2.59 ± 0.04	26 ± 0.1	0.42 ± 0.01	0.75± 0.02	78.6 ± 2.3	1.8 ± 0.2	5.1 ± 0.2
	5	2.54 ± 0.04	32 ± 0.2	0.43± 0.02	0.65± 0.02	51.0± 1.5	1.5 ± 0.1	4.9 ± 0.1

Key: 1, 2, 3, 4 and 5 represent batches 1 to 5 containing MCTS, α-LMH and MCC.

Table 4.10: Tablet properties of various batches of MSCL.

Material	Batch	Comp-action force (KN)	Comp-ression press-ure. (N/M^2)x 10^5	Tablet weight (g) n=3	Tablet thickness (m) x10^{-3}	Crushing strength (N) n=3	Radial tensile strength (N/M^2) X 10^5	Friability % n=3	DT (sec) n =3
	% w/w								
MCTS+	1	4	3.3	0.500±0.001	4.40± 0.01	33± 0.9	3.8± 0.0	7.2± 0.20	50± 0.5
LMH+	45:45:10	5	4.1	0.500±0.001	3.30± 0.00	93± 0.7	13.5± 0.0	5.6± 0.25	180± 1.6
MCC		6	4.9	0.500±0.000	3.45± 0.01	120±2.5	17.7± 0.0	0.73±0.01	240± 2.5
	2	4	3.3	0.500 ±0.001	4.23 ± 0.01	37 ± 0.4	4.5 ± 0.0	3.80 ± 0.20	40 ± 0.2
	40:40:20	5	4.1	0.500 ±0.000	3.52 ± 0.02	93 ± 0.5	13.5 ± 0.0	0.44 ± 0.01	120± 1.2
		6	4.9	0.500 ±0.000	3.42 ± 0.01	127 ± 1.4	18.8 ± 0.0	0.28 ± 0.01	210 ± 2.2

3	4	3.3	0.500 ±0.001	4.27 ± 0.03	40 ± 0.5	4.8 ± 0.0	2.18 ± 0.10	20 ± 0.1
35:35:30	5	4.1	0.500 ±0.001	3.34 ± 0.01	98 ± 0.8	15.0 ± 0.0	0.29 ± 0.01	15± 0.0
	6	4.9	0.500 ±0.000	3.33 ± 0.01	130 ± 2.5	20.0 ± 0.0	0.19 ± 0.01	180± 2.0
4	4	3.3	0.500±0.000	4.27± 0.01	20± 0.2	2.4± 0.0	5.80± 0.31	20± 0.0
30:30:40	5	4.1	0.500±0.000	3.36± 0.02	75± 1.5	11.4± 0.0	4.73± 0.20	60± 0.2
	6	4.9	0.500±0.001	3.00± 0.00	130± 3.0	21.9± 0.0	0.21± 0.01	240± 1.8
5	4	3.3	0.500±0.001	4.30± 0.02	17± 0.3	2.0± 0.0	3.07± 0.23	15± 0.00
25:25:50	5	4.1	0.500±0.000	3.30± 0.02	70± 1.2	10.8± 0.0	0.23± 0.01	135± 2.5
	6	4.9	0.500±0.001	3.00± 0.00	130± 3.5	22.1± 0.0	0.15± 0.01	360± 2.7

Note: Tablet target and Punch/ die diameter were 500 mg, and 10.5 mm respectively. DT denotes disintegration time while: 1, 2, 3, 4 and 5 represent batches 1 to 5 containing MCTS, α-LMH and MCC.

4.8 Comparison between physical mixture, coprocessed and standard marketed filler-binders

Table 4.11 compares the granule characteristics of the physical mixture of the primary excipients, sieved coprocessed MSL and MSCL (the optimized granule size ranges: >75 – 250 µm and >90 – 250 µm), and using Cellactose® and Starlac® (marketed co processed filler-binder) as standards. It can be seen from Table 4.11 that the flow rate of the physical mixtures of combinations of MCTS and α-LMH, and MCTS, α-LMH and MCC were 0.65 g/s and 0.45 g/s respectively. The corresponding angles of repose were 40.2^{o} and 47.8^{o}.for the same physical mixture, while the corresponding compressibility indices were 53 % and 52 % respectively. Following particle restructuring and coprocessing, the flow rate for coprocessed MSL (MCTS 50%: α-LMH 50 %) and MSCL (MCTS 40 %: α-LMH 40 %: MCC 20 %) both having granule size range > 90 – 250 µm, were 3 g/s and 2 g/s respectively with corresponding angles of repose of 32^{o} and 31.6^{o} respectively. More so, the compressibility indices determined were 34 % and 23.4 % respectively.

There was a tremendous increase in flow property, in the case of coprocessed MSL and MSCL over the physical mixture of the corresponding excipients. It can be seen that the granule properties were improved by four fold based on the flow rate. This is essential for effective die filling, weight and dose uniformity. Coprocessing is a method of agglomeration whereby particles form granules, thereby reducing cohesiveness as evidenced by the result obtained in this study.

Table 4.11: Powder characteristics of physical mixture, coprocessed, and standard marketed filler-binders

Material	Flow rate g/sec	Angle of repose (o)	Bulk density g/cm^3	Tapped density g/cm^3	Compres-sibilty index %	Hausner ratio
MCTS+LMH B_5 (50:50) Physical mixture	0.65 ±0.12	40.2±0.2	0.510 ±0.012	0.781±0.016	53.0±0.2	1.53±0.02
MCTS+LMH+MCC B_2 (40:40:20)Physical mixture	0.45 ±0.02	47.8±0.4	0.481 ±0.011	0.735 ±0.012	52.0 ±0.2	1.53 ±0.03
MCTS(>75-250 µm)	2.50 ±0.5	24.5 ±0.2	0.516 ±0.012	0.712 ±0.013	27.5 ±0.4	1.40 ±0.01
MSL-B4 (>90-250µm)	6.00 ±1.2	17.5 ±0.1	0.615 ±0.016	0.696 ±0.014	13.2 ±0.1	1.13 ±0.01
MSL-B5 (>90-250µm) [MSL]	3.00 ±0.5	32.0 ±0.4	0.605 ±0.017	0.813 ±0.018	34.0±0.6	1.12 ±0.01
MSCL-B2 (>90-250µm)	2.00 ±0.40	31.6 ±0.2	0.677 ±0.015	0.768 ±0.011	13.4 ±0.2	1.13 ±0.02
MSCL-B3 (>75-250µm) [MSCL]	1.60±0.30	32.0 ±0.3	0.526 ±0.017	0.685 ±0.022	30.0 ±0.1	1.30 ±0.01
Starlac®	7.10±1.40	19.2 ±0.2	0.641 ±0.013	0.725 ±0.012	13.1 ±0.1	1.13 ±0.03
Cellactose®	1.84±0.20	24.2 ±0.2	0.443 ±0.012	0.532 ±0.010	20.1 ±0.1	1.20 ±0.01
MCC	0.75±0.20	48.0 ±0.5	0.389 ±0.018	0.620 ±0.013	59.4 ±0.2	1.60 ±0.13

Figure 4.15 illustrates the influence of compression pressure on compact density of NTS, ATS, and MCTS. It can be seen that the MCTS showed better volume reduction than ATS and NTS. Figure 4.16 shows the relationship between compression pressure and radial tensile strength of compacts of NTS, ATS, MCTS, α-LMH, Starlac®, and Cellactose®. Tablets made at 12 KN had radial tensile strength of 15, 12.5 and 5 x 10^5 N/m^2 respectively. It could be seen that MCTS formed better compact than ATS and NTS.

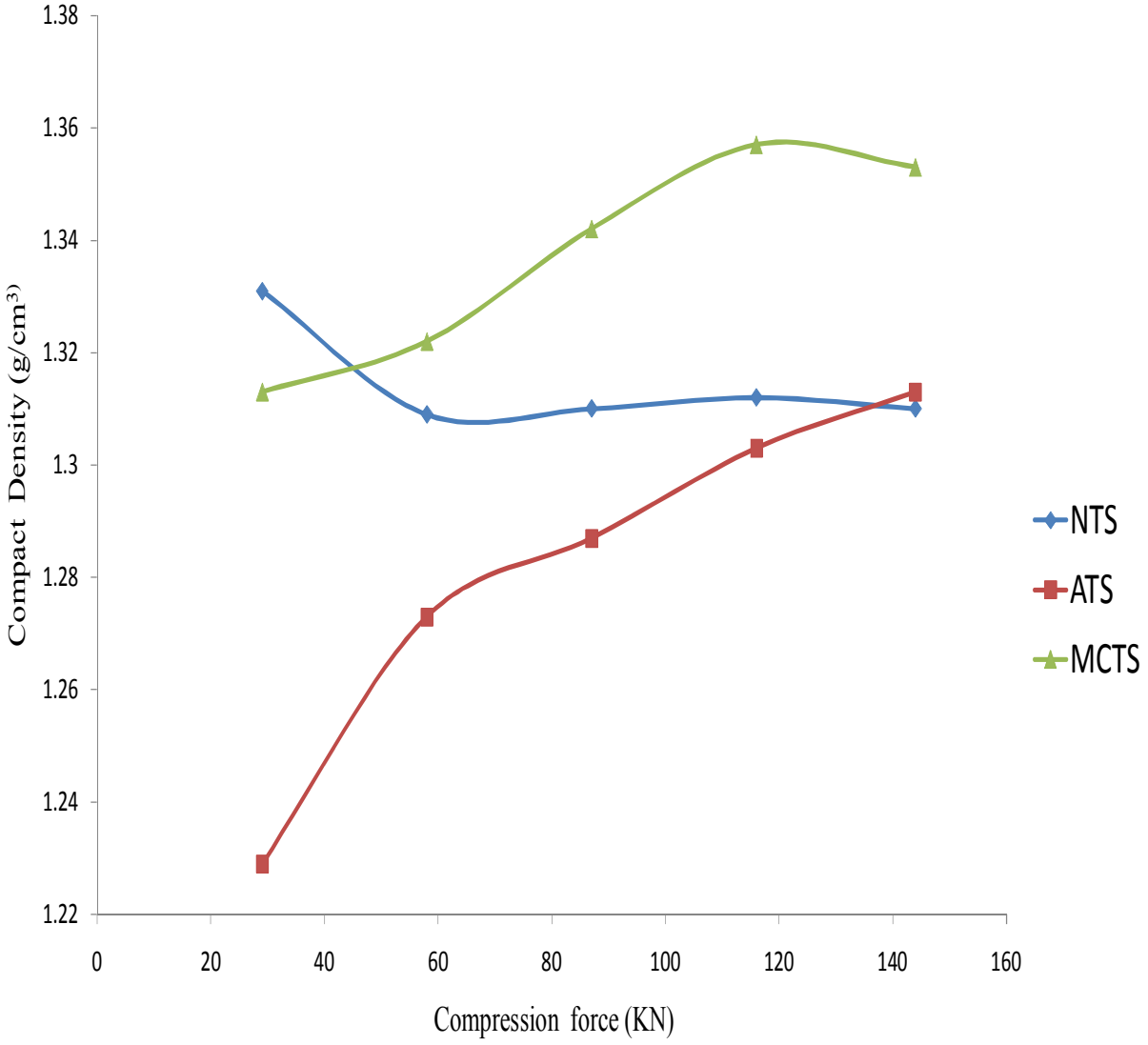


Fig. 4.15: Compact density (g/cm^3) vs compression force (KN) for NTS, ATS, and MCTS placebo tablets.

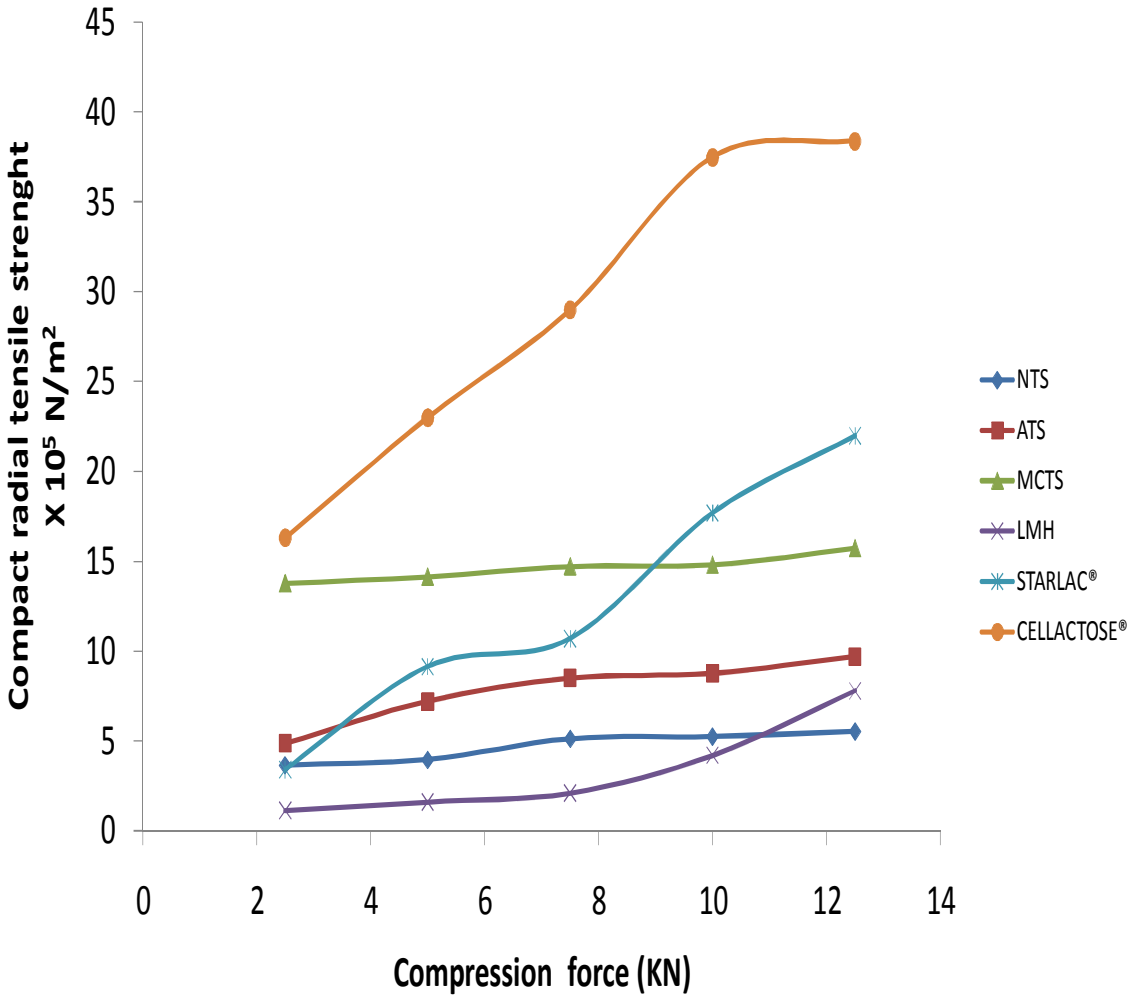


Fig. 4.16: Radial tensile strength (x 10^5 N/m^2)vs compression force (KN) for NTS, ATS, MCTS, αLMH, Starlac®, and Cellactose® placebo tablets.

4.9 Comparison between compactness of coprocessed MSL and the physical mixture of the primary excipients

Figure 4.17 illustrates the effect of compression force on tensile strength of tablet formulated with various particle size fractions of batches 4 and 5 of coprocessed MSL, and direct physical mixture (PM) of the primary excipients of batch 5 (MSL-PM -50:50). The various fractions of the coprocessed MSL showed better compactibility than the direct physical mixture of the primary excipients. Figure 4.18 shows the effect of compression force on tensile strength of tablets formulated with various particle size fractions of batches 4 and 5 of coprocessed MSL, Starlac® and Cellactose®. The fractions of MSL and Cellactose® are characterized by initial steep linear region, which represents plastic deformation. It can be seen that Cellactose® showed better compactness compare to MSL and Starlac®. This could be attributed to the combination of high level of fragmentation, increased surface area, number and strength of bonds formed in the former compared to the latter.

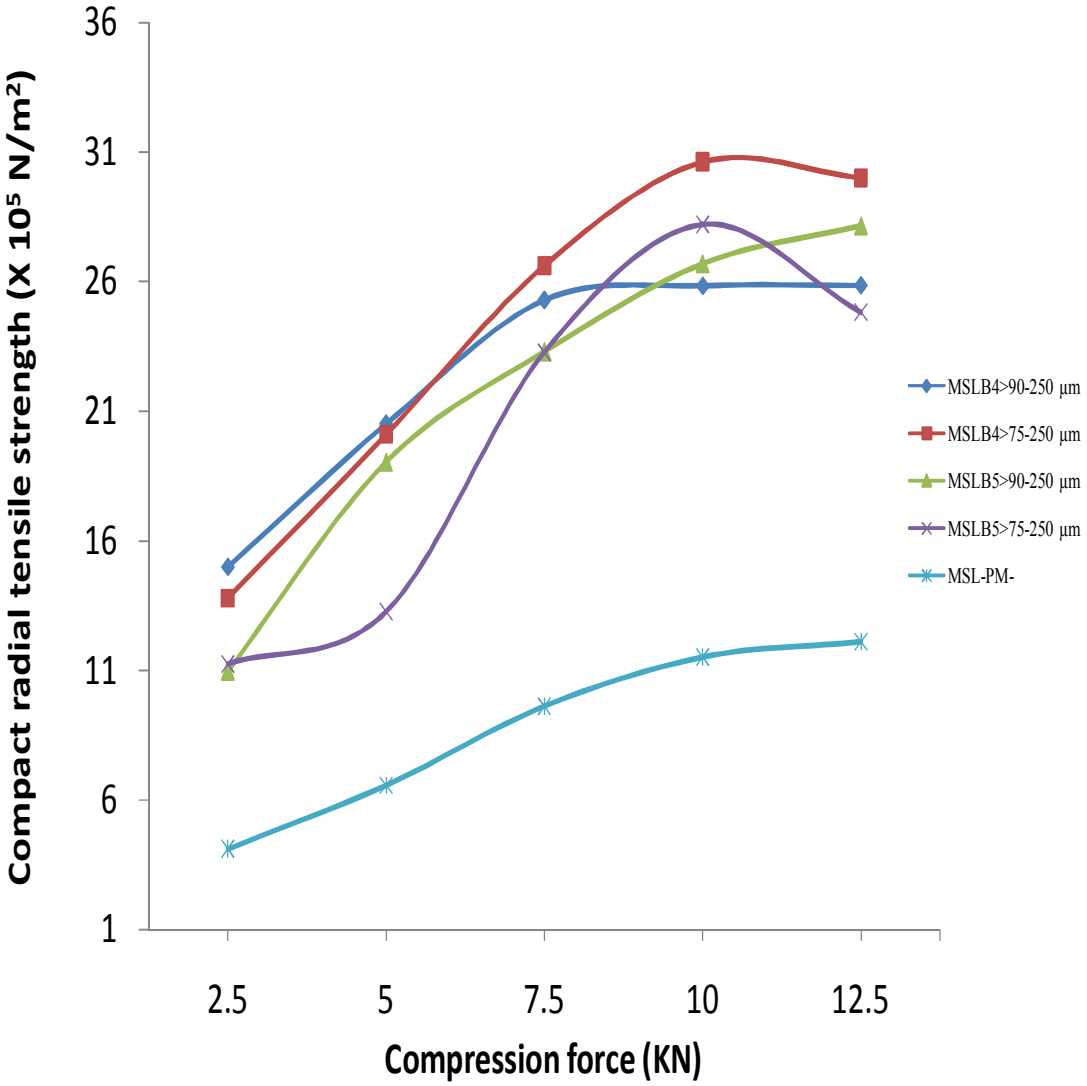


Fig. 4.17: Radial tensile strength (x 105 N/m^2) vs compression force (KN) for MSL and direct physical mixture (PM) (MCTS plus LMH-50:50) placebo tablets.

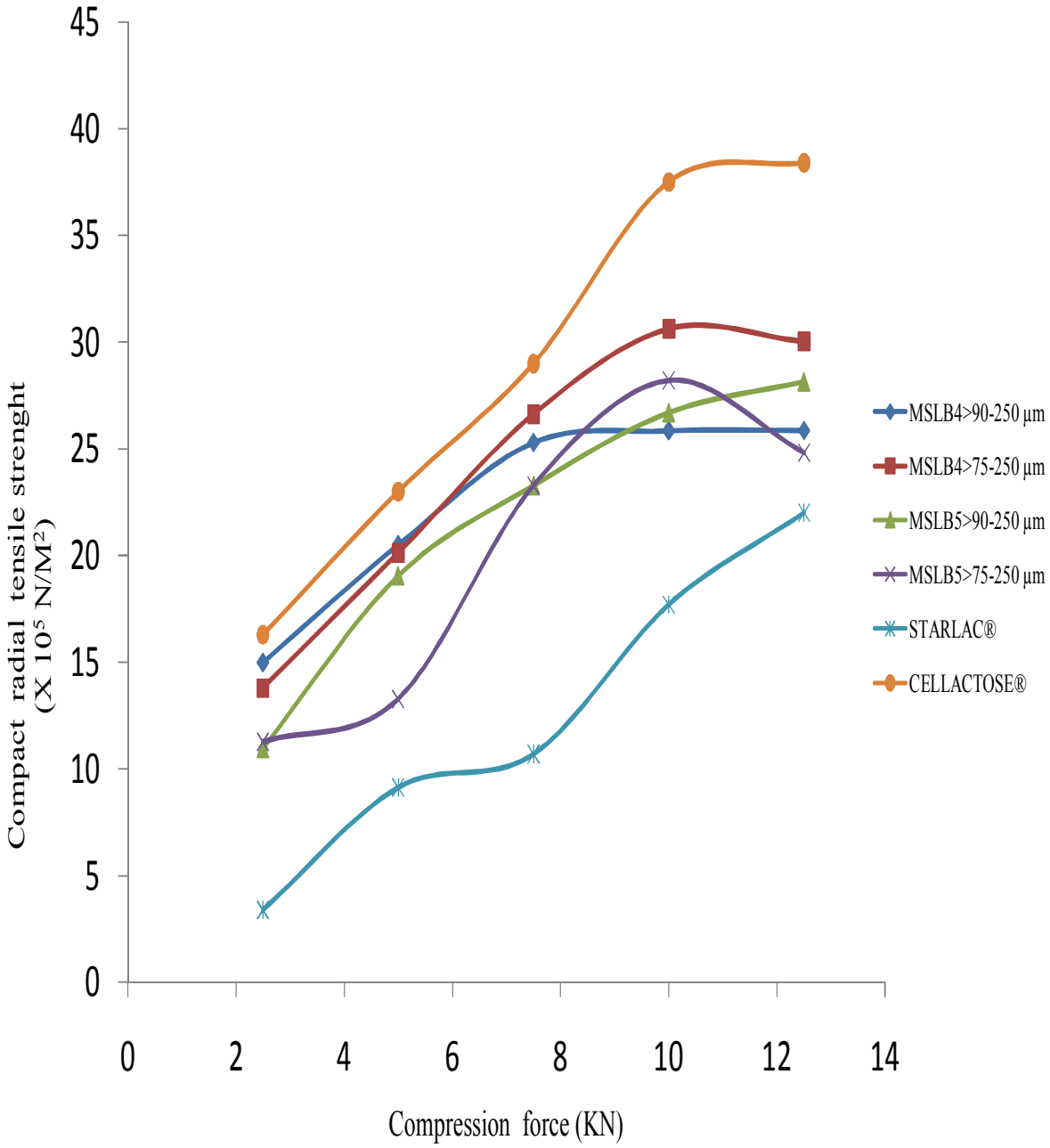


Fig. 4.18: Radial tensile strength (x 10^5 N/m^2) vs compression force (KN) for MSL, Starlac®, and Cellactose® placebo tablets.

4.10 Comparison between compactness of coprocessed MSCL and the physical mixture of the primary excipients

Figure 4.19 shows the effect of compression pressure on tensile strength of tablets formulated with various particle size fractions of the coprocessed MSCL, and direct physical mixture batch 2 (MSCL-PM-40:40:20). The various fractions of the coprocessed MSCL are characterized by initial steep linear region, which represents plastic deformation with better compactibility than the direct physical mixture of the primary excipients. Figure 4.20 illustrates the relationship between compression force and radial tensile strength of compacts made of MSCL, Starlac®, Cellactose® and MCC. The rising trend of Cellactose® showed better compactness compared to MSCL and Starlac®. This could also be attributed to high level of fragmentation, increased surface area, number and strength of bonds formed in the former compared with the latter.

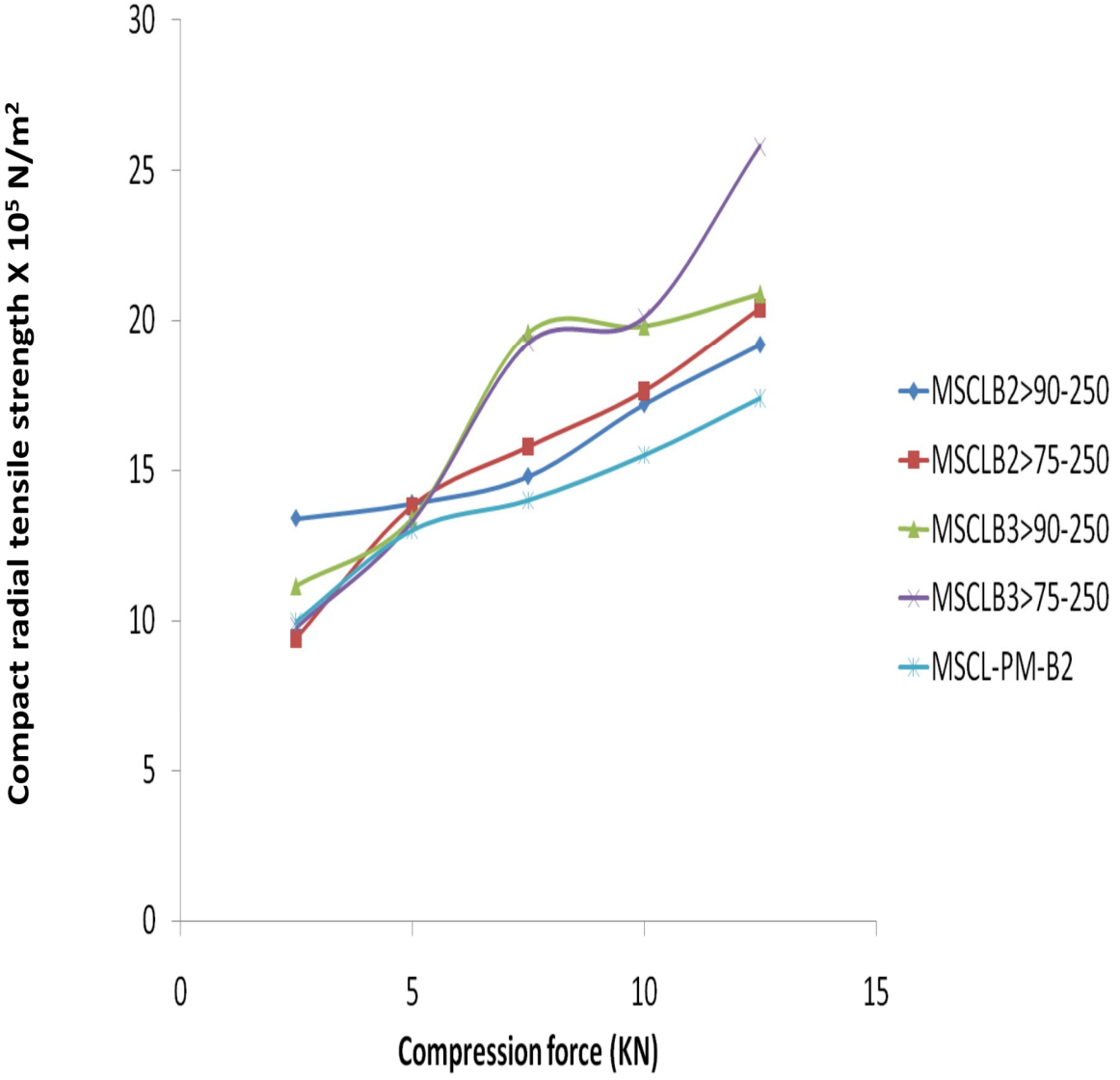

Compact radial tensile strength X 10⁵ N/m²
30
25
20
15
10
5
0
0
5
10
15
Compression force (KN)
MSCLB2>90-250
MSCLB2>75-250
MSCLB3>90-250
MSCLB3>75-250
MSCL-PM-B2

Fig. 4.19: Radial tensile strength (x 10^5 N/m^2) vs compression force (KN) for MSCL and direct physical mixture (PM) (MSCL-PM-40:40:20) placebo tablets.

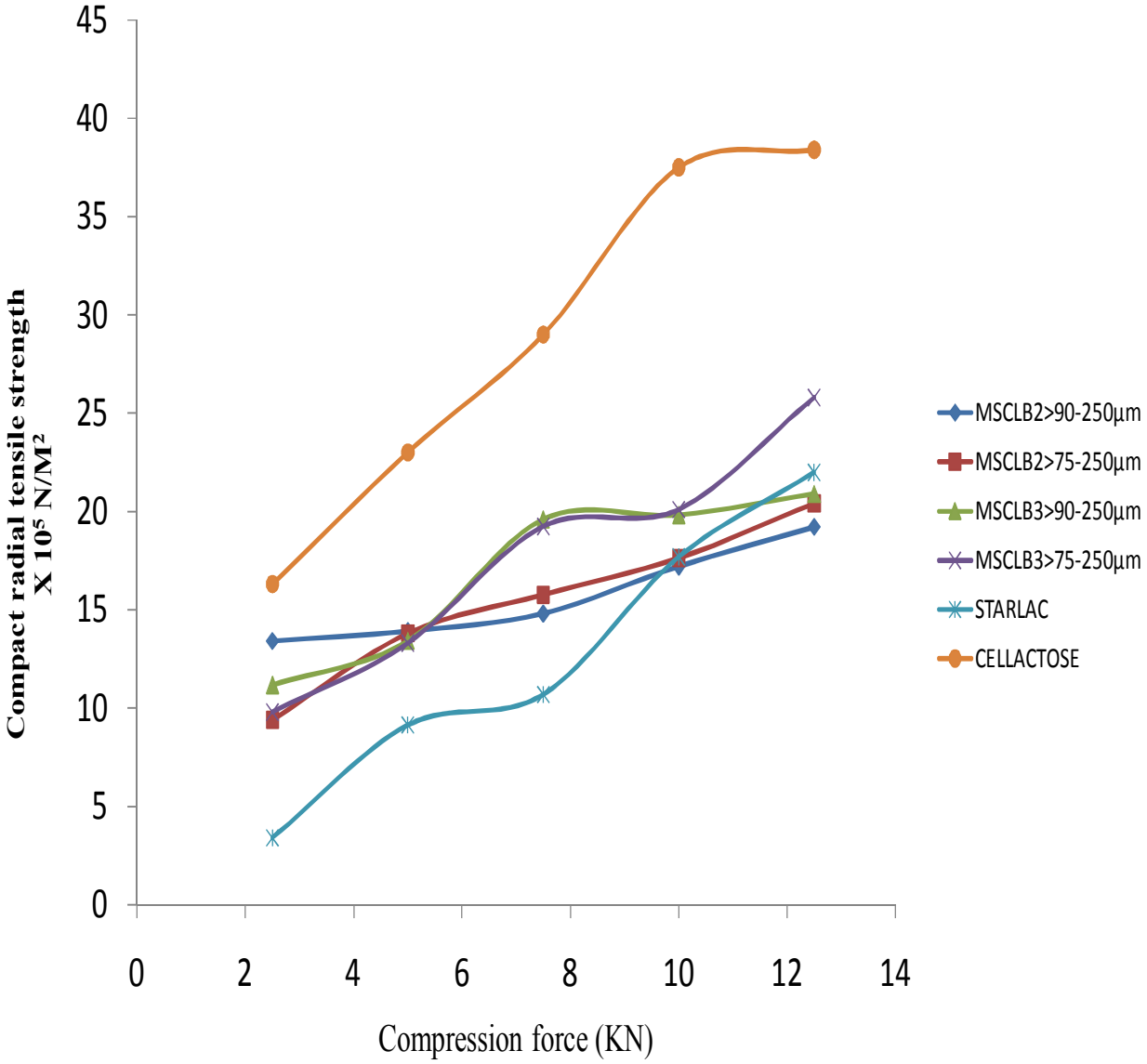


Fig. 4.20: Radial tensile strength (x 10^5 N/m^2) vs compression force (KN) for MSCL, Starlac®, and Cellactose® placebo tablets.

4.11 Disintegration time of placebo tablets

Figure 4.21 illustrates the relationship between disintegration time and compression pressure of compacts containing NTS, ATS, MCTS, α-LMH, Starlac® and Cellactose®. It can be seen that all the tablets disintegrated in less than 2 min. 30 sec., with the exception of Cellactose® that disintegrated completely after 17 min.

Figure 4.22 shows the relationship between disintegration time and compression pressure of compacts containing MSL, Starlac®, and Cellactose®. Compact hardness increased with increase in compression pressure with also a direct effect on disintegration time. It can be seen that MSL batch 5 had shorter disintegration time than the MSL batch 4 and Cellactose®, but higher than that of Starlac®. The disintegration time ranged between 1 min. and 6 min. with the exception of Cellactose® that disintegrated completely after 17 min. Compact hardness plays vital role in disintegration of tablets. Harder tablet is characterized with lower the disintegration, and hence longer disintegration time.

Figure 4.23 illustrates the relationship between disintegration time and compression pressure of compacts of microcrystarcellac (MSCL), Starlac®, and Cellactose®. It can be seen that all the tablets disintegrated in less than 4 min. with the exception of Cellactose® that disintegrated completely after 17 min.

Figure 4.24 shows influence of increasing compression force on friability of MSL, MSCL, Starlac®, Cellactose®, and MCC. Direct relationship exists between compression pressure and tablet hardness, whereas, friability is inversely related to tablet hardness. It can be seen that the friability of all the tablets were less than 1.0 % as the compression pressure

increased from 4 KN to 12 KN with the exception of Starlac® which had friability above 1.0 % until at 12 KN when the friability was less than 1.0 %.

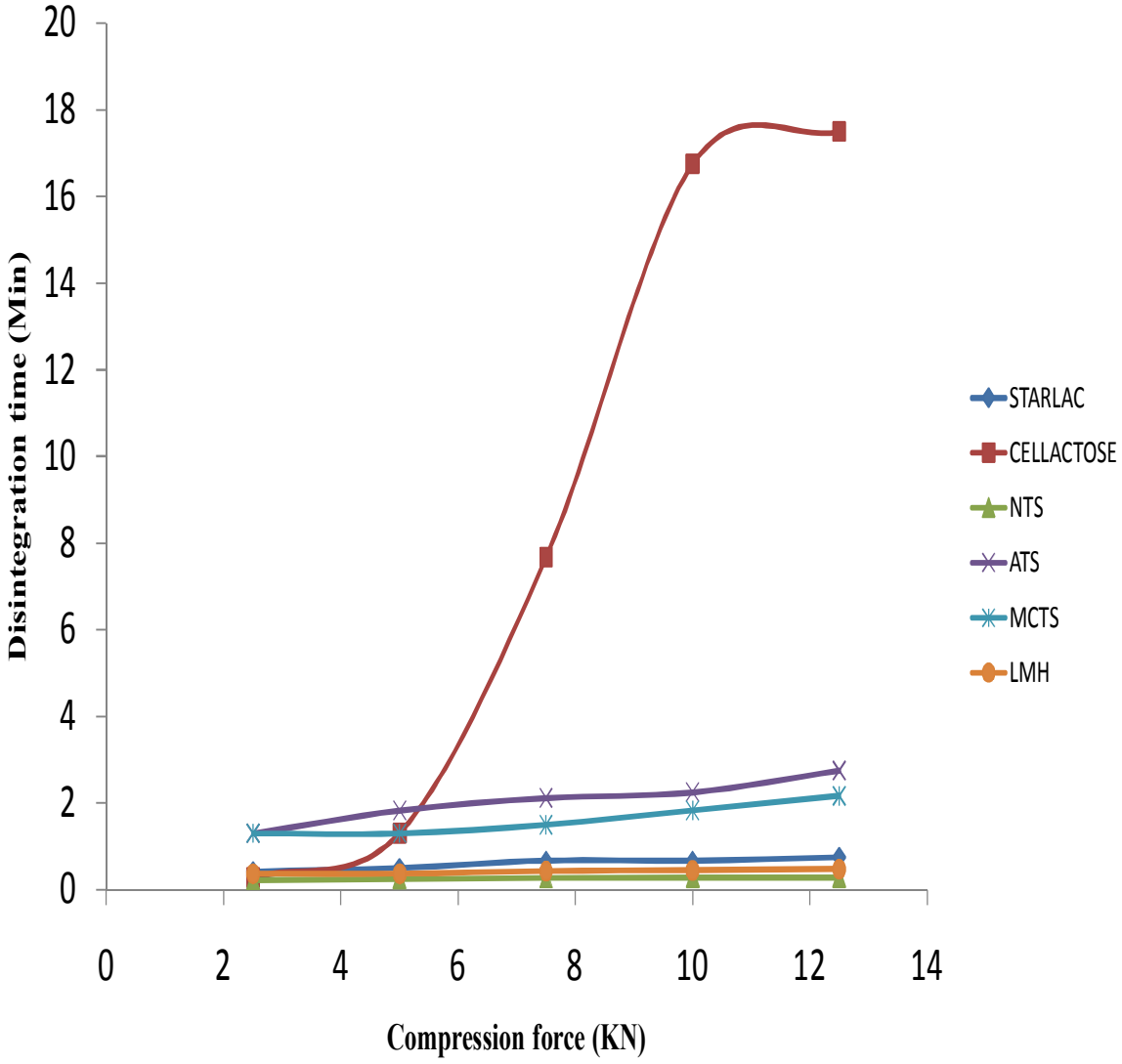


Fig. 4.21: Disintegration time (Min) vs compression force (KN) for NTS, ATS, MCTS, α-LMH, Starlac®, and Cellactose ® placebo tablets

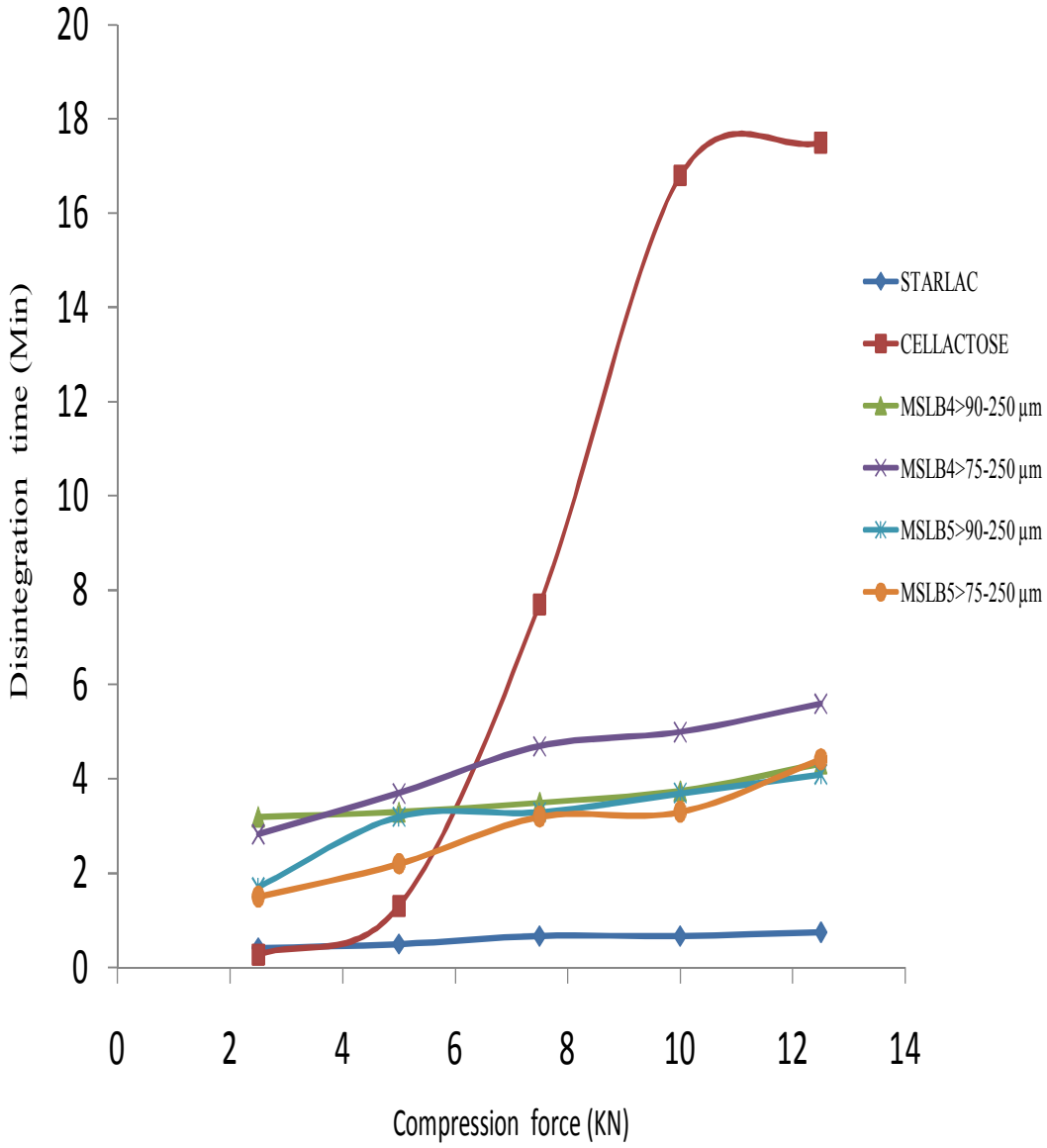


Fig. 4.22: Disintegration time (Min) vs compression force (KN) for MSL, Starlac®, and Cellactose® placebo tablets.

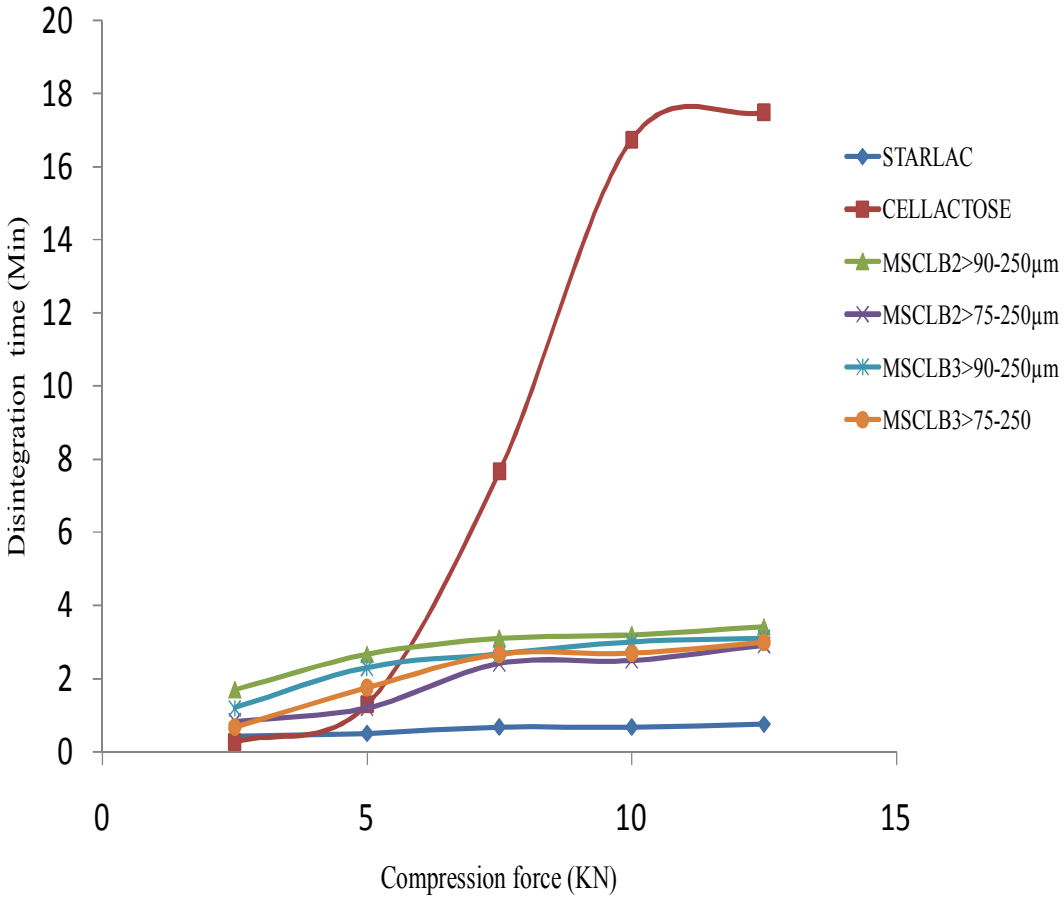


Fig. 4.23: Disintegration time vs compression force for MSCL, Starlac®, and Cellactose® placebo tablets.

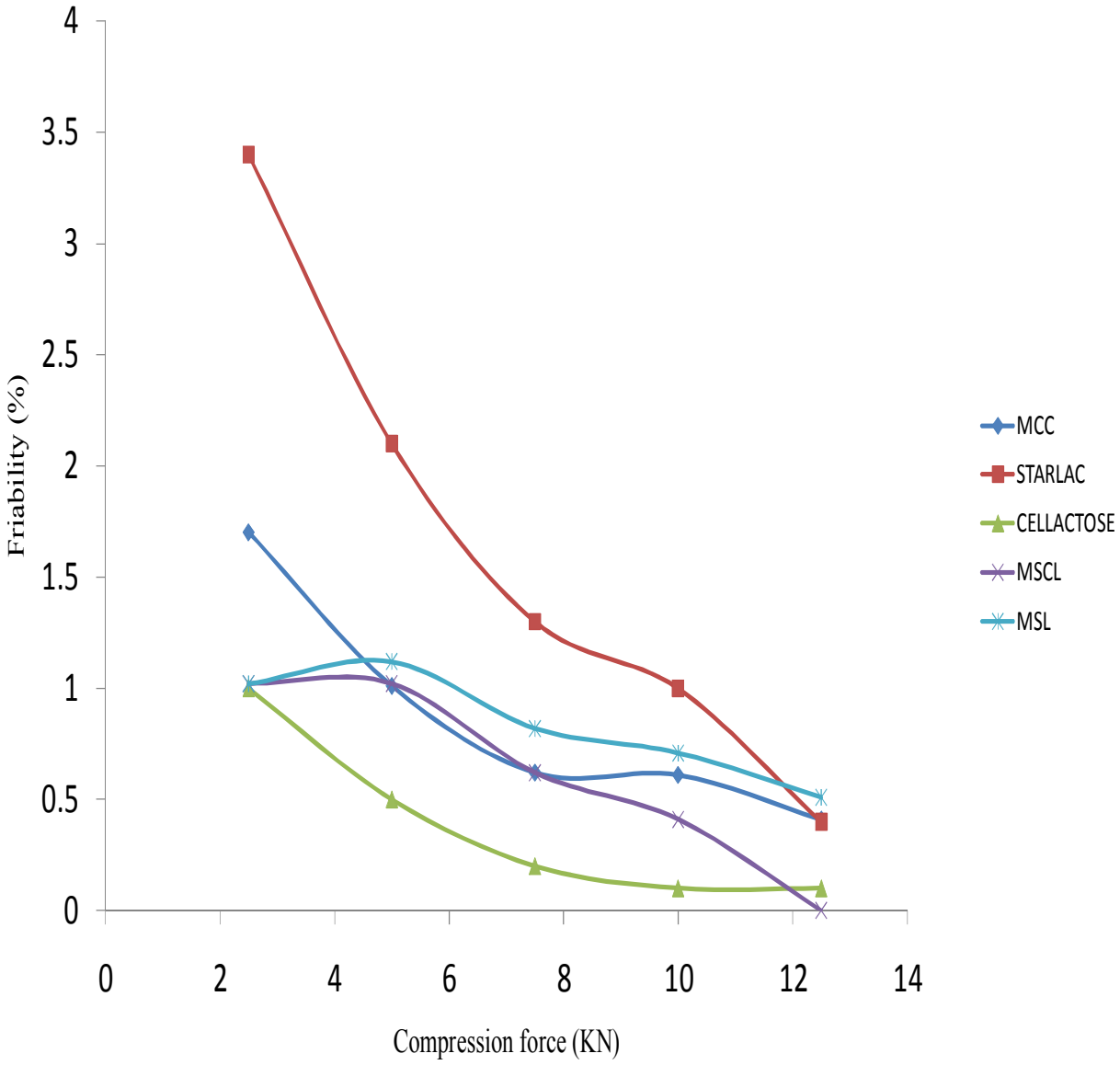


Fig. 4.24: Friability (%) vs compression force (KN) for MSL, MSCL, Starlac® and Cellactose® placebo tablets

4.12 Results of Heckel analysis

Figure 4.25 shows the Heckel plots for MCTS, MSL, MSCL, Starlac® and Cellactose®. Three phases of compression are discernable, with the initial stage representing rearrangement and fragmentation due to die filling, while the second stage is due to consolidation and the third stage represents decompression stage. Values of the mean yield pressure P_Y, of the formulations were calculated from the second compression region, and the intercept, A, was determined from the extrapolation of the region (see Tab. 4.12).

4.13 Results of Kawakita analysis

Figure 4.26 shows the Kawakita plots for MCTS, MSL, MSCL, Starlac®, and Cellactose®. A linear relationship was obtained at all compression pressures with correlation coefficients >0.996 for all the formulations. This suggests that the equation may be used to predict the densification mechanism of the formulations. Values of **'a'** and 'ab' were obtained from the slope and intercept of the plots, respectively. Values of (1-a) give the initial relative density of the formulations, D_I , while P_K , values were obtained from the reciprocal of the values of 'b' (see Tab. 4.13).

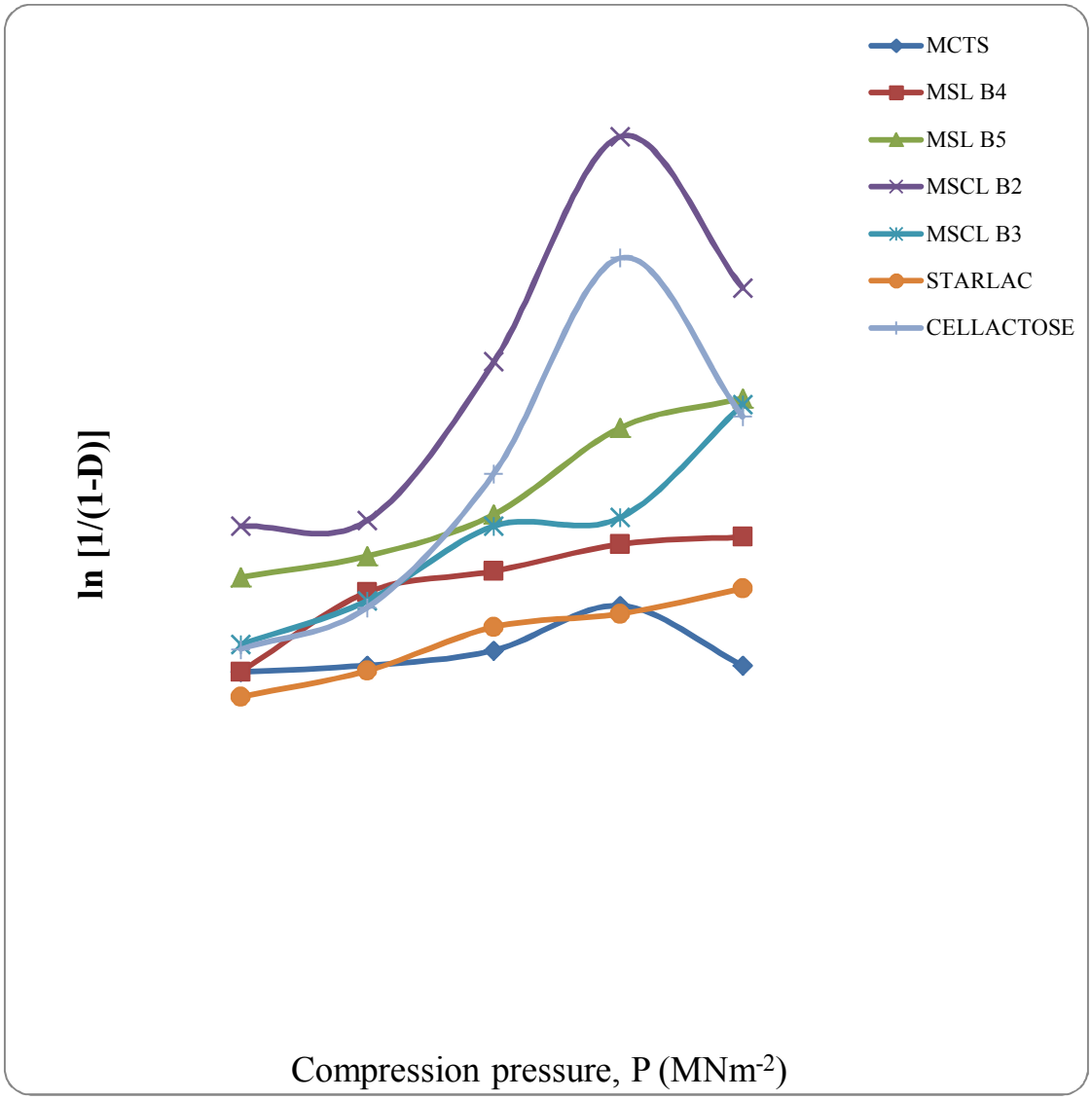


Fig. 4.25: Heckel plots: ln [1/(1-D)] vs Compression pressure P (MNm^{-2}) for MCTS, MSL, MSCL, Starlac® and Cellactose® placebo

Table 4.12: Parameters obtained from Heckel plots for MCTS, MSL, MSCL, Starlac® and Cellactose®.

Material	K	P_Y (MNm^{-2})	A	e^{-A}	D_o	D_A	D_B
MCTS	0.0070	143.0	1.70	0.183	0.337	0.817	0.480
MSL (B4)	0.0052	192.3	2.25	0.105	0.453	0.895	0.442
MSL (B5)	0.0147	68.0	2.15	0.116	0.425	0.884	0.459
MSCL (B2)	0.0480	22.3	1.00	0.368	0.470	0.632	0.162

MSCL (B3)	0.0200	50.0	1.80	0.165	0.318	0.835	0.517
Starlac	0.0070	143.0	1.70	0.183	0.413	0.817	0.404
Cellactose	0.0410	24.2	0.60	0.545	0.298	0.455	0.157

Note: K = slope, P_Y = (1/K)= yield pressure, P_Y = (1/K)= yield pressure, D_o = initial rearrangement phase of densification due to die filling, D_A = total degree of densification at zero and low pressure, D_B = extent of particle or granule fragmentation

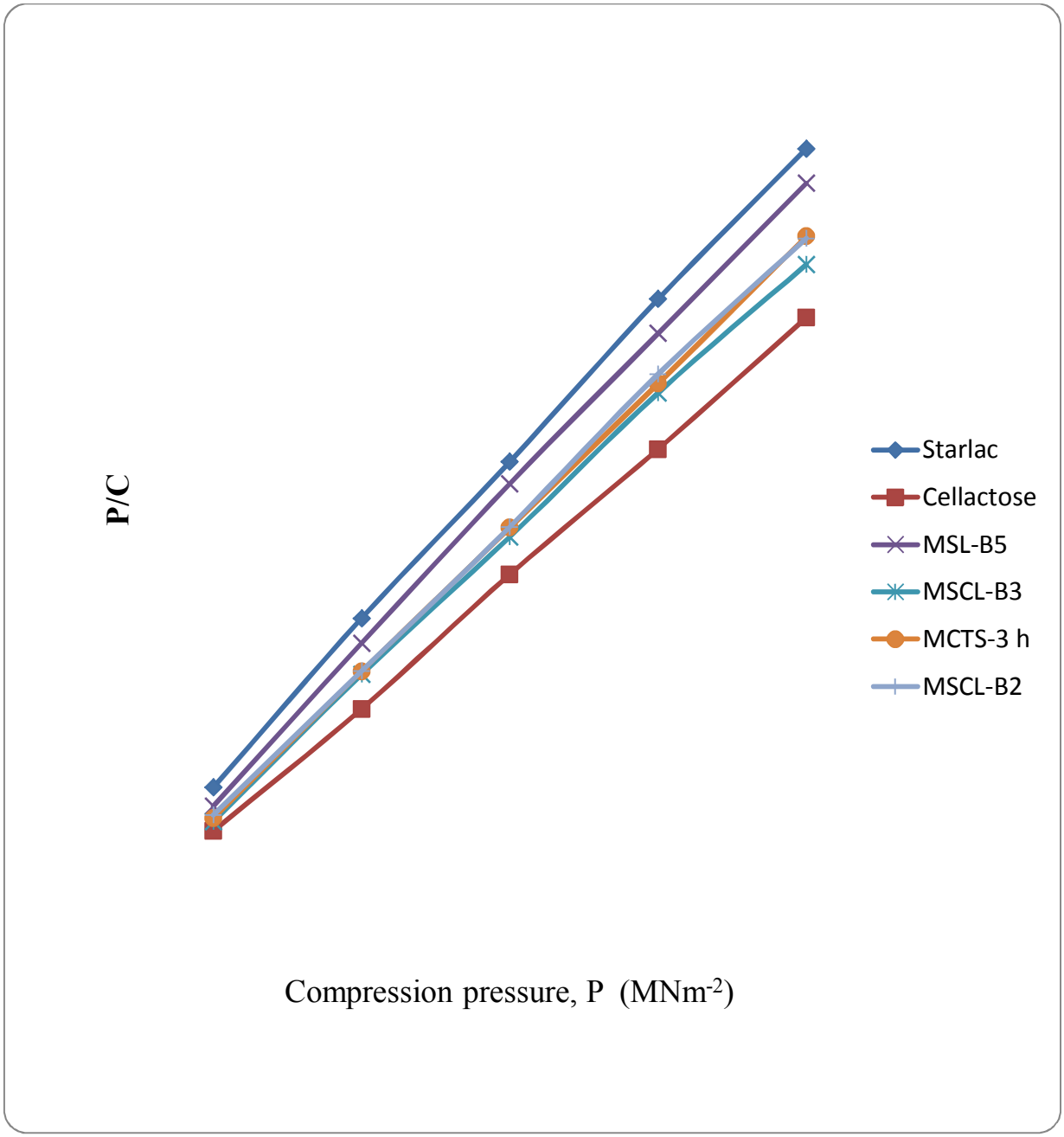


Fig.4.26: Kawakita plots of compacts P/C vs compression pressure P (MNm^{-2}) of MSL, MSCL, Starlac® and Cellactose® placebo tablets

Table 4.13: Parameters obtained from Kawakita plot analysis

Material	a	1/a	D_i (1 – a)	1/b	P_K (MNm^{-2})
Starlac®	0.526	1.90	0.474	19.1	19.1
Cellactose®	0.714	1.40	0.286	17.0	17.0
MSL (B_5) (50:50)	0.581	1.72	0.419	16.7	16.7
MSCL (B_2) (40:40:20)	0.610	1.64	0.390	16.3	16.3
MSCL (B_3) (35:35:30)	0.680	1.47	0.320	17.0	17.0
(MCTS-3h)	0.680	1.47	0.320	17.7	17.7

Note: a = minimum porosity of the bed prior to compression, 1/a =initial relative density of the material, (1 – a) = packed initial relative density of tablets formed with little pressure, 1/b = P_k, compression pressure required to reduce the powder bed by 50 %

4.14 MSL and MSCL placebo tablets

Figure 4.27 shows the photograph of compact of microstructured MSL- B_5 (MCTS 60 %: LMH 40 %) compressed at compression load of 7.5 KN, while Figure 4.27 shows the photograph of compacted microstructured MSCL-B_2 (MCTS 40 %: LMH 40 %: MCC 20%).



Fig. 4.27: MSL placebo tablets,(MSL – B_5)



Fig. 4.28: MSCL placebo tablets, (MSCL-B_2).

4.15 Results of lubricant sensitivity

Table 4.14 shows the LSR for MSL and MSCL. The LSR for MSL increased from 35 % at 5 min to 42 % at 30 min of mixing with 1 % of lubricant. For MSCL, the LSR was 24 % at 5 min and increased to 34 % at 30 min of mixing.

4.16 Results of brittle fracture index (BFI) for MSL and MSCL

Both MSL and MSCL possessed BFI values of 0.1 and 0.08 respectively (Theoretical value range is 0 – 1). BFI has been used as a measure of plastoelasticity of pharmaceutical

powders. A low BFI value indicates the ability of the material to relieve localized stresses while a value approaching unit indicates a tendency of the material to laminate or cap.

Table 4.14: Lubricant sensitivity ratio of MSL and MSCL

	Compact Tensile strength (MNm^{-2})		LSR	
Sample	**MSL**	**MSCL**	**MSL**	**MSCL**
No magnesium stearate (H_o)	1.73±0.23	1.37±0.12	—	—
Magnesium stearate 1 % 5min. mixing (H)	1.12±0.04	1.04±0.02	35.3 ±0.1%	24.1±0.1 %
Magnesium stearate 1 %, 30 min, mixing (H')	1.00±0.01	0.90±0.01	42.2±0.02%	34.3±0.2 %

Note: LSR, Ho, and H represent: lubricant sensitivity ratio, tensile strength without lubricant, tensile strength with lubricant ($LSR = (H_o - H) / H_o \times 100\ \%$).

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Table 4.15: BFI values for MSL and MSCL

	Tablets without hole			Tablets with hole		
Material	Compression force (KN)	Crushing strength (N)	Radial tensile strength (x10)N/M^2	Crushing strength (N)	Radial tensile strength (x10)N/M^2	Brittle fracture index (BFI)
MSL	5.0	136 .0±5.0	19.1	125.0±2.0	17.6	0.09
	7.5	165.0 ±5.0	23.3	150.0 ±3.0	21.2	0.10
MSCL	5.0	95.0 ±1.0	13.9	85.0 ±2.0	12.9	0.08
	7.5	98.0 ±1.0	14.8	90.0 ±1.0	13.7	0.08

4.17 Results of formulation studies

4.17.1 Dilution potential determination for MCTS

The result of determination of dilution potential is presented in Figure 4.29 and Table 4.16. The crushing strength decreased with increase in amount of API incorporated in MCTS for both PCM and AA tablets. It can be seen that the declining trend of the dilution potential for MCTS-AA was gradual and regular. Tablets containing 10 to 40 % AA showed acceptable tablet quality based on crushing strength and friability. MSL-PCM featured irregular and declining trend, however, tablets containing 10 to 25 % were acceptable based on crushing strength and friability results (Figure 4.29).

4.17.2 Dilution potential determination for MSL

The result of determination of dilution potential is presented in Figure 4.30 and Table 4.16. The crushing strength decreased with increase in amount of API incorporated in MSL for both PCM and AA tablets. It can be seen that the declining trend of the dilution potential for MSL-PCM was also gradual and regular. Tablets containing 10 to 45 % PCM showed acceptable tablet quality based on crushing strength and friability. MSL-AA featured irregular declining trend, however, tablets containing 10 to 25 % were acceptable based on crushing strength and friability result (Figure 4.30).

4.17.3 Dilution potential determination for MSCL

The result of determination of dilution potential is presented in Figure 4.31 and Table 4.16. The crushing strength decreased with increase in amount of API incorporated in MSL for both PCM and AA tablets. It can be seen that the declining trend of the dilution potential for MSL-PCM was gradual and regular at the earlier stage followed by irregular portion. Tablets containing 10 to 45 % PCM showed acceptable tablet quality based on crushing strength and friability. MSL-AA featured regular declining trend, with tablets containing 10 to 50 % having acceptable properties based on crushing strength and friability result (Figure 4.31).

Figure 4.32 illustrates the photograph of tablets containing microcrystalline tapioca starch 60 % and ascorbic acid 40 % (MCTS-AA-40 %). This is the maximum capacity or dilution capacity of MCTS with AA as the model drug.

Figure 4.33 shows the photograph of tablets containing microcrystalline tapioca starch 75 % and paracetamol 25 % (MCTS-PCM-25 %). This is the maximum capacity or dilution capacity of MCTS with PCM as model drug.

Figure 4.34 is the photograph of MSL-PCM 45 % tablets (that is: 55 % MSCL: 45 % paracetamol). This is the maximum capacity of PCM that MSL could accommodate while still maintaining acceptable tablet properties.

Figure 4.35 shows the photograph of MSCL-PCM 45 % tablets (that is: 55 % MSCL: 45 % Paracetamol). This is the maximum capacity of PCM that MSCL could absorbed while still maintaining acceptable tablet properties. Figure 4.36 shows the photograph of maximum

capacity of MSCL with ascorbic acid as the model drug. The picture shows that MSCL could accommodate 50 % w/w ascorbic acid.

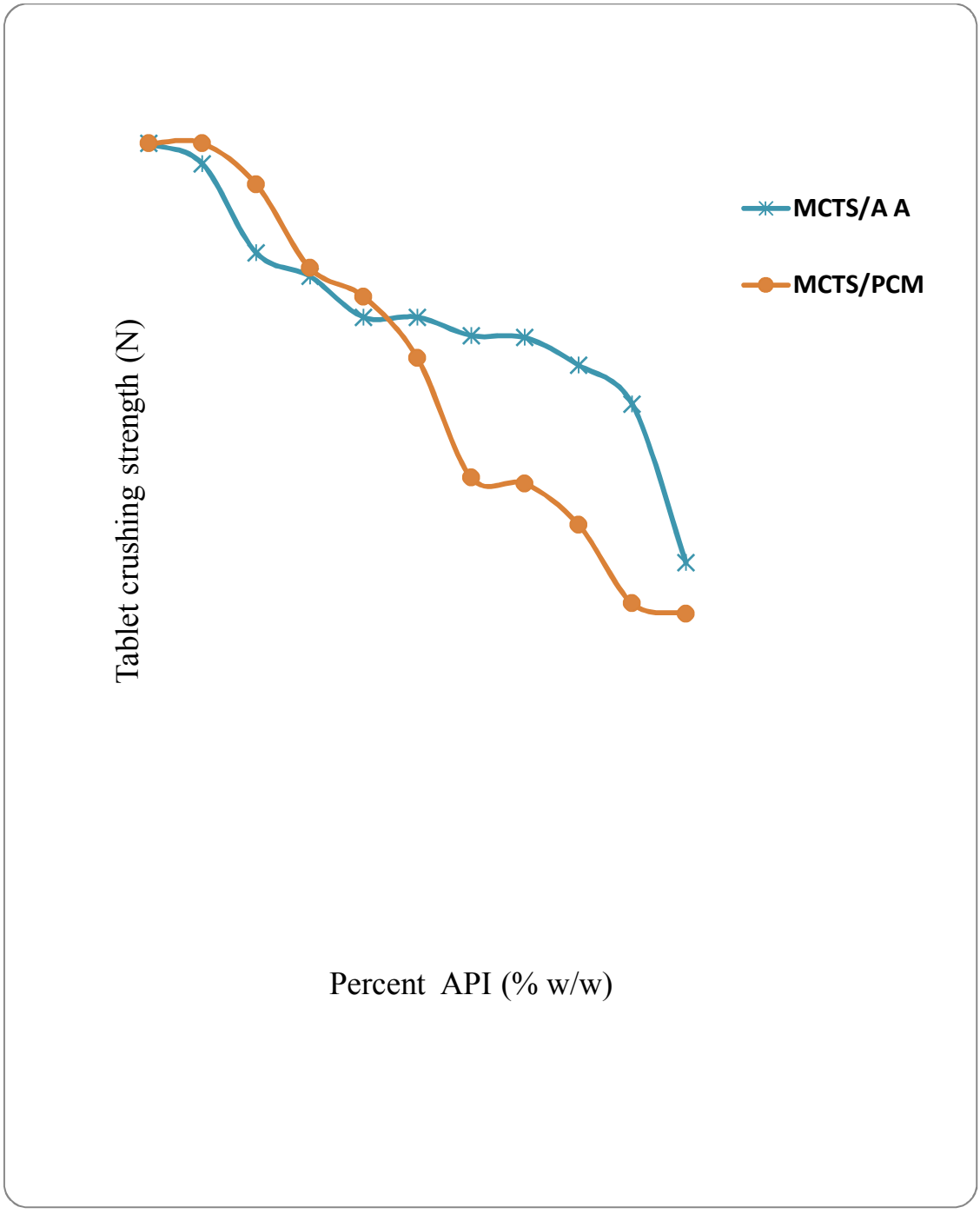


Fig.4.29: Tablet crushing strength (N) vs amount of API (% w/w) in MCTS tablet formulations.

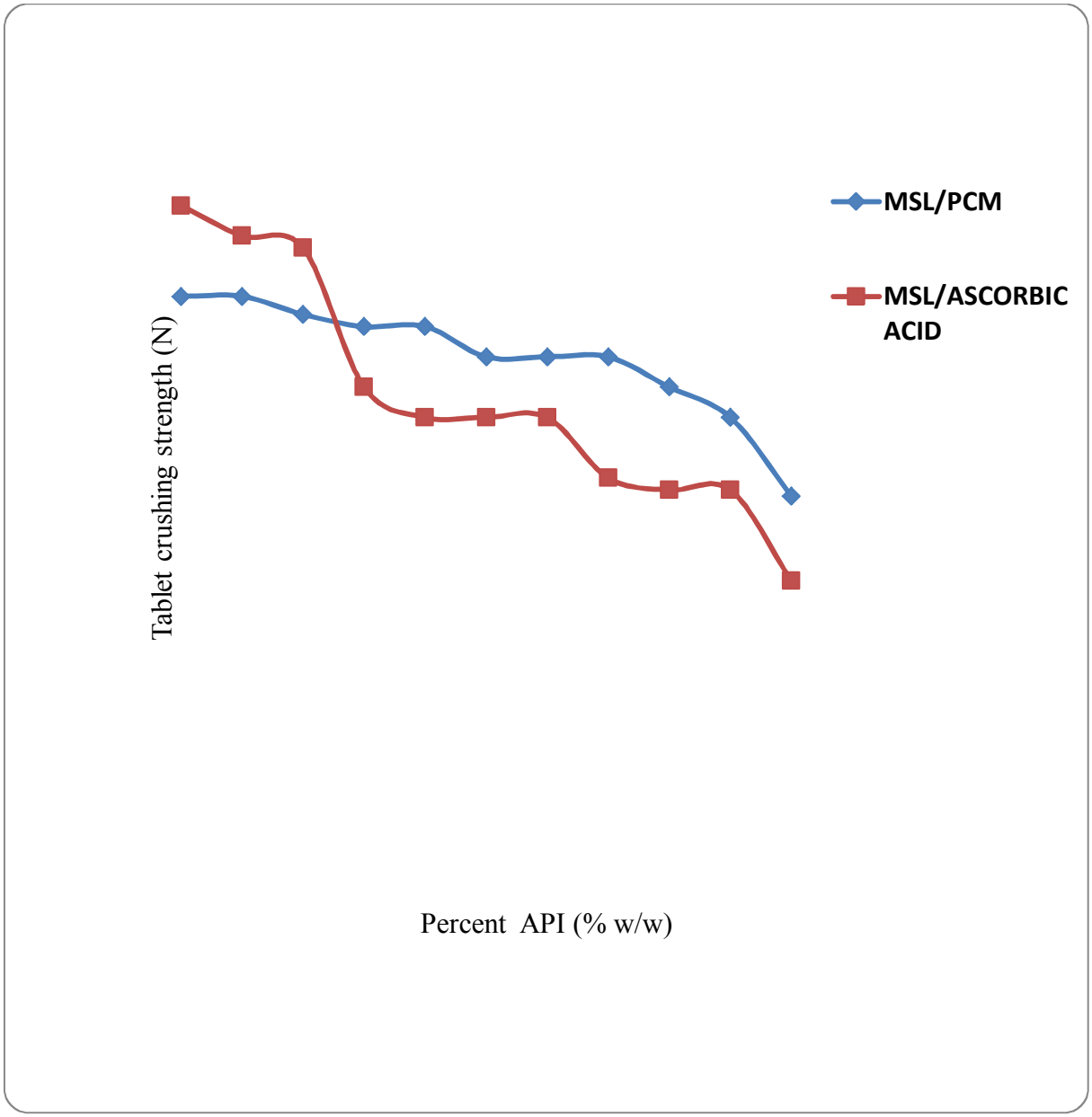


Fig. 4.30: Tablet crushing strength (N) vs amount of API (% w/w) in MSL tablet formulations.

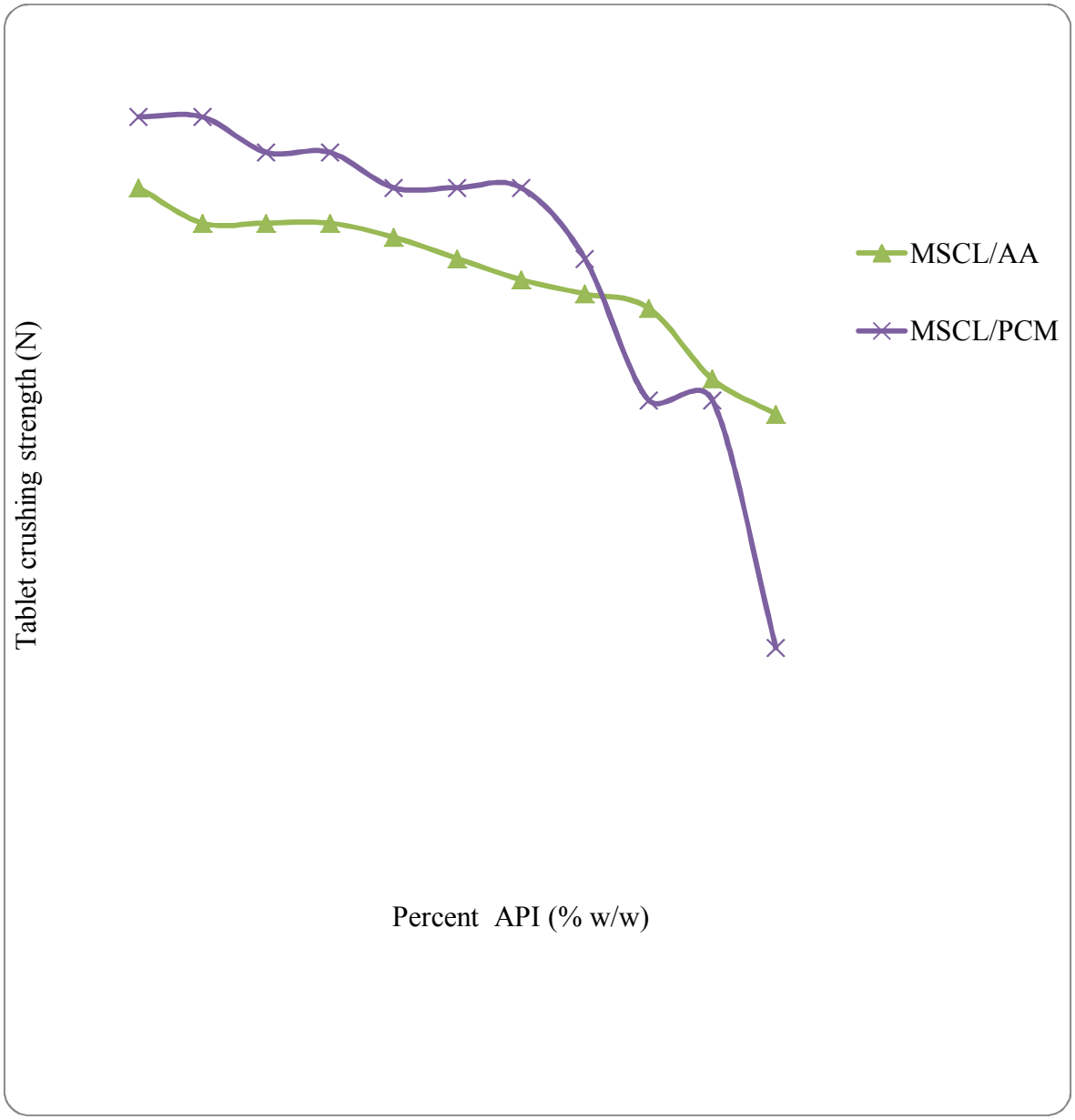


Fig. 4.31: Tablet crushing strength (N) vs amount of API (% w/w) in MSCL tablet formulations.



Fig. 4.32: Tablets containing MCTS 60 % and AA 40 %



Fig. 4.33: Tablets containing MCTS 75 % and PCM 25 %

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Fig. 4.34 : Tablets containing MSL 55 % and PCM 45 %s.



Fig. 4.35: Tablets containing MSCL 55 % and PCM 45 %.

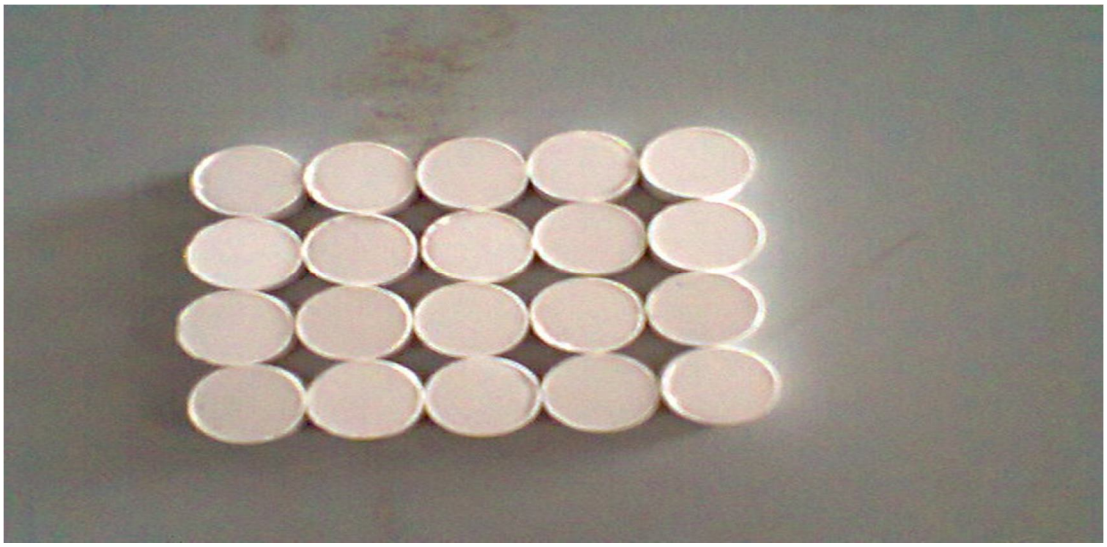


Fig. 4.36: Tablets containing MSCL 50 % and AA 50 %.

Table 4.16: Summary of dilution capacity

COPROCESSED FILLER -BINDER	MODEL DRUG	CAPACITY/POTENTIAL (%)

MSL	PCM	45
MSL	AA	30
MSCL	PCM	45
MSCL	AA	50
MCTS	PCM	20
MCTS	AA	40

4.17.4 Results of disintegration time

4.17.4.1 MCTS-API disintegration time

The result of increase in amount of API on disintegration time is illustrated in Figure 4.37

Tablet disintegration time is directly proportional to the tablet crushing strength/hardness. Disintegration time decreased with increase in amount of API. MCTS-PCM disintegrated faster than MCTS-AA.

4.17.4.2 MSL-API disintegration time

Figure 4.38 shows the plot of disintegration time versus percent (%) of API MSL was able to accommodate. It can be seen that tablet disintegration decreased with increase in amount of API present in both MSL-PCM and MSL-AA. Furthermore, MSL-AA exhibited faster disintegration than MSL-PCM.

4.17.4.3 MSCL-API disintegration time

Figure 4.38 shows the plot of disintegration time versus percent (%) of API incorporated into MSCL. The plot showed steepy and declining disintegration time with increase in

amount of API incorporated into MSCL-PCM and MSCL-AA. MSCL-PCM was characterized by faster disintegration time compared with MSCL-AA.

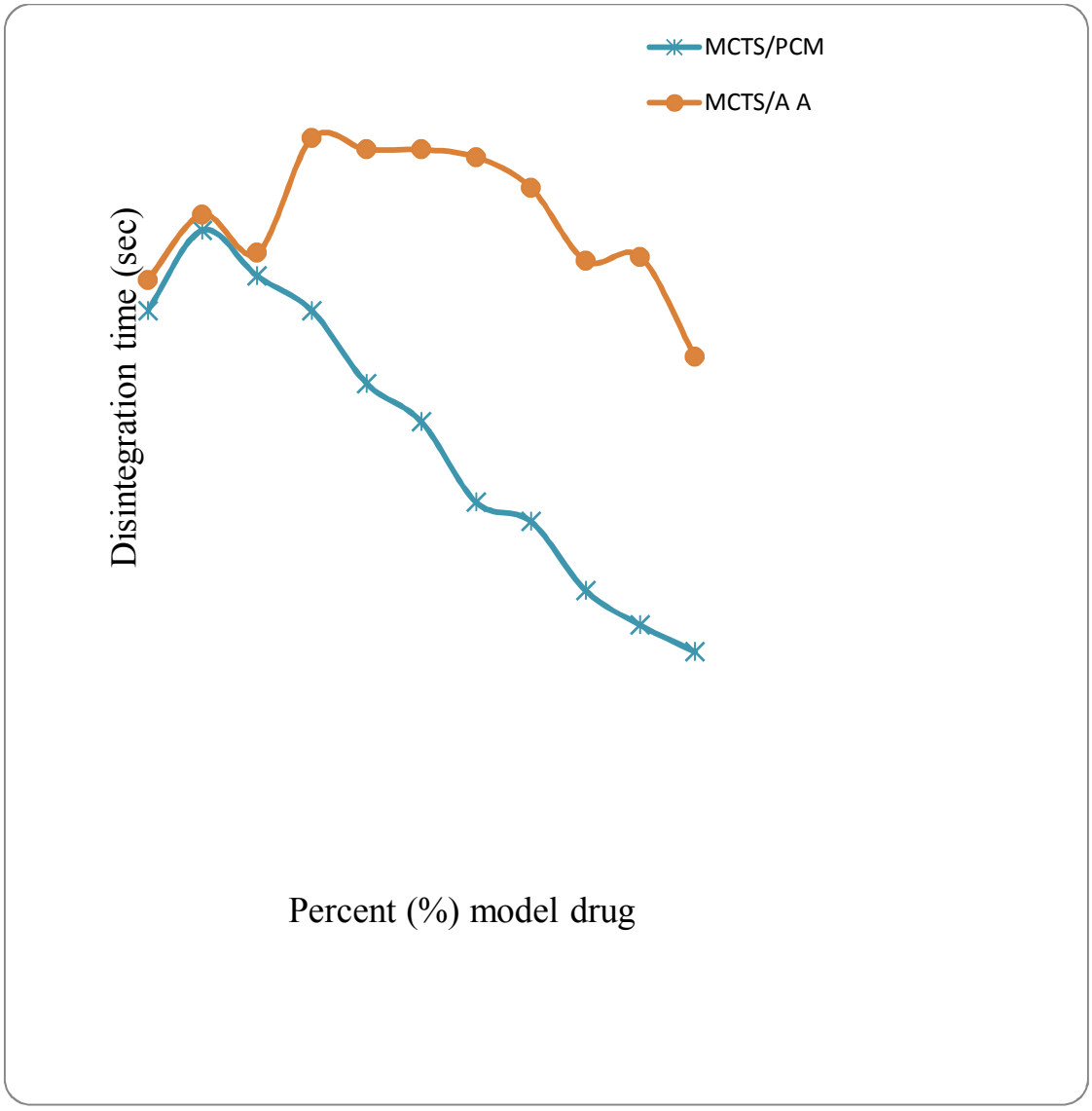


Fig. 4.37: Disintegration time (min) vs amount of API (% w/w) in MCTS tablet formulations.

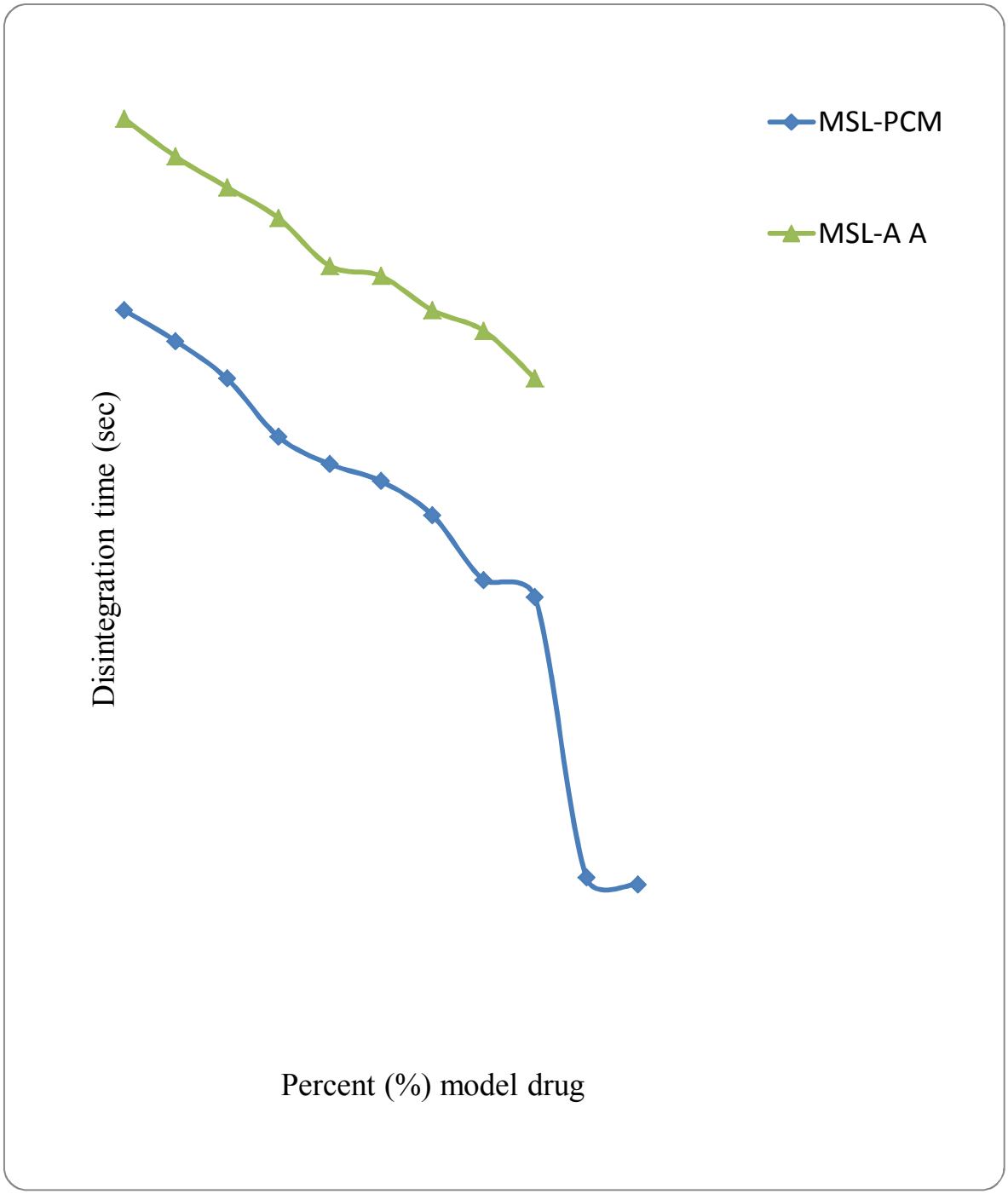


Fig. 4.38 : Disintegration time (Min) vs amount of API (% w/w) in MSL tablet

formulations.

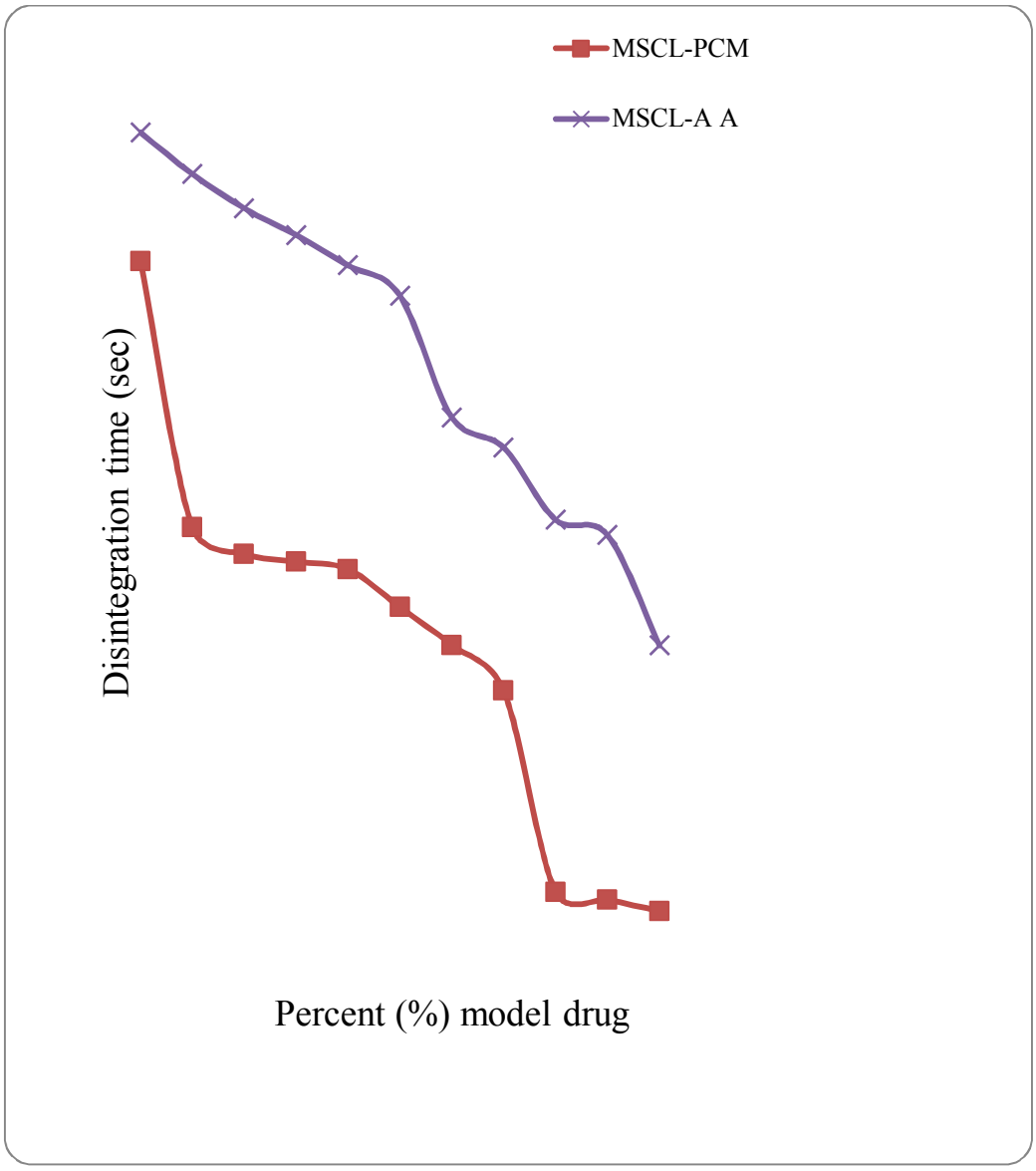


Fig. 4.39: Disintegration time (min) vs amount of API (% w/w) in MSCL tablet formulations.

Table 4.17: Physical properties of paracetamol and ascorbic acid tablets

Tablet	Model drug	Dilution capacity (%)	Tablet hardness (N) n=3	Friabilty (%) n=3	Disintegration time (sec) n=3	REMARK
MSL/PCM	PCM	40	85.0 ± 1.0	0.60± 0.10	138.0 ± 5.0	Good
		45	80.0 ± 0.5	0.70± 0.05	54.0 ± 2.0	Good

MSL/AA	AA	30	80.0 ± 0.5	0.60± 0.02	222.0 ± 6.0	Good
		35	80.0 ± 1.0	1.20 ± 0.11	216.0 ± 4.0	Chipped
MSCL/PCM	PCM	40	70.0 ± 0.2	0.50± 0.01	24.0 ± 2.0	Good
		45	70.0 ± 0.5	0.60 ± 0.1	24.0 ± 2.0	Good
MSCL/AA	AA	45	73.0 ± 1.0	0.40± 0.02	120.0 ± 4.0	Good
		50	68.0 ± 0.5	0.50 ± 0.02	90.0 ± 2.0	Good
MCTS/PCM	PCM	20	59.0 ± 1.0	0.80± 0.10	84.0 ± 2.0	Good
		25	46.7 ± 0.5	1.60 ± 0.5	60.0 ± 3.0	Chipped
MCTS/AA	AA	35	61.5 ± 0.5	0.80± 0.05	144.0 ± 4.0	Good
		40	58.3 ± 0.3	1.00 ± 0.05	126.0 ± 6.0	Good

4.17.5 Results of drug dissolution

The in-vitro drug release per unit time is displayed in Figure 4.40. The $T_{90\%}$ obtained for MCTS-AA (40 %), MSL-PCM (45 %), MSCL-PCM (45 %), MSCL-PCM (50 %), Cellactose®-PCM (45 %), and Cellactose®-PCM (50 %) were in the following decreasing order: 14 =14 > 13 > 12 > 12.5 > 12 min., respectively (see Table 4.18).The dissolution of Starlac®-PCM (45 %) could not be determined due to its failure to pass the friability test.

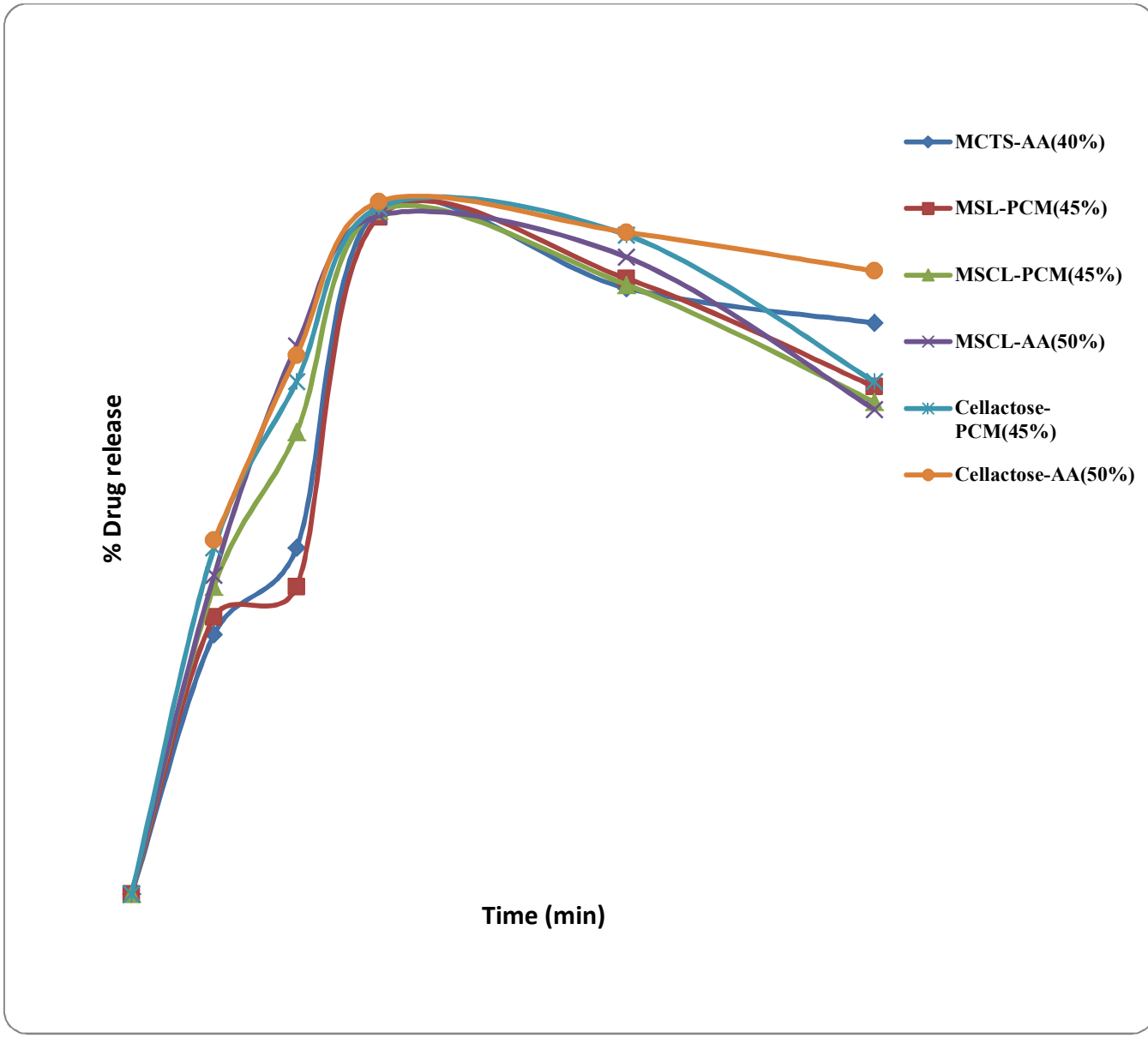


Fig.4.40: Drug release (%) vs time (min). Absorbance: PCM-272 nm, AA 265 nm

Table 4.18: Summary of formulation studies on MCTS, MSL, and MSCL in PCM and AA tablets

	MCTS – AA (60:40)	**MSL – PCM (55:45)**	**MSCL – PCM (55:45)**	**MSCL – AA (50:50)**	**Cellactose® - PCM (55:45)**	**Cellactose® - AA (50:50)**	**Starlac® - PCM (55:45)**
Tablet weight (mg±SD) [a]	502 ± 5	500 ± 1	501 ± 2	502 ± 5	500 ± 0.5	502 ± 1	503 ± 5
Amount of API (mg)	200	225	225	250	225	250	225
Crushing strength (N)[b]	58.0 ± 0.3	80.0 ± 0.5	70.0 ± 0.5	68.0 ± 0.0	85.0 ± 0.1	75.0 ±0.3	50.0 ± 0.1
Friability (%)	1.0	0.7	0.6	0.5	1.28	0.21	100
Disintegration time (min.) [b]	2.05 ± 0.02	0.90 ± 0.02	0.38 ± 0.03	1.50 ± 0.03	0.72 ± 0.05	0.57 ± 0.03	0.44 ± 0.20

Dissolution time (min)[b] $T_{90\%}$	14.0 ±0.2	14.0 ± 0.2	13.0 ± 0.5	12.0 ± 0.2	12.0 ± 0.5	12.0 ± 0.2	ND
Content uniformity (%)[a]	99.0 ± 2.0	97.8 ± 2.1	98.7 ±1.1	98.0 ± 1.5.	100.0 ±2.0	99.2 ± 0.5	ND

[a] *Each value is an average of ten determinations ± SD*

[b] *Each value is an average of three determinations ± SD.*

ND : Signifies Not Determined

100 % means, failed.

4.17.5.1 Results of dissolution rate constant (k_D) determination

The results of the dissolution rate constant (k_D at t=10 min.) obtained were presented in the following order:

MSCL-AA (11.0×10^{-3})> Cellactose-AA (10.3×10^{-3})> MCTS –AA (5.4×10^{-3})

Cellactose -PCM (9.3×10^{-3}) > MSCL- PCM (7.5×10^{-3}) > MSL-PCM (4.5×10^{-3})

Table 4.19: Dissolution rate constant (k_D) obtained from Kitazawa analysis (equation 4, page 18)

Dissolution rate constant	**Samples**					
	MCTS-AA	**MSL-PCM**	**MSCL-PCM**	**MSCL-AA**	**Cellactos-PCM**	**Cellactose-AA**
k_D (mg min^{-1})	5.4×10^{-3}	4.5×10^{-3}	7.5×10^{-3}	11.0×10^{-3}	9.3×10^{-3}	10.3×10^{-3}

4.18 Statistical results

MSL-PCM 6 month interval test (95% confidence interval)

The tests was conducted to compare whether the mean of the differences in tablet crushing strengths vary with age after 6 month interval?

Mean difference = 0.7000 (Mean of paired differences). The 95 % confidence interval of the difference: -0.5639 to 1.964. The P value is 0.0667. The data passed the normality test with $P > 0.05$.

MSCL-PCM 6 month interval test (95% confidence interval)

Mean difference = 0.4000 (Mean of paired differences). The 95 % confidence interval of the difference: -0.4396 to 1.240. The P value is >0.10. The data passed the normality test with $P > 0.05$.

MSCL-AA 6 month interval test Oct 2011- April 2012

Mean difference = -0.2000 (Mean of paired differences). The 95 % confidence interval of the difference: -0.7642 to 0.3642. The P value is 0.0914. The data passed the normality test with $P > 0.05$.

MSL-PCM and Cellactose®-PCM (95 % confidence interval).

Mean difference = -4.700 (Mean of paired differences). The 95 % confidence interval of the difference: -5.529 to -3.871. The P value is > 0.10. The data passed the normality test with P>0.05.

MSCL-AA and Cellactose®-AA

Mean difference = -6.500 (Mean of paired differences). The 95 % confidence interval of the difference: -7.408 to -5.592. The P value is 0.0686. The data passed the normality test with P > 0.05.

CHAPTER FIVE

DISCUSSIONS

5.1 Native tapioca starch

5.1.1 Physicochemical properties.

NTS was successfully extracted and purified. The percent yield was 31.9 %, this is in agreement with the 32.0 % reported by Jaiyeoba and Opakunle (1988). It was odourless, white, tasteless and practically insoluble in water and appeared mostly round and sub spherical microscopically. Other distinguishing features such as striations and hilum were visible at x 10 and x 40 magnification (Figures 4.2 and 4.3). It formed blue colour with iodine solution confirming the starch granules. The result of average granule size from Figure 4.1 was 10.0 $\pm$0.2 µm, and average swelling capacity obtained was 15.5 % (see Tables 4.1 and 4.3).

5.1.2 Granular properties

The flow rate, angle of repose, compressibility index and Hausner ratio were as follow: 2.0 g, 43.4^{o}, 50 %, and 1.5 respectively (see Table 4.5). These values are indications of poor flow and poor compressibility property due to high elastic force inherent with starch granules.

5.1.3 Tablet properties

NTS granules, when compacted at 6 KN to gave highest crushing strength of 30 N (see Table 4.2), and could not stand the abrasion test (i.e., it crumbled). Elastic deformation was predominant during compaction and as such, the granules could not hold together. Therefore, for starch to be used as DC excipients it must be modified singly or coprocessed with other existing excipient to improve its functionality.

5.2 Annealed tapioca starch

5.2.1 Granular properties

Table 4.1 shows some physicochemical characteristics of the native and annealed tapioca starch. The result shows a swelling capacity of 11.1 % for ATs, which was lower than the swelling of NTS. This could be attributed to the reordering of the starch granular structure at the molecular level (Adewale *et al.,* 2009). Nakazawa and Wang (2004) reported a reduction in granular swelling in cassava starch and potato starch after annealing. Nakazawa and Wang, (2004) and Qi *et al.,*(2005) reported a reduction in granular swelling of corn starches after annealing. The decrease in granular swelling has been attributed to the interplay of the following factors:

(1) increased crystalline perfection and decreased hydration (Tester *et al.,* 1998; Waduge *et a!.,* 2006),

(2) AM-AM and/or AMP-AMP interaction (Jacobs *et al.,* 1998b), and

(3) increased intragranular binding forces and reinforcement of the granule (Hizukuri, 1996; Jacobs *el al.,* 1995). Swelling capacity is an index of disintegration. Such reduction in swelling capacity means that the inherent disintegrant functionality may be reduced as a result of annealing.

Average granule size of ATS determined by light microscope was 11.5 $\pm$ 0.5 µm (Figure 4.1 and Table 4.3). An increase in size was observed which confirmed the earlier works by Nakazawa and Wang (2004) and Adewale *et al,* (2009).

The effects of annealing on both granule characteristics and tablet properties were investigated. Table 4.5 compared the granule properties of ATS with that of NTS and MCTS-3 h. The result illustrates an increase in flow properties as reflected by flow rates of 2 .0 g/s and 2.6 g/s for NTS and ATS respectively. The corresponding angles of repose were 43^{o} and 32^{o} respectively, while the compressibility indices were: 32.2 % and 31.2 % respectively. These are indicative of improved flow and compressibility of tapioca starch after annealing, and can be attributed to alteration in shape and increase in size of the granules after annealing at particle level but translated to bulk level (Bansal and Nachaegari, 2002).

5.2.2 Tablet properties (placebo)

The effect of annealing on tablet properties was investigated. Table 4.2 shows the result of compacts formulated from ATS at various times of annealing. The starch granules after three hours (3 h) of annealing gave acceptable tablet properties in terms of crushing strength and friability. Starch annealed for 3 h and compressed at 6 metric ton had crushing

strength of 90 N, friability of 2.5 % and disintegration time of 25 sec. NTS granules, when compacted at the same pressure gave highest crushing strength of 3 N (see Table 4.3), and could not stand the abrasion test (i.e., it crumbled). Improved flow rate and compressibility of the annealed granules translated to the bulk level is responsible for the high crushing strength and improved stability to abrasion.

In Figure 4.15, (plot of compact density vs compression force), NTS showed a decline portion from pressure 2.5 to 5 KN indicating elastic resistance at low pressure followed by a slight rise in volume reduction from pressure of 7.5 to 12.5 KN and compact density stretched over the range of 1.33 to 1.31 g/cm^3. The ATS curve showed a progressive increase in compact density with pressure, which spanned from 1.21 to 1.31 g/cm^3. When external force is applied to a powder mass there is usually a reduction in volume due to closer packing of the powder particles and in most cases this is the mechanism of initial volume reduction. However as the pressure increases, further rearrangement of particles become more difficult and further compression leads to either plastic or elastic deformation. If on removal of the load, the deformation is to a large extent reversible, the deformation is said to be elastic. This was the predominant feature in NTS curve, (Figure 4.15). ATS curve (Figure 4.15) presented two portions of volume reduction, one due to void filling (initial volume reduction), and other due to plastic deformation. It can therefore be asserted that annealing impacted plasticity to NTS and thus annealing improved it compressibility. Moreover, Fig. 4.16 shows the result of the compactibility studies; it illustrates the relationship between compression pressure and radial tensile strength. The compactness of NTS is seen to span over <4 to >5 x 10^5 N/m^2, while that of ATS stretched

across <5 to >9 x 10^5 N/m^2. This result revealed approximately 100 % increase in compactness of native starch after annealing. The high compactibility may have resulted from increased bonding tendency of ATS as a result of changes in granule size, shape and surface area, which favoured more and stronger bonds. Annealing impacted good flow characteristics and compressibility to the tapioca starch.

5.2.3 Disintegration (placebo tablets)

The disintegration time is mostly influenced by tablet hardness. Table 4.2 shows the value of the disintegration time for NTS and ATS tablets as 14.0 $\pm$ 1.0 sec. and 25.0 $\pm$ 1.0 sec respectively. The extension in disintegration time agrees with the reduction in swelling capacity from 15.5 % to 11.1 %. Starch acts as a disintegrant by swelling and capillary action. Therefore, reduced swelling capacity of ATS amounted to extension of disintegration time. Also, increased in tablet hardness as a result of improvement in bonding mechanism due to annealing contributed to increased disintegration time of ATS tablet.

5.3 Microcrystalline tapioca starch

5.3.1 Granular properties

One of the objectives of this research was to modify the starch granules physically by annealing and at molecular level by enzyme hydrolysis.

After annealing and enzyme hydrolysis, the average MCTS granule size was found to be 13.0 $\pm$ 0.5 μm (Figure 4.1 and Table 4.2). This showed a further increase in granule size over NTS and ATS granules. This translated into improved flow property of MCTS over the NTS since starch utilization as filler-binder is hindered by its poor flow due to its smaller granule size. The photomicrograph of MCTS granules (Figure 4.4) revealed all the distinguishing features of native starch granules. The striations became more visible in the former than in the latter. This must be due to over stretched granular wall as a result of increase in granular size following annealing and subsequent enzyme hydrolysis.

Table 4.5 compared the granule properties of ATS with that of NTS and MCTS-3 h. The result illustrated an increase in flow properties as reflected by flow rate of 2 .0 g/s, 2.6 g/s and 2.5 g/s for NTS, ATS and MCTS-3 h respectively. Increased granule size at particle level has been translated to improved flow property at bulk level. The corresponding angles of repose were 43^{o}, 32^{o} and 31^{o} respectively. The compressibility as reflected in the table for NTS, ATS-3 h and MCTS-3 h were: 32.2 %, 31.2 % and 27.5 % respectively. All these results indicate increase in both flow and compressibility of tapioca starch after annealing and enzyme hydrolysis. These results are in agreement with earlier works by Wang *et al*. (1997) and Tukomane *et al*. (2007). Wang *et al*. (1997) explained that, annealing breaks some hydrogen bonds unwinding the interwoven chain of polysaccharides and weakens the granular membrane and aid penetration of the enzyme, while the enzyme drill holes through the membrane to act on the disorganized polysaccharide chains. Tukomane *et al.* (2007) used scanning electron micrographs to study the morphological changes and the mode of enzyme attack during enzyme hydrolysis. They found that, α – amylase

preferentially attacked the interior of the starch granule, leaving a deep round hole on the starch granule surface.

Particle level comprises individual particle properties such as shape, size, surface area and porosity. The bulk level is composed of an ensemble of particles and properties such as flowability, compressibility and dilution potential which are critical factors in the performance of excipients. The interdependency among the levels is the bases of modification at particle level (Reimerdies and Aufmuth 1992; Bansal and Nachaegari, 2002). The findings of Wang *et al*. (1997) and Tukomane *et al*. (2007) mentioned above complement overall improved flow and compressibility of MCTS.

5.3.2 Tablet properties (placebo)

Table 4.6 shows tablet properties of MCTS at various times of hydrolysis. It can be seen that the tablets of MCTS-3 h gave the best compacts in terms of tensile strength, friability and disintegration time.

MCTS was subjected to compressibility and compactibility studies. Fig.4.15 compared the compressibility of MCTS with ATS and NTS. The MCTS curve shows a progressive increase in compact density with pressure, spanning from 1.31 to 1.35 g/cm^3. This showed clear improvement over compressibility of NTS and could be attributed to reduced cohesiveness and plasticity of starch granules. Since compressibility describes the process of densification, higher compact density observed in MCTS tablets is associated with factors such as changes in fragmentations and deformation. Moreover, Fig. 4.16 presents the

result of the compactibility studies. It illustrated the relationship between compression pressure and radial tensile strength. The compactness of MCTS is seen to span over <14 to >15 x 10^5 N/m^2, while that of ATS stretched across <5 to >9 x 10^5 N/m^2, and NTS, <4 to >5 x 10^5 N/m^2. This result revealed higher bonding effect following annealing and enzyme hydrolysis of NTS. Earlier, Tokumane *et al*. (2007) claimed to have obtained increased plasticity following annealing and enzyme hydrolysis of starch granules, which was attributed to alteration in amylase/amylopectin ratio, thereby increasing deformation propensity of MCTS. Based on these results, MCTS-3 h was selected for further works in the next stages.

5.3.3 Disintegration (DT) of placebo tablets

Starch granules possess inherent disintegration property. The disintegration time is mostly influenced by tablet hardness. Table 4.6 shows that the disintegration time of MCTS-3 h tablets was 82 sec. This DT is about six times the value for NTS tablets (which was 14.0 $\pm$ 1.0 sec.) and four times the value for ATS tablets (which was 25.0 $\pm$ 1.0 sec.), (Table 4.3). The U.S.P XXIII standard specified maximum disintegration time for conventional tablets to be 15 min. MCTS-3 h with disintegration time of 75 $\pm$ 5 sec. can be regarded as a good disintegrant.

5.3.4 Densification behavior of MCTS-3 h

5.3.4.1 Plot of Heckel equation

Fig. 4.25 illustrates the plot of ln 1/[1 – D] vs P for MCTS, coprocessed filler-binders and marketed standard coprocessed excipients and MCC. The plot for MCTS can be divided into three-phases, namely: 29 MNm^{-2} < P < 87 MNm^{-2}, 87 MNm^{-2} < P < 116 MNm^{-2} and 116 MNm^{-2} < P < 144 MNm^{-2}, each of which basically obeyed Heckel equation. There is linearity in the first phase at low pressure which suggests that MCTS deformed mainly by plastic deformation (Odeku and Itiola, 2007). Under low pressure (p < 87 MNm^{-2}) the compaction would mainly result in the elimination of voids among the loose particles through rearrangement, fragmentation and some degree of plastic deformation, leading to rapid densification of MCTS. In the second phase (from ~87 MNm^{-2} to ~116 MNm^{-2}), however, the sliding, rearrangement and plastic deformation of MCTS particles would be responsible for the densification of MCTS compact. The third phase (from ~116 MNm^{-2} to ~144 MNm^{-2}), represented decompression stage and this is due to increased in tablet porosity.

Table 4.12 shows values of the mean yield pressure, P_y the relative densities D_o, D_A, and D_B for MCTS, microstructured filler-binders, standard coprocessed excipients and MCC. P_y is inversely related to the ability of the material to deform plastically under pressure. Low value of P_y indicates a faster onset of plastic deformation (Odeku and Itiola, 1998). The P_y obtained for MCTS-3 h, Starlac®, and Cellactose® were: 143 MNm^{-2}, 143 MNm^{-2}, and 24.2 MNm^{-2} respectively. From the values of P_y stated above, both MCTS and Starlac® had the

same P_y value indicating similar onset of plasticity, while Cellactose® with lower P_y had faster onset of plastic deformation compared with the two former filler-binders. The high yield value of MCTS-3 h reflects more resistance to pressure, less densification and low compressibility than Cellactose®, but similar behaviour with Starlac®. Shangraw *et al.* (1981) explains that, a large value of the slope (i.e., low P_y value) is an indication that the onset of plastic deformation occurs at relatively low pressure and vice versa.

Heckel's analysis has been extensively applied to pharmaceutical powders for both single and multi-component systems (Duberg and Nystrom, 1986; Itiola, 1991).

D_A, represents the total degree of densification at zero and low pressures (Paronen and Juslin, 1983; Mitreve *et al*., 1996; Roberts and Rowe, 1985). D_o, is used to describe the initial rearrangement phase of densification as a result of die filling. D_o is equal to the ratio of bulk density at zero pressure to the true density of the powder (Chowhan and Chow, 1981). The relative density, D_B, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation. From Table 4.12 the D_o values for MCTS-3 h, Starlac®, and Cellactose® were 0.337, 0.413, and 0.298 respectively. These results showed that MCTS-3 h is denser during the die filling than Cellactose® but less than Starlac®. The D_B values for MCTS-3 h, Starlac® and Cellactose® were: 0.480, 0.404 and 0.157 respectively. These results reflect the degree of fragmentation at low pressure in the following order: MCTS-3 h > Starlac® > Cellactose®. Khan and Rhodes (1975) reported some degree of fragmentation in MCC with increase in compression pressure. Doelker (1988) and Nystrom *et al.* (1993) observed that high D_B

values are caused by fragmentation while low D_B values are associated with plastic deformation.

5.3.4.2 Kawakita Plots

Fig. 4.26 shows the plot of p*/C vs p* for MCTS, microstructured filler-binders, and standard marketed excipients, Starlac® and Cellactose®. One can see that a linear relationship exists between *p/C* and *p* in the whole pressure range investigated with a correlation coefficient r^2 of 0.999, which indicates that the densification behavior of MCTS is consistent with prediction from the Kawakita equations. By best fitting of the experimental data to the equation 26 one obtains:

$$p/C = 1.47p + 26 \quad - \quad - \quad - \quad - \quad (38)$$

Hence, the value of "a" is obtained as 0.680 and "b as 0.057 (1/b = 17.7).

The D_i (= 1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and Chain, 1995; Odeku and Itiola, 1998). Table 4.13 shows the D_i values for MCTS-3 h, Starlac®, and Cellactose® as: 0.320, 0.474, and 0.286 respectively. It can be seen that at low pressure MCTS-3 h tablet were better packed than Cellactose® tablets, but less in packing relative to Starlac® tablets. This result is not far from the fact that packing of a material with applied pressure is determined by deformation propensity.

Table 4.13 shows that the values of 1/b (P_k) obtained for MCTS-3 h, Starlac® and Cellactose® as: 17.7, 19.1, 17.0, respectively. The reciprocal of b yields a pressure term, P_k, which is the

compression pressure, required to reduce the powder bed by 50 % (Shivanand and Sprockel, 1992). The value of P_k gives an inverse measurement of plastic deformation during compaction process. The lower the value of P_k, the higher the degree of plastic deformation occurring during compression (Itiola, 1991). The pressure term P_k has been shown to provide a measure of the total amount of plastic deformation occurring during compression (Odeku and Itiola, 1998). Hence, from the results of P_k values, MCTS-3 h was more plastically deformed during compression than Starlac® less than Cellactose®.

5.3.4.3 Dilution capacity/potential

The tablets formulated with MCTS 60 % and AA 40 % (Fig. 4.20) were smooth, and free from chipping and lamination. Figure 4.21 illustrates tablets formulated with MCTS 75 % and PCM 25 %. The latter ratio gave good compact beyond which the tablets formed chipped.

Fig. 4.29 shows the relationship between tablet strength and the amount (in percentage) of API that MCTS can incorporate while still maintaining tablet properties. It can be seen that tablet strength declined with increasing amount of API until it reached a point where the tablet strength, friability and the physical structure failed to meet the official standard. Tables 4.16 and 4.17 show the summary of the results of the dilution potential. MCTS was compacted with PCM and AA in predetermined percentages as model drugs (API). One can see that MCTS was able to form acceptable compact with maximum of 20 % of the PCM (crushing strength 59 N; friability, 0.8 %; and disintegration time, 81 sec.) and with 40 % of

AA (crushing strength 58 N; friability, 1.0 %; and disintegration time, 123 sec.). Hence, 40 % of AA could regarded as acceptable dilution capacity/potential of MCTS, while 20 % obtained for PCM may be too low to be recommended.

5.3.4.4 Disintegration time of MCTS tablet containing model drug

Fig. 4.37 shows the reduction in disintegration time with increase percentage API. It can be seen that the disintegration time of MCTS – AA declined from 2.5 min. down to 1.7 min. One can see that the disintegrant property of MCTS and hydrophilicity of ascorbic acid were responsible for the rapid disintegration of the formulation.

5.3.4.5 In-vitro drug release from MCTS

Fig 4.40 depicts the plot of percentage (%) drug release versus time for MCTS-AA. $T_{90\%}$ was found to be 14 min, and 100 % drug release was achieved in 15 min. Dissolution rate constant (K_D) was calculated to be 5.4 x 10^{-3} mg min^{-1}(Table 4.18).

Disintegration is an index of drug dissolution, the lower the disintegration time the faster could be the dissolution. B.P.C (1988) stipulated maximum of 45 min. for $T_{90\%}$ drug release from a conventional tablet, 14 min. ($T_{90\%}$) obtained could be attributed to the high disintegrating effect of starch as a result of its high percentage in the formulation.

5.4 Microcrystarlac (MCTS 50 %: LMH 50 %)

5.4.1 Granular properties

The photomicrograph of MSL (Fig. 4.6) shows the evenly distributed starch granules and lactose. Fig. 4.7 and 4.8 illustrate the pictures of coprocessed products. The semi-solid mass of MSL formed made it easy for effective granulation. Fig. 4.9 shows the granules after sieving. They appeared uniform in size and shape as a result of agglomeration of the composite particles.

Table 4.7 shows the granule properties of coprocessed MSL (MCTS 50 %: LMH 50 %) together with the direct physical mixtures of the same ratio. The result illustrates an increase in flow properties of coprocessed MSL over that of the direct physical mixture as reflected by flow rates of 3.0 g/s, for the former and 0.65 g/s, for the latter. The corresponding angles of repose were 32^{o} and 42^{o} respectively. The compressibility indices as reflected in the table were: 34 % and 53 % respectively. MSL possessed improved flow property and compressibility over direct physical mixture. Improved flow of coprocessed MSL over the direct physical mixture is due effectiveness of the method of particle agglomeration involved, coupled with the use of combination of isopropanol and water, which aids uniformity of drying across granule beds allowing even distribution of the composite particles.

Sieving method of particle restructuring was employed to separate two fractions: 75-250 µ and 90-250 µm. Fig. 4.5 illustrates the granule size distribution of MSL. About 60 % of the granules were greater than 250 µm and all the granules (100 %) were greater than 90 µm.

This granule size distribution was responsible for the improved flow property over individual and the direct physical mixture of the primary excipients.

5.4.2 Tablet properties (placebo)

Fig. 4.18 shows the result of the compactibility studies. The figure illustrates the relationship between compression pressure and radial tensile strength for MSL. The curve (MSL-B_5) is similar to Heckel plot for the same material with the early part showing non-linearity as a result of fragmentation, rearrangement and elimination of voids, followed by a linear portion illustrating the consolidation behavior as a result of plastic deformation. Increasing the fraction of lactose resulted in a sigmoid shape, which is a reflection of an increased densification.

The Cellactose® curve was higher than MSL-B_5, in turn higher than Starlac this is a reflection of diminished densification. The MSL-B_5 curve shows a progressive increase in compact density with pressure, and appears lower than the curves for Cellactose®. This was due to low porosity of the former compare to the latter. As the porosity approaches zero, plastic deformation may become the predominant mechanisms for all powder material (Heresy and Rees, 1971: York and Pilpel, 1972). Comparing MSL-B_5 with Starlac®, higher densification observed for the former could be due to its higher plasticity (presence of MCTS) than the latter, which stored high elastic force due to the presence of native tapioca.

5.4.3 Friability of MSL placebo tablets

Fig. 4.24 shows the effect of increasing compression pressure on the friability of MSL compacts. Friability declined with increase in compression pressure It can be seen that as the compression pressure increased from 2.5 N to 12.5 KN, friability of MSL tablets also decreased from 1.0 % to 0.0 %. Lower friability value is an index of a stronger compact characterized by high crushing strength arising from consolidation of such material with low porosity, high plasticity and brittleness, which are characteristics of MSL.

5.4.4 Disintegration time (DT) of MSL placebo tablets

The presence of starch granules in MSL are expected to impact disintegration property. The disintegration time is mostly influenced by tablet hardness. Fig. 4.22 shows the effect of increasing compression force on disintegration time for MSL, Starlac®, and Cellactose® tablets. Disintegration time increased with increase in tablet hardness, which was proportional to the applied pressure. The DT for all the compacts of MSL formed between compression force of 2.5 N and 12.5 N ranged from < 2 min to 4 min. This range is acceptable compared with U.S.P XXIII specified standard for conventional tablet of 15 min. For most tablets formulated by wet granulation method having internal disintegrant, the disintegration time is usually longer than 4 min. MSL with disintegration time of 4 min can therefore be regarded as a good disintegrant. The percentage of MCTS in MSL is responsible for the rapid disintegration.

5.4.5 Densification behavior of MSL placebo tablets

5.4.5.1 Plot of Heckel equation

Fig. 4.25 shows the plot of ln 1/[1 – D] *vs p* for MSL, Starlac®, and Cellactose. The plot for MSL can be divided into three-phases, namely: 29 MNm^{-2} < *p* < 87 MNm^{-2}, 87 MNm^{-2} < *p* < 116 MNm^{-2} and 116 MNm^{-2} < *p* < 144 MNm^{-2}, each of which basically obeyed Heckel equation. There was linearity in the first phase (early stage) at low pressure which suggests that MSL deformed mainly by plastic deformation (Odeku and Itiola, 2007). Under low pressure (*p* < 87 MNm^{-2}) the compaction would mainly result in the elimination of voids among the loose particles through rearrangement, fragmentation and some degree of plastic deformation, leading to rapid densification of MSL. In the second phase (~87 MNm^{-2} to ~116 MNm^{-2}), however, plastic deformation of MSL particles would be responsible for the densification of MSL compact. In the third phase (~116 MNm^{-2} to ~144 MNm^{-2}), following decompression, an expansion in tablet height is represented by increased tablet porosity.

Table 4.12 shows values of the mean yield pressure, P_y, the relative densities D_o, D_A, and D_B for MSL, Starlac®, and Cellactose®. P_y is inversely related to the ability of the material to deform plastically under pressure. Low value of P_y indicates a faster onset of plastic deformation (Odeku and Itiola, 1998). The P_y obtained for MSL, Starlac®, Cellactose® were 68 MNm^{-2}, 143 MNm^{-2} and 24.2 MNm^{-2} respectively. From the values of P_y, MSL had faster onset of plastic deformation than Starlac®, but slower than Cellactose®. The yield value of MSL reflects better densification at low pressure than Starlac® but less than Cellactose®. Shangraw *et al.* (1981) explains that, a large value of slope (i.e., low P_y value) is an

indication that the onset of plastic deformation occurs at relatively low pressure and vice versa. Heckel's analysis has been extensively applied to pharmaceutical powders for both single and multi-component systems (Duberg and Nystrom, 1986; Itiola, 1991). D_A, represents the total degree of densification at zero and low pressures (Paronen and Juslin, 1983; Mitreveji *et al*., 1996), (Roberts and Rowe, 1985). D_o, is used to describe the initial rearrangement phase of densification as a result of die filling. D_o is equal to the ratio of bulk density at zero pressure to the true density of the powder (Chowhan and Chow, 1981). The relative density D_B, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation. From Table 4.12, the D_o values for MSL, Starlac®, and Cellactose® were: 0.425, 0.413 and 0.298 respectively. These results showed that MSL is denser during the die filling than Starlac®, and Cellactose®. The D_B values for MSL, Starlac®, and Cellactose® were: 0.459, 0.404, and 0.157 respectively. These results reflect the degree of fragmentation at low pressure in the following order: MSL > Starlac® > Cellactose®. Khan and Rhodes (1975) reported some degree of fragmentation in MCC with increase in compression pressure. Doelker (1988) and Nystrom *et al.,* 1993 observed that high D_B values are caused by fragmentation while low D_B values are associated with plastic deformation.

5.4.5.2 Plot of Kawakita equation

Fig. 4.26 shows the plot of *p/C vs p* for MSL, Starlac®, and Cellactose®. A linear relationship exists between *p/C* and *p* in the whole pressure range investigated with a correlation coefficient $r^2 = 0.986$, which indicates that the densification behavior of MSL is consistent with prediction from the Kawakita equations. By best fitting of the experimental data to the equation 26 one obtains:

$$p/C = 1.72\,p + 28.13 \quad - \quad - \quad - \quad - \quad (39)$$

Hence, the value of "a" is obtained as 0.581 and "b as 0.0609 (1/b = 16.7).

The D_i (= 1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and Chain, 1995; Odeku). Table 4.13 shows the D_i values for MSL, Starlac® and Cellactose® as: 0.419, 0.474, and 0.286, respectively. It can be seen that at low pressure MSL tablets were better packed than Cellactose® tablets, but less in packing relative to Starlac® tablets. This result is not far from the fact that packing of a material with applied pressure is determined by deformation propensity.

Table 4.13 shows the values of 1/b (P_k) obtained for MSL, Starlac® and Cellactose® as: 16.4, 19.1, and 17.0 respectively. The reciprocal of b yields a pressure term, P_k, which is the compression pressure required to reduce the powder bed by 50 % (Shivanand and Sprockel, 1992). The value of P_k gives an inverse measurement of plastic deformation during compaction process. The lower the value of P_k, the higher the degree of plastic deformation occurring during compression (Itiola, 1991). The pressure term P_k has been shown to provide a measure of the total amount of plastic deformation occurring during

compression (Odeku and Itiola, 1998). Hence, from the results of P_k values, MSL was more plastically deformed during compression than Starlac® but less than Cellactose®.

5.4.5.3 Dilution capacity/potential

Fig.4.30 shows the relationship between the amounts in percent (%) of API compressed with MSL and the tablet strength. It can be seen that tablet strength declined with increasing amount of API until it reached a point where the tablet strength, friability and the physical structure failed to meet the official standard. Tables 4.16 and 4.17 show the summary of the result of the dilution potential and the physical properties of PCM and AA. MSL was able to form acceptable compact with maximum of 45 % of the former (crushing strength, 80 N; friability, 0.7 %; and disintegration time, 54 sec.), and with 30 % of the latter (crushing strength, 80 N; friability, 0.6 %; and disintegration time, 214 sec.). These results could be attributed to increased binding property of the hydrolyzed starch and lactose in the same proportion (synergistic effect of plastic and brittle materials). The ratio of the component of MSL was optimized. Hence, MSL – PCM- 45 % compact is more acceptable than MSL – AA – 30 %. The poor compactibility observed with MSL-AA can be linked with the brittleness and strong cohesive properties of AA.

Photographs of MSL tablets containing MSL (55 %) and PCM (45 %) are presented in Figure 4.34. The compacts were smooth, free from chipping and lamination.

5.4.5.4 Disintegration time of MSL tablets containing model drug

Fig. 4.38 shows the reduction disintegration time with increase in percentage of API. It can be seen that the disintegration time of MSL – PCM and MSL – AA ranged from ~3.7 min. to ~0.8 min., for the former and ~4.5 min., down to 3.3 min., for the latter respectively. One can see that the disintegrant properties of MSL was more pronounced in the formulation containing poorly compressible and water insoluble API (PCM) than in formulation containing highly water soluble and moisture sensitive API (AA). Starch as a disintegrant depends on the porosity of the powder mixture in other to exercise its swelling property to disintegrate the compact. The strong cohesive property of AA which is an inherent property is responsible for the lower disintegrating effect of starch in AA formulation.

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5.4.5.5 In-vitro drug release from MSL tablets.

Fig 4.40 shows the plot of percentage (%) drug released versus time (min) for MSL-PCM. Table 4.18 shows $T_{90\%}$ to be 14 min and 100 % of the drug was released in 15 min. Dissolution rate constant (K_D) according to Kitazawa equation was determined as $4.5x10^{-3}$ mg. min^{-1} at 10 min. (Table 4.19). A rapid disintegration of drug is an index of a fast dissolution. The faster the disintegration the faster the dissolution because the granules and smaller particles formed from disintegration increased the surface area for absorption. The more surface area is made available, the faster the dissolution. The value of $T_{90\%}$ obtained (14 min.) is far less than the 45 min stipulated by U.S.P XXIII for conventional tablets. This is attributed to super disintegrating action of MSL.

5.5 Microcrystarcellac (MCTS 40 %: LMH 40 %: MCC 20 %)

5.5.1 Granular properties

Figures 4.11 and 4.12 show that the compositions of MSCL were evenly distributed within the composite (i.e. embodiment). Figures 4.14 and 4.15 also illustrate coprocessed products of MSCL. The granules were uniform in shape and free flowing properties.

The coprocessed granules were restructured by sieving to remove the fines and granules retained on 500 µm sieve size. Table 4.11 compares the granule properties of coprocessed MSCL (MCTS 40 %: LMH 40 %: MCC 40 %) with the direct physical mixtures of the same ratio of MCTS, Starlac®, and Cellactose®.

The result illustrates an increase in flow properties of coprocessed MSCL over that of the direct physical mixture as reflected by flow rates of 2.0 g/s for the former and 0.45 g/s, for the latter. The corresponding angles of repose were 32^{o} and 47.8^{o} while the compressibility indices as reflected in the table were 13.4 % and 52 % for MSCL and the physical mixtures respectively. All these results indicate improved flow property and compressibility of MSCL after coprocessing over direct physical mixture of the same ratio.

Fig. 4.14 shows the granule size distribution of MSCL (MCTS 40 % : LMH 40 % : MCC 20 %). More than 50 % of the granules were greater than 250 µm and all the granules (100 %) were greater than 90 µm. This range of granule size distribution was responsible for the improved flow property over the individual powders and the direct physical mixture of the primary excipients.

5.5.2 Tablet properties (placebo tablets)

The MSCL tablets (Fig. 4.28) were smooth, free from chipping and lamination. This is an evidence of a good and acceptable tablet formulation.

Fig. 4.19 shows the result of the compactibility studies of MSCL and the physical mixture of the constituents. It illustrates the relationship between compression pressure and radial tensile strength for MSCL tablets. The curve with two portions is similar to Heckel plot, with the early part representing consolidation as a result fragmentation and some degree of plastic deformation, and the other a linear portion illustrating the consolidation behavior as a result of plastic deformation. The MSCL-B_2 compactness ranged from 14.5 to 18.5 x 10^5 N/m^2 while that of the physical mixture ranged from 10 to 16.5 x 10^5 N/m^2.

Fig.4.20 compared the compactibility of MSCL with the standard coprocessed filler-binders. Cellactose® curve shows higher compact strength (spanned from 15 to 38 x 10^5 N/m^2) than MSCL (from 11 to 22. x 10^5 N/m^2), which in turn was more compacted than Starlac® (3 to 23 x 10^5 N/m^2), this is a reflection of diminished densification as a result of reduced porosity. As porosity approaches zero, plastic deformation may be predominant mechanism for all powder material (Heresy and Rees, 1971: York and Pilpel, 1972). Comparing MSCL with Starlac®, higher densification observed for the former could be due to its higher plasticity (combination of MCTS and MCC) than the latter which stored high elastic force due to the presence of native tapioca starch.

5.5.3 Friability of MSCL placebo tablets

Fig. 4.24 shows the effect of increasing compression pressure on the friability of MSCL compacts. There was a reduction in friability with increase in compression pressure and tablet hardness. As the compression pressure was increased from 2.5 N to 12.5 KN, friability also decreased from 1.25 % to 0.5 % for MSCL tablets. Lower friability indicates stronger compact with high crushing strength. This could arise from consolidation of materials with low porosity and high plasticity, which are characteristics of MSCL. The low friability is an indication of strong binding force holding particles together as a result of optimization of plasticity and brittleness in MSCL.

5.5.4 Disintegration time of MSCL placebo tablets

The presence starch granules in MSCL are expected to impact disintegration property. The disintegration time is mostly influenced by tablet hardness. Fig. 4.23 shows the effect of increasing compression force on disintegration time of MSCL, Starlac®, and Cellactose® tablets. Disintegration time increases with increase in tablet hardness, which is proportional to the applied pressure. The DT for all the compacts of MSCL formed between compression force 2.5 N and 12.5 KN ranged from < 2 min to 3 min. The corresponding values for Starlac® was < 1 min and Cellactose® was < 1 min to 17 min respectively. The B.P.C (1988) standard for conventional uncoated tablet with respect to disintegration states that uncoated tablets must disintegrate within 15 min. MSCL which caused the tablets to

disintegrate after 3 min. can be regarded as having a good inherent disintegrant property. The percentage of MCTS and MCC in MSCL is responsible for the rapid disintegration.

5.5.5 Densification behavior of MSCL placebo tablets

5.5.5.1 Plot of Heckel equation

Fig. 4.25 shows the plot of ln 1/[1 – D] *vs p* for MSCL, Starlac®, and Cellactose®. The plot of MSCL can be divided into three phases, namely phase 1: 29 $MNm^{-2} < p < 58$ MNm^{-2}, phase 2: 58 $MNm^{-2} < p < 116$ MNm^{-2} and phase 3: 116 $MNm^{-2} < p < 144$ MNm^{-2}, each of which basically obeyed the Heckel equation. There was non linearity in the first phase (early stage) at low pressure which suggests that MSCL underwent fragmentation and rearrangement before plastic deformation (Odeku and Itiola, 2007). Under low pressure ($p < 58$ MNm^{-2}) the compaction would mainly result in the elimination of voids among the loose particles through rearrangement, fragmentation and some degree of plastic deformation leading to rapid densification of MSCL. In the phase 2, from ~58 MNm^{-2} to ~116 MNm^{-2}, plastic deformation of MSCL predominates and was responsible for the densification of MSCL compact. In the third phase from ~116 MNm^{-2} to ~144 MNm^{-2}, decompression occurred leading to tablet expansion represented by increased tablet porosity.

Table 4.12 shows the values of the mean yield pressure, P_Y, the relative densities D_o, D_A, and D_B for MSCL, Starlac®, Cellactose® and MCC. P_y, is inversely related to the ability of the material to deform plastically under pressure. Low P_y indicates a faster onset of plastic

deformation (Odeku and Itiola, 1998). The P_y obtained for MSCL, Starlac® and Cellactose® were: 22.3 MNm^{-2}, 143 MNm^{-2}, and 24.2 MNm^{-2} respectively. From these values of P_y it is evident that MSCL showed faster onset of plastic deformation compared with Starlac®, and Cellactose®. The yield value of MSCL reflected better densification at low pressure than Starlac®, and Cellactose®. Shangraw *et al.*(1981) reported that, a large value of slope (i.e., low P_y value) is an indication that the onset of plastic deformation occurs at relatively low pressure and vice versa. Heckel analysis has been extensively applied to pharmaceutical powders for both single and multi-component systems (Duberg and Nystrom, 1986; Itiola, 1991). D_A, represents the total degree of densification at zero and low pressures (Paronen and Juslin, 1983; Mitreveji *et al*., 1996; Roberts and Rowe, 1985). D_o is used to describe the initial rearrangement phase of densification as a result of die filling. D_o is equal to the ratio of bulk density at zero pressure to the true density of the powder (Chowhan and Chow, 1981). The relative density, D_B, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation. From Table 4.12 the D_o values for MSCL, Starlac® and Cellactose® were 0.470, 0.413 and 0.298. These results showed that MSCL is denser during the die filling than Starlac®, and Cellactose®. The D_B values for MSCL, Starlac® and Cellactose® were 0.162, 0.404 and 0.157. These results reflect the degree of fragmentation at low pressure in the following order: Starlac® > MSCL > Cellactose®. Khan and Rhodes (1975) reported some degree of fragmentation in MCC with increase in compression pressure. Doelker (1988) and Nystrom *et al.*(1993) observed that high D_B values are caused by fragmentation while low D_B values are associated with plastic deformation.

5.5.5.2 Plot of Kawakita equation

Fig. 4.26 shows the plot of *p/C vs p* for MSCL, Starlac®, and Cellactose®. One can see that a linear relationship exists between *p/C* and *p* in the whole pressure range investigated with correlation coefficient (r^2) of 0.982, which indicates that the densification behavior of MCTS is consistent with prediction from the Kawakita equations. By best fitting of the experimental data to the equation 26 one obtains:

$$p/C = 1.64\,p + 26.73 \quad - \quad - \quad - \quad - (40)$$

Hence, the value of "a" was obtained as 0.610 and "b as 0.0613 (1/b = 16.3).

The D_i (= 1 – a) indicates the packed initial relative density of tablets formed with little pressure or tapping (Lin and Chain, 1995). Table 4.13 shows that the D_i values for MSCL, Starlac®, and Cellactose® were 0.390, 0.474 and 0.286, respectively. It can be seen that at low pressure, MSCL tablet was better packed than Cellactose® tablets, but less in packing relative to Starlac® tablets. This result indicates that packing of a material with applied pressure is determined by deformation propensity.

Table 4.13 shows that the values of 1/b (P_k) obtained for MSCL, Starlac®, and Cellactose® were 16.3, 19.1 and 17.0 respectively. The reciprocal of b yields a pressure term, P_k, which is the compression pressure required to reduce the powder bed by 50 % (Shivanand and Sprockel, 1992). The value of P_k gives an inverse measurement of plastic deformation during compaction process. The lower the value of P_k, the higher the degree of plastic deformation occurring during compression **(**Itiola, 1991**).** Hence, from the results of P_k

values, MSCL was more plastically deformed during compression than Starlac®, and Cellactose®.

5.5.5.3 Dilution capacity/potential

Fig.4.31 shows the relationship between the amounts of API (%) incorporated into MSCL and the crushing strength. It can be seen that tablet strength reduced with increasing amount of API until it reached a point where the tablet strength, friability and the physical structure failed to meet the official standard.

Photograph of tablets formulated from MSCL (55 %) and PCM (45 %) are as shown in Figure 4.35. They were smooth, free from chipping and lamination. More so, tablets formulated from MSCL (50 %) and AA (50 %) were also characterized with the same good and acceptable tablet qualities (Fig. 4.36). Table 4.16 shows the physical properties of PCM and AA tablets. Table 4.17 summarizes the of result dilution potential. One can see that MSCL was able to form acceptable compact with maximum of 45 % of PCM (crushing strength, 70 N; friability, 0.6 %; and disintegration time, 23 sec.), and with 50 % of AA (crushing strength, 68 N; friability, 0.4 % ; and disintegration time, 90 sec). Hence, MSCL – PCM- 45 % and MCTS – AA – 50 % could be acceptable dilution capacity/potential for the two APIs. The performance of MSCL in both PCM and AA tablets can be attributed to increased functionality as hypothesized in the beginning of this research. There was a synergistic plastic effect between MCTS and MCC that resulted in high binder effect in both PCM and AA tablet.

5.5.6 Disintegration time of MSCL tablets containing model drug

Fig. 4.39 shows the disintegration time decreased with increase in percentage of API. The DT of MSCL-PCM and MSCL-AA tablets ranged from ~0.42 min., to ~2.1 min., for tablets containing PCM and from ~1.5 min., down to 3.8 min for tablets containing AA. It was observed that the disintegrant property of MSCL was more pronounced in the formulation containing poorly compressible and water insoluble API (PCM) than in formulation containing highly water soluble and moisture sensitive API (AA). There was a synergistic disintegrating effect of MCTS and MCC in both PCM and AA tablets. The disintegrant actions of starch depend on the porosity of the powder mixture. Pores are required for swelling to occur for the compact to disintegrate. The strong cohesive property of AA which is an inherent property is responsible for the lower disintegrating effect of starch in AA formulation.

5.5.7 Lubricant sensitivity

The LSR for MSL increased from 35 % at 5 min to 42 % at 30 min of mixing with 1 % of lubricant. For MSCL, the LSR was 24 % at 5 min but increased to 34 % after 30 min of mixing. Therefore, MSL was more sensitive to the lubricant compared with MSCL (Table 4.14).

Lubricants form film coating over the excipients decreasing the crushing strength. But in the case of MSCL, plastic material such as MCC was fixed between or on the particle of the

brittle material to provide good bonding properties because it creates a continuous matrix with a large surface for bonding (Maaschalk and Bolhius, 1999). Hence, this may be the reason for the reduced sensitivity of MSCL to the lubricant.

5.5.8 Brittle fracture index (BFI)

Both MSL and MSCL possessed BFI values of 0.1 and 0.08 respectively (Table 4.15). Theoretically BFI ranges from 0 - 1. BFI has been used as a measure of plastoelasticity of pharmaceutical powders. A low BFI value indicates the ability of the material to relieve localized stresses while a value approaching unit indicates a tendency of the material to laminate or cap.

The combination of plastic and brittle materials in both MSL and MSCL helped to reduce storage of elastic property. Lamination or capping is normally a result of high storage of elastic energy.

5.5.9 *In-vitro* drug release from MSCL tablets

Figs 4.40 shows the graph of percentage (%) drug release versus time (min) for MSCL – PCM and MSCL-AA, while Table 4.18 shows the physical properties of the tablets. The $T_{90\%}$ values of the dissolution profiles were 13 min and 12 min respectively for MSCL-PCM and MSCL-AA. There was 100% release of the drugs from both formulations in 15 min. The dissolution rate constant (K_D) for both formulations at 10 min were calculated to be 7.5×10^{-3} mg min^{-1}

and 11.0 x 10^{-3} mg min^{-1} for MSCL-PCM and MSCL-AA respectively (Fig. 4.19). A rapid disintegration of drug translates to a fast dissolution. The value of $T_{90\%}$ obtained (12 and 13 min.) were far less than the 45 min. stipulated by U.S.P XXIII for this class of tablets. This could be attributed to super disintegrant action of MSCL as a result of synergism between MCTS and MCC.

5.5 Statistics

The P values obtained at 95 % confidence interval for MSL and MSCL sampled at 6 months interval were greater than 0.05, hence, the mean of differences does not differ significantly.

The P value obtained for MSL-PCM paired with Cellactose-PCM was greater than 0.05, the result was considered not significant.

The P value for MSCL-AA paired with Cellactose-AA was greater than 0.05, the result was also considered not significant.

CHAPTER SIX

SUMMARY AND CONCLUSION

6.1 Summary

The average crushing strength for NTS, ATS and MCTS were 30 N, 90 N and 90 N after 3 h of annealing and hydrolysis respectively, and at a compression load of 6 KN.

MSL showed improved functionality over direct physical mixture of the primary excipients. MSCL also had improved functionality over direct physical mixture of the primary excipients. The compression pressure, required to reduce the powder bed by 50 % (onset of plastic deformation) P_y (yield value) were in the following order: MSCL (22.3 MNm^{-2}) > Cellactose® (24.2 MNm^{-2}) > MSL (68 MNm^{-2}) > MCTS (143 MNm^{-2}) = Starlac® (143 MNm^{-2}). The degree of plastic deformation occurring during compression (P_k) was in the following order: MSCL (16.3 MNm^{-2}) > MSL (16.7 MNm^{-2}) > Cellactose® (17 MNm^{-2}) > MCTS (17.7 MNm^{-2}) > Starlac® (19.1 MNm^{-2}). From these two parameters (P_y and P_k), MSCL was established to be more superior to MSL and both in turn were more superior to the two standard excipients namely: Starlac®, and Cellactose®.

The dilution potentials obtained for MCTS, MSL and MSCL using paracetamol (PCM) and ascorbic acid (AA) as active drug (API) were: 40 % AA with MCTS; 45 % PCM with MSL, 30 % AA with MSL; 50 % AA with MSCL and 45 % PCM with MSCL. MSCL and MSL were more superior in functionality than MCTS, Starlac®, and Cellactose®. The hardness of MCTS containing 40 % AA was found to be 58 N; MSL containing 45 % PCM, 80 N; MSCL containing 45 % PCM, 70 N; MSCL containing 50 % AA, 68 N. MSL can be employed in the

formulation of tablet containing poorly soluble and poorly compressible API, while MSCL can be used to formulate tablets of both poorly compressible and moisture sensitive API.

Tables 4.18 and 4.19 summarized the results of the formulation studies carried out on MCTS, MSL and MSCL containing PCM and AA. All the formulations released 100 % of the active ingredient within 15 min, and it can be seen from the table that the $T_{90\%}$ values of the dissolution profiles ranged from 12-14 min for the formulations. The results compared favourably with those of Cellactose® and were much better than those of Starlac®.

The rate constants (K_D at t = 10 min) obtained from the dissolution data were in the following order: MSCL – AA (11.0×10^{-3} mg min^{-1}) > Cellactose® – AA (10.3×10^{-3} mg min^{-1}) > MCIS – AA (5.4×10^{-3} mg min^{-1}) and Cellactose® – PCM (9.3×10^{-3} mg min^{-1}) > MSCL – PCM (7.5×10^{-3}mg min^{-1}) > MSL - PCM (4.5×10^{-3} mg min^{-1})

6.2 Conclusions

From the hypothesis made earlier, annealing and enzyme hydrolysis of tapioca starch helped to improve flow and compressibility of the starch. MCTS, MSL and MSCL were able to exhibit self disintegrating functionality proposed. The placebo studies were characterized with rapid disintegration while the formulation studies showed rapid/fast release of API in which 100 % of the drugs were released in 15 min. The combination of MCTS and MCC in MSCL exhibited synergistic effect as expressed in its more rapid disintegration than MSL.

MCTS, MSL and MSCL possessed good binding property, as a result of this they were adjudged to be good filler-binder for direct compression. They have improved flow property over direct and physical mixture of the primary excipients

Based on the formulation studies, MSL could be rated as being equal with Cellactose® in PCM tablet formulation and better than Starlac® in terms of compressibility, compactibility, dilution potential and stability. It can be used to formulate dose up to 225 mg poorly soluble and poorly compressible API (i.e., 45 % of tablet weight for dose upto 500mg) in which PCM represents the group.

MSCL performed better than MSL and Starlac® and was rated as being equal with Cellactose® in PCM and AA tablet formulations in terms of compressibility, compactibility and stability (functionality). It can be used to formulate low dose up to 225 mg poorly soluble and poorly compressible API (i.e., 45 % of tablet weight) in which PCM represents the class of drug. Moreover, it formed better tablet with dose up to 250 mg poorly compressible, highly soluble and moisture sensitive API (i.e., 50 % of tablet weight for dose up to 500 mg) e.g., AA.

6.3 Contribution to knowledge

In this work we have been able to improve the flow and binding functionality of tapioca starch by annealing and subsequently hydrolyzing with enzyme (α-amylase). Through particle restructuring and tailoring of MCTS plus LMH, and MCTS plus LMH plus MCC we were able to design MSL and MSCL respectively. The two

composite component filler-binders possessed better flow compared with physical mixtures.

Both filler-binders have improved compressional functionality, inherent disintegrant property, high dilution capacity and rapid drug release comparable to standard marketed directly compressible filler-binders.

With these results, we are moving from surface mining into deep mining to bring out the best from the oldsafe and already existing excipients.

6.4 Recommendation

Future work should focus on spray drying to further improve the functionalities of MSL and MSCL.

There is need to try other API in order to have library information on dose related problems that is common with directly compressible filler-binders.

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APPENDICES

APPENDIX I: Characteristics of ATS Powder at various times

Time of Annealing (Min)	Flow Rate g/sec n=3	Angle of Repose n=3	Bulk Density g/cm^3 n=3	Tapped Density g/cm^3 n=3	Compr-essibility Index %	Hausner Ratio	Moisture Content %
60	3.2	32	0.512	0.700	26.9	1.4	6.9
120	3.1	32	0.613	O.884	30.7	1.4	6.5
180	2.6	32	0.616	0.895	31.2	1.5	6.0
240	1.8	38	0.572	0.934	38.5	1.6	7.2

APPENDIX II: Compaction Characteristics of NTS at various Compression Pressure

Comp-action Force (KN)	**Comp-ression Press-ure N/M^2**	**Weight of Tablet (g)**	**Thick-ness of Tablet (m) $x10^{-3}$**	**Crushing Strength (N) Without Mg. Stearate**	**Radial Tensile Strength (N/M^2) With Mg. St.**	**Radial Tensile Strength (N/M^2) Without Mg. St.**	**Comp-act Density g/cm^3**	**Fri-ability**	**DT (Min) n =3**
4		NC	NC	NC	NC	NC			

5		NC	NC	NC	NC	NC			
6	7.6	500	3.30	3	4.6	5.79	1.235	Failed	14Sec
6.5	8.3	500	3.05	4	6.6	8.37	1.336	Failed	20Sec
7		NC	NC	NC	NC	NC			

APPENDIX III: Powder Characteristics of selected MSL and MSCL

Material	Batch	Flow Rate (g/sec) n=3	Angle of Repose (o) n=3	Bulk Density (g/cm^3) n =3	Tapped Density (g/cm^3) n =3	Compr-essibility Index (%)	Hausner Ratio	Loss on drying (%w/w)
MCTS+LMH (2-CC) (Fine -500µm)	4	2.8	43	0.560	0.833	49	1.5	4.4
	5	2.2	48	0.577	0.882	53	1.5	4.8
MCTS+LMH+ MCC (3-CC) (Fine -500µm)	2	3.13	28	0.500	0.650	30	1.3	5.2
	3	3.52	24	0.450	0.630	40	1.4	4.8

APPENDIX IV: Summary of Powder Characteristics of NTS, ATS-3 h, MCTS-3 h, MSL and MSCL

Material (Fine -500µm)	Batch	Flow rate g/sec	Angle of Repose (degree)	Bulk density g/cm^3	Tapped density g/cm^3	Compres-sibilty index %	Hausner Ratio
NTS		2.0	43.4	0.545	0.817	50	1.5
ATS-3 h		2.6	32.0	0.616	0.895	45.3	1.5
MCC		0.75	48.0	0.389	0.620	59.4	1.6
Lactose		0.77	49	0.556	0.862	55	1.6
MCTS-3 h		2.5	35^o	0.614	0.844	37.5	1.4
MCTS+LMH	4	2.8	43^o	0.560	0.833	49	1.5
	5	2.2	48^o	0.577	0.882	53	1.5

MCTS+LMH+	2	3.1	28^{o}	0.500	0.650	30	1.3
MCC	3	3.5	24^{o}	0.450	0.630	40	1.4

APPENDIX V: Characteristics of the Physical Mixtures of the Primary Excipient

Material PHYSICAL MIXTURE %w/w	**Flow rate g/sec**	**Angle of Repose (o)**	**Bulk Density g/cm^3**	**Tapped Density g/cm^3**	**Compressibilty index %**	**Hausner Ratio**
MCTS+LMH B4 (60:40)	0.52	39.6	0.439	0.656	49.4	1.50
MCTS+LMH B5 (50:50)	0.65	40.2	0.510	0.781	53	1.53
MCTS+LMH+MCC B2 (40:40:20)	0.45	47.8	0.481	0.735	52	1.53
MCTS+LMH+MCC B3 (35:35:30)	0.41	45.6	0.455	0.735	61.5	1.61

APPENDIX VI: Comparison between Powder Characteristics of the Primary,

Coprocessed filler-binders, and Standard Coprocessed

Excipients

Material	Flow rate g/sec	Angle of Repose (o)	Bulk density g/cm^3	Tapped density g/cm^3	Compressibilty index %	Hausner Ratio
NTS	2	43.4	0.545	0.817	50	1.5
ATS(>75-250 µm)	2.6	32	0.616	0.895	45	1.5
MCTS(>75-250 µm)	2.5	24.5	0.516	0.712	38	1.4
MSL-B4 (>90-250µm)	6	17.5	0.615	0.696	13.2	1.13
MSL-B4 (>75-250µm)	2.5	27.4	0.625	0.833	33.3	1.33
MSL-B5 (>90-250µm)	3	32	0.605	0.813	34	1.12
MSL-B5 (>75-250µm)	2.1	33	0.683	0.833	22	1.2
MSCL-B2 (>90-250µm)	2	31.6	0.677	0.768	13.4	1.13
MSCL-B2 (>75-250µm)	1.8	37	0.555	0.758	36.6	1.4
MSCL-B3 (>90-250µm)	1.8	31	0.483	0.744	54	1.5
MSCL-B3 (>75-250µm)	1.6	32	0.526	0.685	30	1.3
Starlac®	7.1	19.2	0.641	0.725	13.1	1.13
cellactose®	1.84	24.2	0.443	0.532	20.1	1.2
MCC	0.75	48	0.389	0.620	59.4	1.6
Lactose	0.77	49	0.556	0.862	55	1.55

APPENDIX VII: Radial tensile strength of compacts of primary excipients, standard coprocessed excipients, and various particle fractions of MSL and MSCL

Material	RADIAL TENSILE STRENGHT X 10^5(N/M^2)				
	← Compression pressure (Load)			→	
	2.5 KN	5.0 KN	7.5 KN	10.0 KN	12.5 KN
NTS	3.65±0.15	3.95±0.15	5.12±0.16	5.24±0.16	5.53±0.16
ATS	4.86 ±0.16	7.21 ±0.16	8.49 ±0.17	8.76 ±0.17	9.69 ±0.17
MCTS	13.78 ±0.14	14.14 ±0.16	14.72 ±0.16	14.81 ±0.18	15.72 ±0.18
LMH	1.12 ±0.16	1.6 ±0.18	2.10 ±0.19	4.20 ±0.20	7.80 ±0.20
MCC	15.8 ±0.20	32.1 ±0.20	34.90 ±0.45	38.2 ±0.50	38.50 ±0.50
STARLAC®	3.40±0.20	9.14 ±0.20	10.7 ±0.30	17.70 ±0.40	22.00 ±0.60
CELLACTOSE®	16.30 ±030.	23.00 ±0.40	29 ±0.50	32.50 ±0.50	34.40 ±0.60
MSL-B4 (>90-250µm)	15.00 ±0.50	20.51 ±0.51	25.3 ±0.60	25.85 ±0.80	25.87 ±0.80
MSL-B4 (>75-250 µm)	13.8 ±0.50	20.12 ±0.12	26.62 ±0.20	30.62 ±0.20	30.02 ±0.20
MSL-B5 (>90-250 µm)	10.97 ±0.50	19.06 ±0.07	23.3 ±0.70	26.7 ±0.70	28.16 ±0.80
MSL-B5 (>75-250 µm)	11.27 ±0.25	13.28 ±0.26	23.29 ±0.25	28.21 ±0.26	24.82 ±0.32
MSCL-B2 (>90-250 µm)	13.4 ±0.40	13.9 ±0.60	14.8 ±0.80	17.20 ±0.80	20.20 ±0.80
MSCL-B2(>75-250 µm)	9.4 ±0.20	13.8 ±0.40	15.77 ±0.60	17.63 ±0.63	20.41 ±0.80

MSCL-B3(>90-250 µm)	11.17 ±0.12	13.41±0.21	19.60 ±0.40	19.82 ±0.42	20.90 ±0.50
MSCL-B3(>75-250 µm)	9.79 ±0.29	13.30 ±0.30	19.24 ±0.50	20.10 ±0.50	25.80 ±0.50

APPENDIX VIII: Compact densities of tablets of primary excipients, standard coprocessed excipients, and various particle fractions of MSL and MSCL

Material	COMPACT DENSITY (g/cm^3)				
	← Compression pressure (Load)			→	
	2.5 KN	5.0 KN	7.5 KN	10.0 KN	12.5 KN
NTS	1.331	1.309	1.310	1.312	1.310
ATS	1.229	1.273	1.287	1.303	1.313
MCTS	1.313	1.322	1.342	1.391	1.322
LMH	1.300	1.336	1.379	1.401	1.428
MCC	1.455	1.481	1.482	1.507	1.510
STARLAC®	1.291	1.332	1.388	1.403	1.426
CELLACTOSE®	1.305	1.349	1.432	1.501	1.449
MSL-B4 (>90-250µm)	1.225	1.258	1.296	1.311	1.359
MSL-B4 (>75-250 µm)	1.249	1.370	1.392	1.382	1.382

MSL-B5 (>90-250 µm)	1.220	1.239	1.311	1.307	1.375
MSL-B5 (>75-250 µm)	1.337	1.351	1.374	1.407	1.414
MSCL-B2 (>90-250 µm)	1.357	1.356	1.415	1.430	1.451
MSCL-B2(>75-250 µm)	1.327	1.384	1.407	1.432	1.433
MSCL-B3(>90-250 µm)	1.314	1.310	1.387	1.429	1.457
MSCL-B3(>75-250 µm)	1.368	1.414	1.468	1.472	1.515

APPENDIX IX: Friability values of tablets of primary excipients, standard coprocessed excipients, and various particle fractions of MSL and MSCL

Material	FRIABILITY (%)				
	← Compression pressure (Load) →				
	2.5 KN	5.0 KN	7.5 KN	10.0 KN	12.5 KN
NTS	5.20±0.8	2.10±0.2	4.00±0.08	1.90±0.04	1.69±0.04
ATS	9.30 ±0.9	2.00 ±0.2	3.00 ±0.07	1.51 ±0.04	1.50 ±0.03
MCTS	0.92 ±0.05	0.50 ±0.05	0.52 ±0.01	0.41 ±0.01	0.40 ±0.01
LMH	12.5 ±0.05	6.10 ±0.05	4.10 ±0.04	6.20 ±0.04	4.10 ±0.04
MCC	1.70 ±0.04	1.01 ±0.02	0.62 ±0.01	0.61 ±0.01	0.41 ±0.01

STARLAC®	3.40 ±0.08	2.10 ±0.06	1.30 ±0.05	1.0 ±0.04	0.40 ±0.04
CELLACTOSE®	1.00 ±0.02	0.50 ±0.01	0.20 ±0.01	0.10 ±0.01	0.10 ±0.01
MSL-B4 (>90-250µm)	1.02 ±0.02	1.01 ±0.01	0.82 ±0.01	0.61 ±0.01	0.50 ±0.01
MSL-B4 (>75-250 µm)	1.03 ±0.02	1.03 ±0.02	1.02 ±0.02	1.02 ±0.01	0.62 ±0.01
MSL-B5 (>90-250 µm)	1.02 ±0.02	1.02 ±0.01	0.41 ±0.01	0.21 ±0.01	0.00 ±0.00
MSL-B5 (>75-250 µm)	1.03 ±0.03	1.02 ±0.01	0.62 ±0.01	0.41 ±0.01	0.00 ±0.00
MSCL-B2 (>90-250 µm)	1.02 ±0.02	1.12 ±0.02	0.82 ±0.01	0.71 ±0.01	0.51 ±0.01
MSCL-B2(>75-250 µm)	1.53 ±0.03	1.03 ±0.03	0.83 ±0.01	0.72 ±0.01	0.52 ±0.01
MSCL-B3(>90-250 µm)	1.02 ±0.01	0.92 ±0.02	0.82 ±0.01	0.61 ±0.01	0.61 ±0.01
MSCL-B3(>75-250 µm)	1.02±0. 02	1.02 ±0.02	0.80 ±0.01	0.71 ±0.01	0.60 ±0.01

APPENDIX X: Disintegration time of tablets of primary excipients, standard coprocessed excipients, and various particle fractions of MSL and MSCL

Material	Disintegration Time (Min)				
	← Compression pressure (Load)			→	
	2.5 KN	5.0 KN	7.5 KN	10.0 KN	12.5 KN

NTS	0.23±0.02	0.25±0.02	0.27±0.01	0.28±0.01	0.28±0.01
ATS	1.30 ±0.02	1.83 ±0.02	2.12 ±0.02	2.25 ±0.05	2.75 ±0.05
MCTS	1.33 ±0.02	1.30 ±0.02	1.50 ±0.03	1.83 ±0.05	2.17 ±0.05
LMH	0.37 ±0.02	0.37 ±0.02	0.43 ±0.03	0.45 ±0.03	0.48 ±0.04
MCC	>60	>60	>60	>60	>60
STARLAC®	0.42 ±0.02	0.5 ±0.01	0.67 ±0.02	0.67 ±0.02	0.75±0. 03
CELLACTOSE®	0.27±0. 01	1.33 ±0.03	7.67 ±0.03	16.75 ±0.03	17.50 ±0.03
MSL-B4 (>90-250µm)	3.20 ±0.20	3.30 ±0.06	3.5 ±0.05	3.75 ±0.05	4.33 ±0.05
MSL-B4 (>75-250 µm)	2.83 ±0.03	3.67 ±0.04	4.67 ±0.05	5.00 ±0.05	5.58 ±0.05
MSL-B5 (>90-250 µm)	1.70 ±0.10	3.25 ±0.06	3.3 ±0.05	3.67 ±0.04	4.1 ±0.04
MSL-B5 (>75-250 µm)	1.5 ±0.05	2.2 ±0.05	3.25 ±0.03	3.30 ±0.03	4.42 ±0.03
MSCL-B2 (>90-250 µm)	1.7 ±0.04	2.67 ±0.04	3.1 ±0.04	3.2 ±0.05	3.42 ±0.05
MSCL-B2(>75-250 µm)	0.83 ±0.01	1.20 ±0.01	2.42 ±0.01	2.5 ±0.02	2.92 ±0.02
MSCL-B3(>90-250 µm)	1.2 ±0.01	2.30 ±0.01	2.67 ±0.01	3.0 ±0.02	3.10 ±0.02
MSCL-B3(>75-250 µm)	0.67 ±0.01	1.75 ±0.01	2.67 ±0.01	2.7 ±0.01	3.00 ±0.01

APPENDIX XI: Heckel Plot Parameters for the Selected Composite Excipient, ANEHTS, and Avicel PH 101.

Material	Compression Force (KN)	Compression Pressure (MNm^2)	Compact Density (D_p) g/cm^3	True Density (D_m) g/cm^3	Relative Density (D) $=D_p/D_m$	1 - D	1/(1 – D)	ln 1/(1 -D)
MCTS	2.5	29	1.313 ± 0.003	1.532 ± 0.001	0.857	0.143	6.993	1.945
	5.0	58	1.322 ± 0.001		0.863	0.137	7.299	1.988
	7.5	87	1.342 ± 0.000		0.876	0.124	8.065	2.088
	10.0	116	1.391 ± 0.003		0.908	0.092	10.870	2.386
	12.5	144	1.322 ± 0.001		0.863	0.137	7.299	1.988
MSL (B4)	2.5	29	1.293 ± 0.002	1.508 ± 0.001	0.857	0.143	6.993	1.945
	5.0	58	1.381 ± 0.002		0.916	0.084	11.905	2.477
	7.5	87	1.398 ± 0.001		0.927	0.073	13.699	2.617
	10.0	116	1.416 ± 0.003		0.939	0.061	16.393	2.797
	12.5	144	1.421 ± 0.004		0.942	0.058	17.241	2.847
MSL (B5)	2.5	29	1.337 ± 0.001	1.447 ± 0.003	0.924	0.076	13.158	2.577
	5.0	58	1.351 ± 0.000		0.934	0.066	15.152	2.718
	7.5	87	1.374 ± 0.000		0.950	0.050	20.00	2.996
	10.0	116	1.407 ± 0.003		0.972	0.028	35.714	3.576
	12.5	144	1.414 ± 0.002		0.977	0.023	43.478	3.772
MSCL (B2)	2.5	29	1.357± 0.003	1.441 ± 0.001	0.942	0.058	17.241	2.847
	5.0	58	1.356± 0.001		0.941	0.059	16.949	2.830
	7.5	87	1.415± 0.005		0.982	0.018	55.556	4.017
	10.0	116	1.430± 0.002		0.992	0.008	125	4.828
	12.5	144	1.451± 0.004		1.007	-0.007	142.857	4.962
MSCL (B3)	2.5	29	1.368± 0.001	1.552 ± 0.004	0.881	0.119	8.403	2.129
	5.0	58	1.414± 0.001		0.911	0.089	11.236	2.419

	7.5	87	1.468± 0.003		0.946	0.054	18.519	2.919
	10.0	116	1.472± 0.000		0.951	0.049	20.408	3.016
	12.5	144	1.515± 0.004		0.976	0.024	41.667	3.730
Starlac®	2.5	29	1.291± 0.000	1.553 ± 0.002	0.831	0.169	5.917	1.778
	5.0	58	1.332± 0.005		0.858	0.142	7.042	1.952
	7.5	87	1.388± 0.001		0.894	0.106	9.434	2.244
	10.0	116	1.403± 0.004		0.903	0.097	10.309	2.333
	12.5	144	1.426± 0.003		0.918	0.082	12.195	2.501
Cellactose®	2.5	29	1.305± 0.001	1.488 ± 0.001	0.877	0.123	8.130	2.096
	5.0	58	1.349± 0.002		0.907	0.093	10.753	2.375
	7.5	87	1.432± 0.002		0.962	0.038	26.316	3.270
	10.0	116	1.501± 0.004		1.009	-0.009	111.111	4.711
	12.5	144	1.449± 0.002		0.974	0.026	38.462	3.650
MCC	2.5	29	1.455± 0.003	1.508 ± 0.001	0.965	0.035	28.571	3.352
	5.0	58	1.481± 0.001		0.982	0.018	55.556	4.017
	7.5	87	1.492± 0.005		0.989	0.011	90.909	4.510
	10.0	116	1.507± 0.001		0.999	0.001	1000	6.908
	12.5	144	1.510± 0.004		1.001	-0.001	1000	6.908

D indicates relative density; $D_{p,}$ compact density at pressure P; D_m, true density of composite particles; D, is the ratio of D_p to D_m, and is called relative density. ln 1/ (1 – D) = KP + A

APPENDIX XII: Compacts Parameter for Kawakita's plot

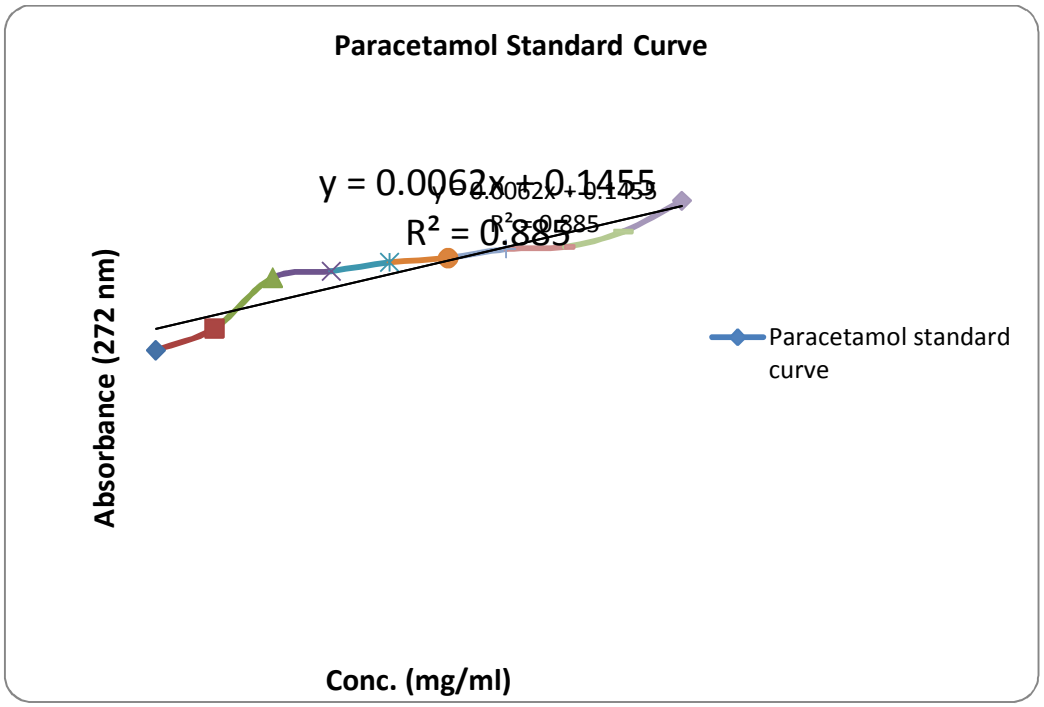
Material	**V_o**	**V**	**C**	**P**	**P/C**

	(m^3)	(m^3)		(MNm^{-2})	
STARLAC	0.772	0.383	0.500	29	58
	0.764	0.367	0.519	58	111.8
	0.764	0.353	0.538	87	161.7
	0.761	0.348	0.543	116	213.6
	0.764	0.344	0.550	144	261.8
CELLACTOSE	1.111	0.377	0.661	29	43.9
	1.106	0.363	0.672	58	83.3
	1.106	0.342	0.691	87	125.9
	1.106	0.335	0.697	116	166.4
	1.108	0.339	0.694	144	207.5
MCC	1.260	0.337	0.733	29	39.6
	1.262	0.332	0.737	58	78.7
	1.247	0.325	0.739	87	117.8
	1.249	0.323	0.742	116	156.3
	1.249	0.322	0.742	144	194.1
MICROCRYSTARLAC	0.810	0.366	0.549	29	52
(>90-250µm)	0.810	0.363	0.553	58	104.9
	0.810	0.357	0.560	87	155.4
	0.810	0.348	0.570	116	203.5
	0.810	0.347	0.572	144	251.8
MICROCRYSTARCELLAC	0.883	0.361	0.591	29	49.1
(>90-250µm) B_2	0.883	0.360	0.592	58	95.1
	0.883	0.347	0.607	87	141.2
	0.883	0.343	0.612	116	189.6
	0.883	0.338	0.617	144	233.4

MICROCRYSTARCELLAC (>75-250µm) B_3	0.932	0.360	0.614	29	47.2
	0.932	0.359	0.616	58	94.2
	0.932	0.346	0.629	87	138.3
	0.932	0.341	0.630	116	184.1
	0.932	0.336	0.640	144	225
MICROCRYSTALLINE TAPIOCA STARCH (>75-250µm)	0.940	0.370	0.607	29	47.8
	0.940	0.367	0.610	58	95.1
	0.940	0.361	0.616	87	141.2
	0.940	0.357	0.621	116	186.8
	0.940	0.362	0.615	144	234.2

Note:V_o (Initial volume of powder)=weight of powder/bulk density of powder, V (Final volume/Compact volume after compression)= $h\pi r^2$, C (degree of Volume reduction) = $V_o - V / V_o$, P = Compression pressure

Appendix: XIII


Paracetamol Standard Curve
y = 0.0062x + 0.1455
R² = 0.885
Absorbance (272 nm)
Conc. (mg/ml)
Paracetamol standard curve

Appendix: XIV

