

**DEVELOPMENT AND EVALUATION OF A CO-PROCESSED EXCIPIENT  
FROM ACID HYDROLYZED CASSAVA STARCH, GELATIN AND LACTOSE  
(STARGELAC) IN TABLET FORMULATIONS**

**BY**

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**DECEMBER, 2015.**

## DECLARATION

I hereby declare that the work reported in this dissertation was carried out solely by me under the supervision of Prof. A.B. Isah and Dr. K. Mshelbwala of the Department of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University, Zaria. The works of other researchers are duly acknowledged and referred to accordingly. I declare that no part of this work has been submitted elsewhere for a degree.

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## CERTIFICATION

This dissertation titled “DEVELOPMENT AND EVALUATION OF A CO-PROCESSED EXCIPIENT FROM ACID HYDROLYZED CASSAVA STARCH, GELATIN AND LACTOSE (STARGELAC) IN TABLET FORMULATIONS” by MUKOSOLU UCHECHUKWU NZEKWE, meets the regulations governing the award of the degree of Master of Science (Pharmaceutics) of Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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## **DEDICATION**

This work is dedicated to my husband, Kene for his encouragement and to our sons:

Tochukwu Daniel, Chidubem Joshua and Chiemelie Praise. Much love always.

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God bless you all!

## ABSTRACT

Co-processed excipients are a mixture of two or more existing excipients at subparticle level. These multipurpose excipients have significantly reduced the number of incorporating excipients in the tablet. The aim of this work is to design and prepare a co-processed excipient from acid hydrolyzed cassava starch, gelatin and lactose and evaluate its functionality in tablet formulations. Native cassava starch (NCS) extracted from cassava tubers (*Mannihot esculenta* crantz ) was modified chemically by acid hydrolysis using the process described by the World Intellectual Property Organization, to obtain acid hydrolyzed cassava starch. The flow, compression and tableting properties of acid hydrolyzed cassava starch were evaluated using flow rate, angle of repose, bulk and tapped densities, Hausner's ratio, Carr's (compressibility) index, friability, crushing strength and disintegration time. Acid hydrolyzed starch (AHS-24) was co-processed with gelatin and lactose in ratios of 52.5:5:42.5; 42.5:5:52.5; 32.5:5:62.5; 22.5:5:72.5 and 12.5:5:82.5 using the co-drying method. These initial batches of co-excipients that were developed were evaluated for their physicochemical and tableting properties. Further characterization utilized: hydration capacity, Fourier Transform Infrared Spectroscopy (FTIR) study, Differential Scanning calorimetry (DSC), compaction indices from Heckel and Kawakita analyses, dilution potential and mechanical strength properties such as tensile strength and brittle fracture indices as indicators. Paracetamol and ascorbic acid tablets were prepared by direct compression using StarGeLac as filler-binder-disintegrant and the tablet properties were evaluated and compared with those prepared with Starlac® and Ludipress® as reference materials. The evaluation showed that the average flow rate, angle of repose and Carr's index of native cassava starch were 0.9 g/sec, 38.7° and 36.84 %, respectively. The corresponding values for acid hydrolyzed cassava starch (after 24 h

exposure time) were 4.6 g/sec, 16.2 ° and 14.9 % , showing improved functionality. Also the average flow rate, angle of repose and Carr's index of StarGeLac (batch IV, component ratio of acid hydrolyzed cassava starch, gelatin, lactose 22.5:5:72.5) were 50.8 g/sec, 28.9° and 16.6 %, respectively. Tablets prepared, without model drugs, using StarGeLac IV had crushing strength of 7.9 Kgf, friability of 0.8 % and disintegrated within 6.53 minutes. The results also show that StarGeLac IV exhibited satisfactory hydration capacity, showed no evidence of chemical changes through FTIR and DSC studies and satisfactorily compressed 40 % and 33.3% of paracetamol and ascorbic acid respectively. Heckel and Kawakita plots also showed that StarGeLac consolidates by plastic deformation but that the onset was slow (higher  $P_y$  value). The study also revealed that tablets of paracetamol and ascorbic acid, used as model drugs, that were prepared using StarGeLac were comparable to those prepared with Starlac ® and Ludipress®. Paracetamol tablets prepared with StarGeLac exhibited higher mean crushing strength and mean disintegration time than the ascorbic acid counterpart but both paracetamol and ascorbic acid tablets prepared with the commercial co-processed excipients had faster disintegration times.

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## LIST OF ABBREVIATIONS

A	Intercept on Heckel plot
AHS	Acid hydrolyzed starch
AM	amylose
ANN	Annealing
AP	amylopectin
API	Active Pharmaceutical Ingredient
b	Plasticity
BFI	Brittle Fracture Index
BP	British Pharmacopoeia
C	Degree of volume reduction in Kawakita plot
CS	Cassava starch
D	Relative density
DC	Direct compression
DSC	Differential Scanning Calorimetry
FTIR	Fourier Transform Infra red Spectroscopy
HCL	Hydrochloric acid
HHP	High hydrostatic pressure
HMT	Heat moisture treatment
H <sub>2</sub> SO <sub>4</sub>	Sulphuric acid
K	Slope of linear portion of Heckel plot
Kgf	Kilogram force
MCC	Microcrystalline cellulose
NaOH	Sodium Hydroxide

P	Applied pressure
$P_y$	Mean yield pressure
RH	Relative Humidity
SDRS	Spray Dried Rice Starch
SGL	StarGeLac
SGL-P	StarGeLac + Paracetamol
SGL-AA	StarGeLac + Ascorbic acid
$T_{50\%}$	Time taken to release 50% of the drug
$T_{90\%}$	Time taken to release 90% of the drug
$T_s$	Tensile Strength
USP-NF	United States Pharmacopoeia- National Formulary
$V_0$	Initial volume
V	Volume of tablet
W	Weight of tablet
$\rho_0$	bulk density
$\rho_a$	compact apparent density

## CHAPTER ONE

### INTRODUCTION

#### 1.1 PHARMACEUTICAL TABLETS

The oral route is the most common way of administering drugs and among the oral dosage forms, tablets of various kinds are the most common type of solid dosage form in contemporary use (Kaur *et al.*, 2011).

Modern tablet compression was instituted in England in 1844 by William Brockedon (1787-1854) who established early procedures for making compressed pills.

Tablets contain one or more active ingredients as well as a series of other components used to formulate a complete preparation usually by compression in a confined space. They contain a single dose of one or more active substances and usually obtained by compressing uniform quantities of particles (Swarbarick and Boylan, 2002).

The European Pharmacopoeia (2002) defines tablets as “solid preparations each containing a single dose of one or more active ingredients and usually obtained by compressing uniform volumes of particles; some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active ingredient is liberated”. Tablets vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration.

The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form

that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process (Gohel *et al.*, 2007).

### **1.1.1 Properties of a Good Tablet**

A good tablet irrespective of the method of preparation should have the following properties (Rudnic and Schwartz, 2000; Alderborn, 2007). The tablet:

- i. must contain a known amount of drug
- ii. should be uniform in weight, appearance and diameter
- iii. should be formulated in such a way that the drug therein is bioavailable
- iv. should withstand handling during manufacturing, packaging, transport and use
- v. should be stable to light, moisture, temperature of the environment over a reasonable period of time
- vi. other desirable properties include safety, elegance and efficacy

### **1.1.2 Advantages And Disadvantages Of Tablet as a Solid Dosage Form**

#### **1.1.3 Advantages**

The popularity of tablet as a dosage form is due to the advantages of tablet medication ( Rudnic and Schwartz, 2000) which include:

- i. ease of administration
- ii. economy of production due to large scale production
- iii. suitable for high speed production
- iv. accurate and stable dose
- v. convenience in packaging, transport and dispensing

#### **1.1.4 Disadvantages**

- i. Swallowing of tablets may be problematic in children, the elderly, very ill or unconscious patient
- ii. Tablets are frequently associated with problems like pitting and melting
- iii. They may cause gastrointestinal irritation.

### **1.2 MANUFACTURE OF TABLETS**

In the tablet pressing process, the main guideline is to ensure that the appropriate amount of active ingredient is in each tablet. Hence, all the ingredients should be well-mixed. The pharmaceutical industry uses different processing techniques (wet granulation, dry granulation and direct compression) to modify the characteristics of raw particles/powder in order to obtain the final dosage form with improved stability, mechanical integrity and acceptable drug release characteristics (Arnaud *et al.*, 1998).

Powders that mix well, exhibiting properties such as low tendency for segregation, good flowability and high compactability may not require granulation and can be compressed into tablets through direct compression.

#### **1.2.1 Dry Granulation**

There are two main processes. Slugging, in which a large tablet known as 'slug' is produced and roller compaction, where the powder is squeezed between two counter rotating rollers to form a compressed sheet of material. The resultant intermediate products are broken using a suitable milling technique to produce granular material that is separated to the desired size fraction before compression.

During slugging dry powders are compacted using a conventional tablet machine or a large heavy duty rotary press producing slugs typically 25 mm diameter by about 10-15 mm thick, that are broken to suitable sizes using a hammer mill.

Roller compactors of assorted roller diameters and roller lengths allow a wide range of active pharmaceutical ingredients and excipients to be processed or co-processed (Aulton, 2007).

### **1.2.2 Wet Granulation**

It is the massing of a mix of dry primary powder particles using a granulating fluid. The wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules yielding material of desired particle size for subsequent compression (Aulton, 2007).

### **1.2.3 Direct Compression**

Direct compression involves the compression of a dry blend of powders that comprises drugs and various excipients.

The main advantage of direct compression over other tablet manufacturing methods is its simplicity, since it requires few unit operations and utilizes much less energy, making the process more economical (Bolhuis and Chowan, 1996).

## **1.3 TABLET PRESSES**

There are two types of press commonly used during tablet production, the single punch press and the rotary press; choice of press is informed by the desired output (Aulton, 2007).

### **1.3.1 Single Punch Press**

A single punch press possesses one die and one pair of punches. The powder is held in a hopper which is connected to a hopper shoe located at the die table. The hopper shoe moves to and fro over the die, by either a rotational or a translational movement. When the hopper is located over the die, the powder is fed into the die by gravitational powder flow. When the hopper shoe is located beside the die, the upper punch descends and the powder is compressed. The lower punch is stationary during compression and the pressure is thus applied by the lower punch and controlled by the upper punch displacement. After ejection, the tablet is pushed away by the hopper shoe as it moves back to the die for the next tablet (Aulton, 2007).

### **1.3.2 Rotary Press**

A rotary press operates with a number of dies and sets of punches which can vary from three for small rotary presses up to sixty or more for large presses. The dies are mounted in a circle in the die table and both the die table and the punches rotate together during the operation of the machine so that one die is always associated with a set of punches. The vertical movement of the punches is controlled by tracks that pass over cams and rolls used to control the volume of powder fed into the die and the pressure applied during compression. The powder flows by gravity onto the die table and is fed into the die by a feed frame. During powder compression both punches operate by vertical movement. After tablet ejection, the tablet is knocked away as the die passes the feed frame (Aulton, 2007).

Outputs of up to 15 000 tablets per minute can be achieved by rotary presses, depending on the number of tool stations (Alderborn, 2002). This speed of production gives the tablet form its superior edge over other solid dosage forms such as capsules.

#### **1.4 TABLETING EXCIPIENTS**

The use of appropriate excipients is important in the development of the optimum tablets. Excipients determine the bulk of the tablet, the speed of disintegration, rate of dissolution /release of drug, protection against moisture, stability during storage, and compatibility (Banakar and Makoid, 1996).

##### **1.4.1 Diluents (Fillers):**

Diluents or fillers are used to add bulk to the size of the tablet to facilitate production and for easy handling by the patient. Tablets containing a very small quantity of a potent active pharmaceutical ingredient would be very small without addition of a suitable diluent. A good diluent should have good flow and compactability, acceptable taste and be chemically inert.

Lactose is popular as a diluent because of its cost effectiveness, ease of availability, blandness in taste, low hygroscopicity, good physical and chemical stability and water solubility (Gohel and Jogani, 2005).

Other diluents are sucrose, glucose, mannitol, sorbitol, calcium phosphate, calcium carbonate and cellulose.

### 1.4.2 Binders

Binders are materials of high bonding capacity added to tablet formulations to impart cohesiveness and structural strength to the tablet (Musa *et al.*, 2010). Binders are usually ductile materials that are prone to undergo plastic deformation during compression leading to a decrease in tablet porosity; this results in increase in contact area between the particles, which promotes the creation of interparticulate bonds with a subsequent increase in tablet strength (Mattson and Nystrom, 2000).

There are various binders available for use depending on the method of tablet manufacture to be employed. Dry binders are used in direct compression of tablets; they are added dry and serve the same purpose as binders in other methods of tablet manufacture. Microcrystalline cellulose, (Avicel) is used for direct compression;

Starches as pharmaceutical excipients used in tablet formulations are also used as fillers, binders, disintegrants and lubricants due to their inherent physicochemical properties and relative inertness (Odeku and Itiola, 2007).

Gelatin in tableting is used for its binding properties usually in 10 % concentration. It is employed in direct compression or after granulation of the powder to be used in compression, Gelatin or hydrolyzed collagen imparts cohesiveness, resistance, hardness to the tablet. The dissolution of the tablet will depend on the type of gelatin used; Usually the stronger the binder, the higher the compactibility of the tablet, and conversely, the longer the disintegration time of the resulting tablet (Ayorinde *et al.*, 2011).

Emeje *et al.* (2007), have reported that the crushing strength and disintegration times of tablets increased with increased binder concentration while their friability decreased.

Although gelatin produced tablets with higher crushing strength, okra gum produced tablets with longer disintegration times than those containing gelatin (Emeje *et al.*, 2007).

Other examples of binders include polyethylene glycol, polyvinyl pyrrolidone, sucrose and cellulose derivatives like hydroxypropylmethyl cellulose.

### **1.4.3 Disintegrants**

These are added to tablet formulations to aid in the break-up of resultant tablets when they are placed in an aqueous environment. Tablet break-up results in increase in surface area of the fragments promoting the release of the drug. Starch is the commonest disintegrant in tablet formulations and is believed to act by swelling (Rubinstein, 1988), however current research has shown that most starches exert their disintegrant actions by deformation (Ofoefule *et al.*, 2004).

Other disintegrants include cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate and sodium carboxymethyl cellulose.

### **1.4.4 Lubricants**

Lubricants ensure that tablet formation and ejection occurs with low friction between the solid and the die wall (Aulton, 2007). Substances like magnesium stearate, stearic acid are used in concentrations as low as 1% or below, often 0.25-0.5%. Because many lubricants are hydrophobic, tablet disintegration and dissolution are often retarded by the addition of a lubricant. In order to avoid these negative effects, more hydrophilic substances have been suggested as alternatives to the hydrophobic lubricants, Examples are surface-active agents and polyethylene glycol. A combination of hydrophobic and hydrophilic substances might

also be used. Other lubricants include sodium lauryl sulphate, sodium tearyl fumarate and liquid paraffin.

#### **1.4.5 Sweeteners, Flavourants and Colouring Agents**

Sweeteners and flavourants are used in chewable, sublingual tablets and lozenges. They are used to mask objectionable taste and odour consequently improving patient acceptability and compliance. Examples include sorbitol, glycerin and sugars.

Colouring agents improve appearance of tablets; colours can also be used for identification. Examples include amaranth and tetrazine.

### **1.5 NEED FOR DEVELOPMENT OF NEW EXCIPIENTS**

With the increasing number of new drug moieties with varying physicochemical, pharmacokinetic, permeation and stability properties, there is a growing interest among formulators to search for new excipients that have minimal scale-up problems, low manufacturing costs, and little environmental impact (Marwaha *et al.*, 2010).

In recent years, it has been recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated adequately (Ajay *et al.*, 2012). These deficiencies have brought about relying on combination excipients which are either physical mixtures or co-processed excipients (Ajay *et al.*, 2012).

Rojas and Vijay (2011) has also reported shortcomings of existing excipients such as loss of compaction upon wet granulation, high moisture sensitivity and poor die filling as a result of agglomeration .

Thus the demand of excipients with improved functionalities, mainly in terms of flow and compression properties, has increased with the advancement of tablet manufacturing process (Marwaha *et al.*, 2010).

Furthermore, the growing popularity of the direct compression process and demands for an ideal filler-binder that can replace two or more excipients avoiding the need for multiple excipients (i.e., disintegrant, lubricant, glidant, etc.) contributes to the above factors driving the search for new excipients (Rojas and Vijay (2011).

### **1.5.1 New Excipient Sources**

Excipients with improved functionality can be obtained by developing a new chemical entity, new grades of existing materials or their combinations (Moreton, 1996).

Excipient co-processing offers a valuable tool to alter compression and/or flow behaviour of a material. A combination of plastic and brittle materials is necessary for optimum tableting performance (Nachhaegari and Bansal, 2004).

Drug-excipient compatibility studies employ analytical techniques such as Fourier Transform Infrared (FTIR) Spectroscopy (Joshi and Xavier, 2002).

## **1.6 MODIFICATION OF STARCH**

In order to improve on the desirable functional properties and overcome its limitations, native starches are often modified (Kaur *et al.*, 2012). Modification, (alteration of the physical and chemical characteristics to improve structural properties) can be used to improve inherent poor physico-chemical properties of native starch thus tailor it to specific industrial applications (Miyazaki *et al.*, 2006).

Starch modification can be broadly grouped into four classes namely: physical, chemical, enzymatic and biological modifications.

### **1.6.1 Physical Modification**

Physical modification of starch can improve water solubility and reduce particle size. The methods involve the treatment of native starch granules under different temperature/moisture combinations, pressure, shear, and irradiation. Physical modification also includes mechanical attrition to change the physical size of starch granules. Physical modification techniques are generally given preference as they do not involve any chemical treatment that can be harmful for human use. Physical modification is simple, cheap, and safe because it requires no chemicals or biological agents. Classification of starches from different botanical sources based on physical modifications depends on whether the molecular integrity of the starches are destroyed or preserved after the modification (Ashogbon and Akintayo, 2014).

### **1.6.2 Chemical Modification**

Chemical modification involves the introduction of functional groups into the starch molecules, resulting in markedly altered physicochemical properties. Such modification of native granular starches profoundly changes the proximate compositions, gelatinization, retrogradation, and pasting characteristics. Chemical modification is intended to facilitate intra- and inter-molecular bonds at random locations in the starch granule for their stabilization. The chemical and functional properties achieved by modified starches depend, *inter alia*, on starch source, reaction conditions (reactant concentration, pH, reaction time, and the presence of catalyst), type of substituent, degree of substitution

(DS), and the distribution of the substituent in the starch molecule (Hirsch and, Kokini, 2002; Wang and Wang, 2002).

Modification is generally achieved through derivatization, such as acetylation, cationization, oxidation, acid hydrolysis, and cross-linking. These techniques are however limited due to issues concerning consumers' safety and the environment. There is an evolving new trend called dual modification, which involves the combination of physical and chemical agents, e.g., microwave-assisted acetylation or high hydrostatic pressure (HHP) assisted phosphorylation (Ashogbon and Akintayo, 2014).

### **1.6.3 Enzymatic Modification**

This involves the exposure of starch suspensions to a number of enzymes primarily hydrolysing enzymes that tend to produce highly functional derivatives (Neelam *et al.*, 2012). Initial hydrolysis of most starch granules starts on the surface, though this depends on the type of starch. Two pathways of corrosion have been reported; Endocorrosion which involves digestion of channels from marked points on the granule surface into the granule centre and exocorrosion in which enzymatic corrosion of the whole granular surface or portions of it (Gallant *et al.*, 1992).

### **1.6.4 Genetic Modification**

This involves transgenic technology that targets the enzyme involved in starch biosynthesis. Genetic modification can be carried out by the traditional plant breeding techniques or through biotechnology (Johnson *et al.*, 1999).

Among these modification methods, chemical means is the most frequently used process (Daramola and Osanyinlusi, 2006).

Modifications at the particle level of an excipient could affect tableting behaviour and formulation success in a solid dosage form (Rojas and Vijay, 2011).

Agubata *et al.* (2012) have investigated the application of starch-gelatin binary binder mixture in the formulation of sodium salicylate tablets. They reported that formulations prepared with gelatin, had lower granule friability than those produced with cassava starch – gelatin binder mix. Also, flow properties did not follow any definite pattern, whereas moisture uptake studies showed that gelatin batches absorbed more moisture than cassava starch-gelatin batches.

As the gelatin content decreased, the tablet crushing strength and CSFR (crushing strength friability ratio) decreased while the friability increased. Also, the mechanical strength and moisture uptake of the gelatin based granules or tablets reduced with the incorporation of cassava starch.

## **1.7 POWDER COMPACTION AND PARTICLE BONDING**

An optimum excipient should be able to form a successful compact with the intended drug to withstand handling and storage.

The compaction process is a composite of several events: particle movement into void spaces, particle fracture, elastic deformation, plastic deformation and cohesion between particle surfaces. The compaction properties of an excipient is described by its compressibility and compactability (Ahmat *et al.*, 2011). Compressibility refers to the ability of the powder to change in volume when subjected to pressure (Ilic *et al.*, 2009) whereas compactability is the ability of powders to convert from small particles into coherent dosage form (Yap *et al.*, 2008)

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

Two different types of interactions are normally considered in direct compression of pharmaceutical materials: intermolecular interactions and mechanical interlocking.

*Van der Waals* forces are probably the most important intermolecular forces responsible for holding the particles together in a tablet.

Hydrogen bonding is another example of forces that act over a short distance between particles. The nature of these forces depends on the chemical composition of the material.

The dominant bond type depends on various factors, including the degree of compression and the inherent properties of the material. In the high porosity range, the principal attraction between particles has been suggested to be intermolecular forces; whereas in the low porosity range, solid bridges play a major role (Adolfsson and Nyström, 1996).

### **1.7.1 Powder Consolidation Models**

The knowledge of the volume reduction ability of a powder makes it possible to predict the compaction behaviour of a pharmaceutical material (Bassam *et al.*, 1990).

Mathematical models have been used to describe the consolidation or volume reduction of powders. Such models were derived from empirical mathematical relationships and were based on the proposal that different mechanisms occur in distinct ranges of applied pressure (Kennedy *et al.*, 1996). These models are used to characterize tableting excipients for compact development. They also identify and describe the predominant powder densification and deformation behaviour (plastic, brittle and elastic) (Picker, 2000).

The Heckel equation relates the compact density to applied pressure. The equation is based on the assumption that the powder compression follows first-order kinetics; the interparticulate pores and the compactability of the powder as the product and reactant respectively. In expressing porosity in terms of relative density, D, of the compact,

$$D = \frac{\text{current density}}{\text{True zero porosity density}} \dots\dots\dots(1)$$

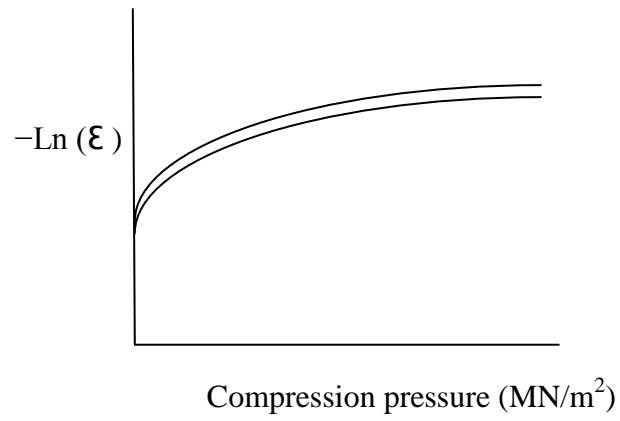
The equation can be derived as:

$$\text{Ln} \left( \frac{1}{1-D} \right) = KP + A \dots\dots\dots(2)$$

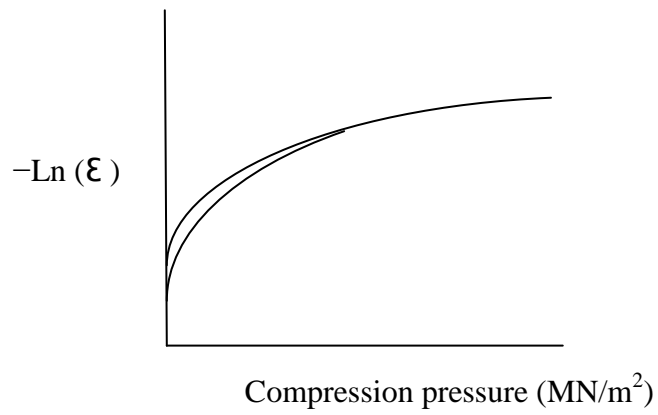
D is the relative density, (1-D) represents the pore fraction, P is the applied pressure, K is the slope of the straight linear portion of the plot and the reciprocal of K is the mean yield pressure (Py), while A represents the intercept of the prolonged linear portion of the plot with the y axis.

Alderborn, 2002, defines the yield pressure as the stress at which plastic deformation of the particles is initiated. It can be derived from the linear portion of the Heckel plot. The plot is curved at high and low pressure ends. Suggested inference indicates high and low pressure curvatures as likely capping and lamination of the powder and particle fragmentation and re-arrangement, respectively. Three types (A, B and C) of powder behaviour can be obtained from the shape of these curves.

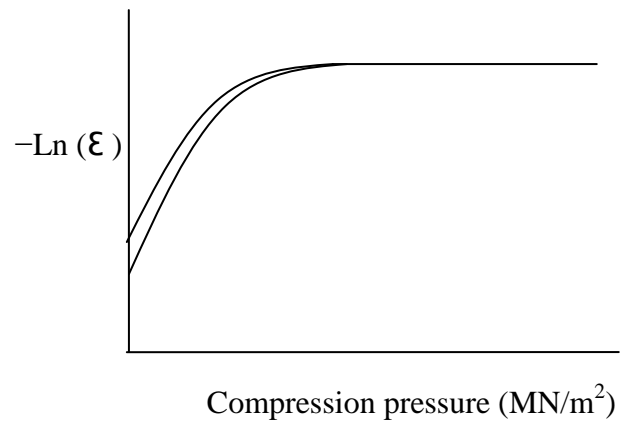
Type A



Type B



Type C



**Figure 1.1: The three different types of Heckel plots (Adapted from Fassihi, 1998)**

In Type A, the different sized fractions have different initial packing densities and the plots remain parallel as the applied pressure is increased, owing to plastic deformation. For type B, plots merge at a high pressure; this is attributed to particle fragmentation during rearrangement at low pressures. In type C, i.e., mixtures of lactose and fatty acids, curves are initially steep and then merge into a common plateau close to a solid fraction of 1 at low pressures. For this reason, type C curves have no practical use for this model.

Sodium chloride and lactose are examples of types A and B materials, respectively, while C applies to lipid materials (Fassihi, 1988). This latter behaviour (type C) is exhibited for materials that do not show particle rearrangement before plastic deformation occurs but possibly, melting of particles.

For plastically deforming materials, such as sodium chloride and potassium chloride, the measured yield pressure varied with particle size. However, for materials which deform by particle fragmentation, such as lactose and calcium carbonate, yield pressure increased with reduced particle size (Roberts and Rowe, 1986).

The Kawakita linear model is another porosity-pressure function used to characterize powder compressibility. It is expressed by Kawakita and Ludde (1971) as:

$$P/C = P/a + 1/ab \quad \dots\dots\dots(3)$$

$$C = [1-\rho_0/\rho_a] \quad \dots\dots\dots(4)$$

Where, P is the applied pressure and C is the degree of volume reduction,  $\rho_0$  is the bulk density,  $\rho_a$  is the compact apparent density, “a” is indicative of powder compressibility and

“b” determines the likelihood of volume reduction. However, the actual physical meaning of the latter is not well understood. The plot of P/C vs. P gives a straight line.

The constants “a” and “b” can be determined from the slope and intercept, respectively.

### **1.7.2 Factors that affect the Mechanical Properties of Powders**

Wong and Pilpel (1990) investigated the effect of particle shape on the mechanical properties of powders. They concluded that materials that consolidate by plastic deformation, such as Starch Rx 1500<sup>®</sup> and sodium chloride exhibit a large increase in compressibility and a significant decrease in yield values and elastic recovery in going from regular to irregular particles. This accounts for the increase in tensile strength, which is due to the increased in area of particle contact as they deform. For materials which consolidate by fragmentation such as lactose and dicalcium phosphate, particle shape has no effect on the above properties, but irregular particles fracture more than regular ones (Wong and Pilpel, 1990). The value of parameters related to compact mechanical properties, such as, tensile strength and brittle fracture index depend on the deformation mechanism, compression speed, dwell time, type and amount of lubricant, compression pressure, amount of sample and particle size employed (Narayan and Hancock, 2003).

### **1.7.3 Brittle Fracture Index**

Brittle fracture index (BFI) has been used as a measure of plastoelasticity of pharmaceutical powders (Ejiofor *et al.*, 1986; Esezobo and Pipel, 1987; Okor *et al.*, 1998; Eichie and Okor, 2002; Onyekweli *et al.*, 2004) and also to estimate the tendency of a tablet to cap or laminate under a diametral stress (Hiestand *et al.*, 1977; Alebiowu and Itiola, 2002; Iwuagu and Onyekweli, 2003; Eichie *et al.*, 2005).

BFI is measured by comparing the tensile strength ( $T_o$ ) of a tablet with a centre hole to the tensile strength ( $T$ ) of a similar tablet without a centre hole. The centre hole is a built in model defect, which simulates the actual voids formed in the tablets (due to air entrapment) during manufacture.

$$BFI = 0.5 \left( \frac{T}{T_o} - 1 \right) \dots\dots\dots(5)$$

Where  $T_o$  is the tensile strength of a tablet with a centre hole and  $T$  is the tensile strength of a similar tablet without a centre hole.

**1.7.4 Tableting Behaviour of Pharmaceutical Materials**

Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials. Generally, materials are not entirely elastic, plastic or brittle, but have some of all three characteristics. Thus, pharmaceutical materials may exhibit all three types of behaviour, with one type being the predominant response. Opposed to brittle materials, a ductile material can withstand large deformations without breaking. Brittleness is caused by progressive failure along weak points in the crystals, whereas ductility favours sliding of crystal planes. Ductility and brittleness favour bonding because new surfaces are produced and, consequently, an increase in contact area between particles occurs during compression. Picker developed a three dimensional model based on compression pressure, dwelling time and porosity data to characterize tableting behaviour of pharmaceutical materials (Picker, 2004).

## **1.8 STATEMENT OF THE RESEARCH PROBLEM**

Native starches which are undesirable for many applications (Wang *et al.*, 1993) are often modified and find applications as fillers, binders and adhesives (Daramola and Osanyinlusi, 2006). Starch has good disintegrating property, but poor compressibility and so cannot be used to formulate poorly compressible drugs. This has nullified the use as a directly compressible excipient.

Single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately (Ajay *et al.*, 2012). Also, the demand for excipients with improved functionalities, mainly in terms of flow and compression has increased due to the more recent developments occurring in the tablet manufacturing process.

The recognition of direct compression as a preferred approach to tablet manufacturing over granulation compression creates a demand for an ideal directly compressible filler-binder-disintegrant that can substitute two or more excipients. (Ajay *et al.*, 2012). Co-processed excipients, by virtue of combining properties of two or more excipients by appropriate methods to exhibit synergistic functionality improvements, fulfill the increasing demand for multifunctional excipients in direct compression.

### **1.8.1 Justification for the Study**

Nigeria is the world largest producer of cassava; therefore it is prudent that cassava starch should be the focus for modification (Daramola and Osanyinlusi, 2006).

Nyerhovwo (2004) has reported that cassava starch can perform most of the functions where maize, rice and wheat starch are currently being used. Evaluation of the industrial potentiality of excipients locally processed from locally available materials is a national aim in developing countries (Almuaikel, 2011)

Single-component excipients do not always provide the requisite performance/physicochemical properties to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Co-processed excipients on the other hand, by virtue of combining properties of two or more excipients fulfill the increasing demand for multifunctional excipients in direct compression.

### **1.8.2 Aim**

The aim of this work is to develop a co-processed excipient and evaluate its use as a direct compression material in tableting.

### **1.8.3 Objectives**

- 1 To produce and characterize direct compression starch from native tapioca starch
- 2 To prepare a direct compression excipient, using acid hydrolyzed starch: gelatin: lactose (StarGeLac)
- 3 To prepare and evaluate the properties of paracetamol and ascorbic acid tablets using StarGeLac as filler-binder-disintegrant

### **1.8.4 Scope of Work**

- Extraction and modification of Tapioca (cassava) starch by acid hydrolysis
- Physicochemical characterization of native and modified starch

- Preparation of co-excipients using modified starch: gelatin: lactose (StarGeLac) in ratios: 50:10:40, 40:10:50, 30:10:60, 20:10:70 and 10:10:80.
- Physicochemical characterization of StarGeLac
- Preparation of tablets by direct compression using StarGeLac
- Evaluation of the tableting properties of StarGeLac

## **CHAPTER TWO**

### **LITERATURE REVIEW**

#### **2.1 TABLET MANUFACTURING**

The development in the field of active pharmaceutical ingredients (API), excipients and tableting machines during the past decades has made tablet manufacturing a science and the tablets the most commonly used dosage form (Sam and Fokkens, 1997).

Since the introduction of the tableting process in the early 1840s numerous changes have taken place in tablet manufacturing. The development of high-performance tableting machines that can produce 100,000-200,000 tablets per hour among other changes has affected the manufacturing process negatively because the number of materials that can fulfill such performance requirements has decreased substantially.

Tablets are manufactured primarily by either dry granulation compression, wet granulation or direct compression. Considering the above mentioned methods, direct compression is the simplest, fastest and more economical method to study the tableting behaviour of new excipients alone or in mixtures with drugs (Rojas and Vijay, 2011).

##### **2.1.1 Direct Compression**

Direct compression (DC) involves the compression of a dry blend of powders that comprise drugs and various excipients.

In a 1993 survey (Shangraw and Demarest, 1993) of 58 pharmaceutical companies in the US about the selection of a tableting process, 41.5% of the companies indicated that direct compression was their

preferred method. On the contrary, 1.5 % indicated that they never used direct compression and 15.5 % indicated that direct compression was not appropriate for their APIs. The other 41.5 % indicated that they used both direct compression and wet granulation processes (Shangraw and Demarest, 1993).

Compacts made by direct compression disintegrate into primary particles, rather than granules, and hence, can provide faster API release (Saha and Shahiwala, 2009).

The main advantage of direct compression over other tablet manufacturing methods is its simplicity, since it requires few unit operations and utilizes much less energy, making the process more economical (Bolhuis and Chowan, 1996).

Direct compression is highly influenced by material characteristics such as flowability, compressibility and dilution potential since approximately 70 % commercial formulations contain excipients at higher fractions than APIs (Jacob *et al.*, 2007).

Shangraw (1988) estimated that about 20 % of pharmaceutical materials are directly compressible, so ideal direct compression excipient should possess adequate flow and compressibility and enable one to prepare compacts with APIs even at levels lower than 50 % excipient.

### **2.1.2 An Ideal Direct Compression Excipient**

The International Pharmaceutical Excipient Council (IPEC) defines an excipient as any substance other than the active drug or pro-drug that is included in the pharmaceutical process or is contained in a finished pharmaceutical dosage form.

A compendial excipient is a well characterized material other than the active ingredient, which possesses the desirable purity, strength and quality requirements specified by the United States Pharmacopoeia-National Formulary (USP/NF). Pharmacopoeial standards however do not take into account particle characteristics or powder properties that determine functionality of excipients (Reimerdes, 1993).

Functionality describes the activity of an excipient. A multifunctional excipient is defined as a material that has more than one functional property. Banker, (1994) reported multiple functions of many excipients and the lack of awareness that excipients from different manufacturers behave differently as reasons why control of functionality is as important as the control of identity and purity.

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

In order to ensure a robust and successful manufacture of tablets, a direct compression (DC) excipient ideally should possess the following characteristics:

- i.** excellent compressibility is required for satisfactory tableting, the mass must remain in the compact form once the pressure is removed.
- ii.** adequate powder flow is required in order to ensure homogenous and rapid flow of powder for uniform die filling. Many common manufacturing problems are attributed to incorrect powder flow, including non uniformity in blending, under or over dosage and inaccurate filling (Smewing, 2002).
- iii.** resistance to segregation during handling and storage ,

- iv.** fast compact disintegration and subsequent release of the active pharmaceutical ingredient
- v.** low sensitivity to lubricants is desired. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient.
- vi.** it should also be easily scaled up and allow higher drug loading even at low usage levels
- vii.** it should not have a complex production, should be relatively cost effective (Jacob *et al.*, 2007).

In addition, a Direct Compression multifunctional excipient should preferably have the following characteristics:

- viii.** It should be physiologically safe and it should not affect drug bioavailability;
- ix.** It should be physically and chemically stable to heat, moisture and air; it should also be compatible with the packaging material
- x.** It should not adversely affect the functional properties of other excipients and the API;
- xi.** It should have a particle size that matches the active ingredient; particle size distribution should be consistent from batch to batch. This ensures uniform blending and helps to avoid segregation (Jivraj *et al.*, 2000)
- xii.** It should possess ability to be reworked without loss of flow or compactibility; On recompression the excipient should exhibit satisfactory tableting characteristics
- xiii.** It should have pleasant organoleptic properties, be well characterized and accepted by the industry and regulatory agencies;
- xiv.** It should not contribute to the microbiological load of the formulation;

**xv.** It should be preferably white in colour.

Direct compression has the following advantages:

i. The prime advantage of direct compression over wet granulation is economic since the 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.

ii. 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.

iii. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. 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 in the case of tablets of poorly soluble API 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.

iv. 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.

v. 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 requirement of current good manufacturing practices (Rubinstein, 1998).

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

The following are limitations of direct compression:

i. 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 weight variation and content uniformity.

ii. Directly compressible excipients are the specialty products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively costly than the respective raw materials.

iii. 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 create difficulty in swallowing.

iv. All the spray-dried directly compressible adjuvants show poor rework ability 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.

v. Lubricants have a more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch Rx1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimising 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 substitution from one source to that of another is not possible (Banker, 1994).

In the design and development of a drug product, it is not uncommon to use two or more excipients/co-adjuvants to obtain a mixture with adequate tableting properties.

Excipient co-processing could lead to the formation of materials with superior properties compared to simple physical mixtures (gravity driven blending) of components (Rojas and Vijay, 2011).

Direct compression excipients or adjuvants can be prepared by various methods. Co-processing is one of the most widely explored and commercially utilized methods for the preparation of direct compression excipients.

## **2.2 CO- PROCESSING**

Co-processing is the combination of two or more established excipients by an appropriate process. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality and price (Patel and Patel, 2009). Co-processing enhances excipient functionality by retaining the favourable attributes and supplementing with newer ones, while processing the parent excipient with other excipients (Nachhaegari and Bansal, 2004). The process is generally conducted with one excipient that is plastic and another that is brittle (Nachhaegari and Bansal, 2004). A combination of plastic and brittle materials is necessary for optimum tableting performance. Co-processed excipients have been used mainly in direct compression tableting (Moreton, 1996).

Development of co-processed direct compression adjuvant starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get

optimized product with desired physico-chemical parameters and it ends with minimizing avoidance with batch-to-batch variations. An excipient of reasonable price has to be combined with the optimal amount of a functional material in order to obtain integrated product, with superior functionality than the simple mixture of components.

Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within minigranules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable (Reimerdes and Aufmuth, 1992).

The randomized embedding of the components in special minigranules minimizes their anisotropic behaviour. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression.

The use of one-body components is justified if it results in a potentiation of the functionalities over that of the mere dry blend of the components prepared by gravity mixing. This synergistic effect should improve the quality of the tablet equally in all aspects ranging from hardness to dissolution and/or stability.

Excipient mixtures in co-processing are produced to make use of the advantages of each component and to overcome specific disadvantages, if any. Most important characteristics are the binding and blending properties of the co-processed excipients, which must be better than those of a physical mixture of the starting materials.

Cost is another factor to be considered in the selection of co-processed product. A major limitation of co-processed excipient mixture is that the ratio of the excipients in a mixture

is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the API and the dose per tablet under development (Bolhuis and Chowhan, 1996). Co-processed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler /binder will not be accepted by the pharmaceutical industry until it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients. Although the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are co-processed products, they are commonly considered as single components and are official in USP/NF.

## **2.3 EXAMPLES OF DIRECTLY COMPRESSIBLE EXCIPIENTS**

### **2.3.1 Soluble Fillers**

#### **2.3.1.1 *Lactose***

It is one of the main constituents of human and mammalian milk. Lactose is produced from whey, as a by-product of cheese and casein production. Lactose may appear in different polymorphs depending on the crystallization conditions. Each polymorph has its specific properties,  $\alpha$ -lactose monohydrate has very hard crystals and is non hygroscopic.

Lactose is the most widely used filler-diluent in tablets. The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, easy in the availability, bland taste, low hygroscopicity, excellent physical and chemical stability and water solubility (Guo, 2004). Lactose from different suppliers exhibits different properties and therefore could not be treated as interchangeable in direct compression formulations. The compaction profile of the lactose samples depends on the machine speed (Whiteman and Yarwood, 1998).

Crystalline lactose mainly consolidates by fragmentation and amorphous lactose by plastic deformation. Tablets containing amorphous lactose show high crushing strength with

increasing water content (Lerk, 1993). Lactose based tablets exhibit better stability than mannitol and cellulose containing tablets at 40 °C and 90 % RH over a 10 week period. The amorphous lactose yields tablets of higher tensile strength than crystalline lactose. Tensile strength increases with reduced particle size (Sebhatu and Alderborn, 1999).

#### **2.3.1.2 *Spray-dried lactose***

Spray-dried lactose is produced by spray drying the slurry containing lactose crystals.

The final product contains mixture of crystals of lactose monohydrate and spherical agglomerates of small crystals held together by glass or amorphous material. The former contributes fluidity and the latter gives the compressibility to the product. It has excellent flow and binding properties. It deforms plastically compared to the same sized  $\alpha$ -lactose monohydrate particles (Gohel and Jogani, 2005). A disintegrant is required in the formulations containing spray-dried lactose. The tablets require a lubricant, but the lubricant does not affect binding. It has poor reworkability (Gohel and Jogani, 2005).

### **2.3.2 Cellulose Derivatives**

#### **2.3.2.1 *Microcrystalline Cellulose***

Microcrystalline cellulose (MCC) is purified partially depolymerized cellulose, prepared by treating  $\alpha$ -cellulose with mineral acids. Microcrystalline cellulose occurs as a white odourless, tasteless crystalline powder composed of porous particles of an agglomerated product.

Apart from its use in direct compression, microcrystalline cellulose 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, microcrystalline cellulose is available under the brand names Avicel, Emcocel, Vivacel etc.

### **2.3.2.2 Hydroxy propyl cellulose**

Alvarez-Lorenzo (2001) reported that the difference in flow and compaction properties, the mechanical and micro-structural properties of the tablets prepared from various grades of low-substituted hydroxypropyl celluloses is attributed to difference in the specific surface.

### **2.3.2.3 Ethyl Cellulose**

Ethyl cellulose is a non-toxic, biocompatible and biodegradable polymer (Murtaza *et al.*, 2009). Crowley *et al.*,(2004) reported that the release rate of guaifenesin from ethyl cellulose matrix tablets prepared by direct compression was dependent on the ethyl cellulose particle size, and compaction force.

## **2.3.3 SUGARS**

### **2.3.3.1 Sucrose**

Sucrose is widely used as filler in chewable tablets and as a binder in wet granulation. Bowe (1998) reported a co-processed sucrose based directly compressible adjuvant containing 95 % sucrose and 5 % sorbitol. The author demonstrated that tablets with higher strength, which disintegrate faster can be produced using this material than tablets made with commercially available directly compressible sugars.

### **2.3.3.2 Emdex and Maltrin**

Emdex is produced by hydrolysis of starch and consists of aggregates of dextrose microcrystals intermixed with a small quantity of higher molecular weight sugars. Emdex occurs as white, free flowing, porous spheres which are water soluble and non-hygroscopic. Emdex is generally used in directly compressible chewable tablets because of its sweet taste. It has good binding properties and slight lubricant sensitivity. Tablets containing theophylline prepared using Emdex exhibited higher mechanical strength, faster

disintegration and rapid drug release than the tablets prepared from Maltrin M150 (Ahjel and Lupuliasa, 2008).

### **2.3.3.3 Mannitol**

It is water soluble, non-hygroscopic and produces a semi-sweet, smooth, cool taste. It can be advantageously combined with other direct compression excipients. Preparation and evaluation of a mannitol and cellulose based directly compressible excipient, using freeze-thawing technique indicated that the physical modification of mannitol and cellulose resulted in considerable improvement in its functionality as directly compressible material (Patel and Patel, 2009).

### **2.3.4 Starch**

Mullick et al, (1992) as reported by Gohel and Jogani, (2005) concluded that dextrinized rice, corn, wheat and tapioca starches prepared by dextrinization exhibited very good flow, compression properties and disintegration qualities for direct compression tableting; dextrinized tapioca starch was found to be the best.

Due to improved flowability and compressibility pregelatinized starch can be used as a binder in direct compression (Heinze, 2002).

#### **2.3.4.1 Starch Rx 1500**

It is a directly compressible, free flowing, USP grade of partially hydrolyzed corn starch. It is prepared by subjecting corn starch to physical compression or shear stress in high moisture conditions causing an increase in temperature and a partial gelatinization of some of the starch granules (Ahjel and Lupuliasa, 2008). The product consists of about 5 % free amylose, 15 % amylopectin and 80 % unmodified starch. It provides fair to good binding properties and dilution potential, but requires high pressures to produce hard

tablets. It also produces a dense tablet with good disintegration properties (Ahjel and Lupuliasa, 2008).

Uni-Pure is a fully gelatinized maize starch. It gives tablets with strong binding properties and significantly faster disintegration (Heinze, 2002). It was also reported that co-processed polymethacrylic acid starch was used as a pH-sensitive, directly compressible excipient for controlled delivery of model drugs amoxicillin and rifampicin (Clausen and Bernkop-Schnurch, 2001).

### **2.3.5 Dicalcium Phosphate Dihydrate**

Dicalcium phosphate is the most common inorganic salt used in direct compression as a filler-binder. Advantage of using dicalcium phosphate in tablets for vitamin and mineral supplement is the high calcium and phosphorous content. Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.4, which precludes its use with active ingredients that are sensitive to even small amount of alkali (i.e. ascorbic acid). It exhibits high fragmentation propensity (Ahjel and Lupuliasa, 2008). Water of crystallization of dicalcium phosphate dihydrate could possibly be released during processing and thus chemically interact with hydrolysable drug (Schlak *et al*, 2001).

Schüssele and Bauer-Brand (2003) characterized the flowability of commonly used directly compressible adjuvants using Sotax Powder Flow Tester from good flow to poor flow in following order: Emcompress, Tablettose 80, Fujicalin, Tablettose 100, Starch and Avicel.

## 2.4 EXAMPLES OF CO-PROCESSED DIRECTLY COMPRESSIBLE EXCIPIENTS

**Table 2.1: Co-processed Directly Compressible Excipients**

Co-processed Excipients	Trade name	Manufacturer	Added advantage
Lactose, 3.2% kollidon 30, Kollidon CL	Ludipress	Basfag, Ludwigshafen, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed.
Lactose 25% cellulose	Cellactose	Meggle GMBH & Co Kg Germany	Highly compressible, good mouth feel, better tablet at low cost
85% $\alpha$ Lactose, mh 15 % maize starch	Starlac	Roquette, France	Good flow, low lubricant sensitivity
Sucrose 3% dextrin	DiPac	Penwest Pharm company, USA	Directly compressible
Microcrystalline cellulose, silicon Dioxide	Prosolv	Penwest Pharm company, USA	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability

(Adapted from Marwaha *et al.*, 2010)

## 2.5 STARCH

Starch has been identified by the Joint Conference on excipients as one of the top ten excipients used by the Pharmaceutical industry (Adebayo and Itiola, 2003). Itiola and Odeku, (2005) have reported the significant potential of several starches obtained from different food crops as excipients in tablet formulations.

In Nigeria, cassava is a staple food for both rural and urban areas and in recent years it has been transformed from being a subsistent crop to an industrial cash crop.

Starch's use now extends far beyond its original design as a source of biological energy. Practically every industry in existence uses starch or its derivatives in one form or another. In foods and Pharmaceuticals, starch is used to influence or control such characteristics as texture, moisture, consistency and shelf stability. It can be used to bind or to disintegrate; to expand or to densify; to clarify or to opacify; to attract moisture or to inhibit moisture; to produce smooth texture or pulpy texture, soft coatings or crisp coatings. It can be used to stabilize emulsions or to form oil resistant films. Starch truly serves as a multifunctional ingredient in the food industry (Miyazaki *et al.* 2006).

Starch is a naturally occurring, biodegradable, cheap, renewable, and abundantly available polysaccharide molecule. The different botanical sources of starches are cereal (wheat, corn, rice, barley, oat, sorghum, millet, and rye), legume (lima bean, garbanzo bean, lentil bean, red kidney bean, navy bean, faba bean, mung bean, pinto bean, adzuki bean, field pea, cowpea, beach pea, green pea, grass pea, soybean, and groundnut), some under-utilized legume (sword bean, jack bean, and pigeon pea), root and tuber (cassava, potato, yam, cocoyam, and sweet potato), and unripe fruit (banana, plantain, mango, and pawpaw).

Starch granules are mainly found in seeds, roots and tubers, as well as in stems, leaves, fruits and even pollens. The granules occur in all shapes and sizes (spheres, ellipsoids, polygon, platelets, and irregular tubules).

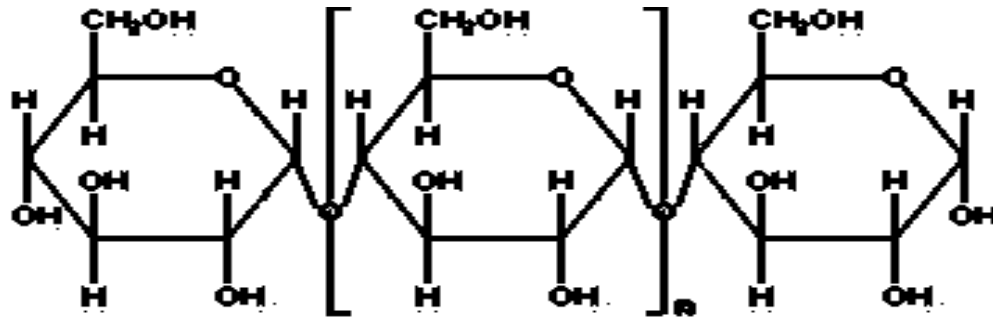
Starch is extracted in its native form using various procedures that separate starch from other constituents of the starch source. The recovered starch is often washed and dried before further processing.

### **2.5.1 Structure of Starch**

Starch is a carbohydrate polymer made up of hydroglucose units linked primarily through alpha- 1, 4glucosidic bonds (Figure 2.1). Diversity stems from a starch's mixture of two types of polymers- amylose (AM) and amylopectin (AP). The difference in their properties and functionality plays a central role in the versatility of starch in foods. AM has a high tendency to retrograde and produce tough gels and strong films. In contrast, AP, when dispersed in water, is more stable and produces soft gels and weak films (Perez and Bertoft, 2010). It is possible for entanglements to occur between AM and AP, along with the presence of minor components (proteins and lipids), all also have important impacts on the physicochemical properties of the starches from different botanical origin. Physical and chemical modifications lead to other differences, which expand the uses of starch.

In amylose, the glucose molecules are linked together in a linear fashion and it is made up of about 3000-6000 glucose molecules joined together. It is however reported to contain few branch networks (Nep *et al*, 2012). Amylopectin on the other hand has a branched structure due to the different kinds of linkage between two glucose units. The  $\alpha$ -1,4- linkages in amylopectin serves as the backbone while the  $\alpha$ -1,6- serves as the branching point.

In native (unmodified) starch, the amylose molecules and the amylopectin region with chain branching forms the amorphous region while the outer amylopectin linear chains coiled into double helices forms the crystalline region (Nep *et al*, 2012).



n = number of repeating glucose units.

Fig 2.1: Structure of starch (Adapted from Nep *et al.*, 2012)

## **2.6 MODIFICATION OF STARCH**

Native starch irrespective of their source are not desirable for many applications (Wang *et al.*, 1993) because of their inability to withstand processing conditions such as high temperature, high shear rate, freeze-thaw variation, and different pH. They also have large molecular size, insolubility in water, instability in the viscous solution and are susceptible to microorganisms (Trease and Evans, 1983); they also have tendency to easily retrograde and undergo syneresis and therefore form unstable pastes and gels. (Ashogbon and Akintayo, 2014).

In order to improve the desirable functional properties and broaden their range of physicochemical properties, modifications are often desired (Wang *et al.*, 1993). The functionality of starch can be modified through physical, chemical, enzymatic, biotechnological, or their combinations (Ashogbon and Akintayo, 2014).

### **2.6.1 Properties of Starch Granules**

Microscopically, granules vary in size, shape and composition depending on the source of starch. The shape of the granule can be oval, spherical and polygonal or truncated (Wang *et al.*, 1993).

Amylose stains a blue/black colour in the presence of iodine due to the formation of a complex in which the amylose forms a helical coil around iodine molecules.

Gelatinisation is a term that describes hydration in the starch granule leading to irreversible granule swelling that enhances viscosity. Cooking and cooling of starch causes retrogradation. This is as a result of dispersal of the simpler and more linear form of starch,

which is amylase, making it more mobile resulting in more ordered molecular structure. Consequently, a three dimensional frame, an opaque gel, is formed.

### **2.6.2 Aim of Modification**

The aim of starch modification is to stabilize starch granules during processing and make starch suitable for many food and industrial applications (Ashogbon and Akintayo, 2014).

Starch modification does not only decrease retrogradation, gelling tendencies of pastes and gel syneresis but also improves paste clarity and sheen, paste and gel texture, film formation and adhesion ( Whistler and BeMiller, 1997).

In the native state, starch is insoluble in cold water and consists of granules whose size, composition, physiochemical and functional properties depend on the botanical origin (Rahman, 2007) and culture conditions (Jaisut, 2008). These properties can change depending on the treatment to which the granules are subjected. Properties like flowability, gelatinizing temperature, gel viscosity, hydrophilicity, or swelling characteristic all improve with modification (Lefnaoui and Moulai-Mostefa, 2015).

### **2.6.3 Methods of Modification**

There are many different methods of modifying starch biopolymers (Piacquadio *et al.*, 2000).

#### **2.6.3.1 Physical modification**

Physical modification of starch can improve water solubility and reduce particle size. The methods involve the treatment of native starch granules under different

temperature/moisture combinations, pressure, shear, and irradiation. Physical modification also includes mechanical attrition to change the physical size of starch granules. Physical modification techniques are generally given preference as they do not involve any chemical treatment that can be harmful for human use.

Physical modification is simple, cheap, and safe because it requires no chemicals or biological agents. Classification of starches from different botanical sources based on physical modifications depends on whether the molecular integrity of the starches are destroyed or preserved after the modification (Ashogbon and Akintayo, 2014).

#### I. Pre-gelatinized starch (PGS):

Pre-gelatinized starches (PGS) refer to cooked starches that are prepared by complete gelatinization and drying. Destruction of the granular structure is the major physical event leading to the rearrangement of intra- and inter-molecular hydrogen bonding between water and starch molecules resulting in the collapse of molecular orders within the starch granules (Mazoobi *et al.*, 2011). The main properties of PGSs are increased water absorption and water solubility upon dispersion in cold water; this leads to “instant starch slurries” without heating. Depending on the method of production, condition and source of starch, the produced PGS has different properties (Kalogianni *et al.*, 2002).

Pre-gelatinization can be brought about by drum drying, spray drying, and extrusion cooking. Of these, drum drying is a common industrial practice for pre-gelatinization (Anastasiades *et al.*, 2002) and PGSs have been mainly applied as thickener in many food products.

## **II.** Hydrothermal modifications

Two hydrothermal treatments that modify the physicochemical properties of starch without destroying the granule structure are annealing (ANN) and heat moisture treatment (HMT). Essentially, hydrothermal modification can only take place when the starch polymers in the amorphous phase are in the mobile rubbery state of the semi-crystalline region. A few minutes are sufficient to bring about detectable changes in the physicochemical properties of the starch. Both HMT and ANN occur below the onset temperature of gelatinization and have been shown to modify starch structure and properties to different extents (Jayakody and Hoover, 2008).

## **III.** Non-thermal physical modification of starches

Most foods are thermally preserved by subjecting the products to boiling (or even higher) temperatures for a few seconds to several minutes. These high-energy treatments usually diminish cooking flavours, and cause loss of vitamins, essential nutrients, and food flavours in the product. To overcome or minimize such disadvantages, the concept of non-thermal treatment was born.

Recent studies have indicated that different non-thermal treatments affect the physicochemical properties of starch differently. Some of the non-thermal processes are conducted at high hydrostatic pressure (HHP) (Wang *et al.*, 2008).

Generally, HHP treatment restricts the swelling power of starch granules, so that their viscosity is lower compared to heat processed starches (Nasehi and Javaheri, 2012). Furthermore, starch gelatinization is achievable at room temperature or below 0°C with

HHP treatment of starches from different botanical sources. It was reported that the properties of starch pastes and gels obtained under high pressure treatment differed from those of the heat-gelatinized ones (Stolt *et al.*, 2001).

### **2.6.3.2 Chemical modification**

Chemical modification involves the introduction of functional groups into the starch molecules, resulting in markedly altered physicochemical properties. Such modification of native granular starches profoundly changes the proximate compositions, gelatinization, retrogradation, and pasting characteristics. Chemical modification is intended to facilitate intra- and inter-molecular bonds at random locations in the starch granule for their stabilization. The chemical and functional properties achieved by modified starches depend, *inter alia*, on starch source, reaction conditions (reactant concentration, pH, reaction time, and the presence of catalyst), type of substituent, degree of substitution (DS), and the distribution of the substituent in the starch molecule (Wang and Wang, 2002). Modification is generally achieved through derivatization, such as acetylation, cationization, oxidation, acid hydrolysis, and cross-linking. These techniques are however limited due to issues concerning consumers' safety and the environment. There is an evolving new trend called dual modification, which involves the combination of physical and chemical agents, e.g., microwave-assisted acetylation or HHP-assisted phosphorylation (Ashogbon and Akintayo, 2014).

#### **I Cationic starch**

Cationic starch is produced from the reaction of starch with reagents containing amino, imino, ammonium, sulphonium, or phosphonium groups. The free hydroxyls of the native

starch is commonly altered by using cationic monomer such as 2,3-epoxypropyltrimethylammonium chloride (ETA) or 3-chloro-2-hydroxypropyltrimethyl ammonium chloride (CTA) under wet or dry processes or a process in between the two processes.

## **II** Cross-linked starch

Cross-linking has been used to modify native starch utilizing various cross-linking agents such as sodium trimetaphosphate (STMP), sodium tripolyphosphate (STPP), epichlorohydrin (ECH), and phosphoryl chloride ( $\text{POCl}_3$ ) (Jayakody and Hoover, 2008). Other cross-linking agents are adipic–acetic mixed anhydride, and mixture of STMP and STPP. ECH is no longer used for food grade manufacturing in the U. S. because the chlorohydrins are carcinogens. Chung *et al.*, (2004) reported cross-linking of starch to be affected by many factors, such as starch source, cross-linking reagent concentration and composition, the extent of substitution, pH, reaction time and temperature.

## **III.** Acetylated (Ac) starch

Acetylation is one of the common chemical method of starch modification, it is achieved by esterification of native starch with either acetic anhydride or vinyl acetate in the presence of alkaline catalyst, e.g., NaOH, KOH,  $\text{Ca}(\text{OH})_2$ ,  $\text{Na}_2\text{CO}_3$  ( Wang and Wang, 2002).

## **IV.** Acid modified starch

Acid modification is one of the oldest methods of starch modification, and the derived degradation products have a vast application potential. Acid-modified starch is widely used

in the food, paper, and textile, pharmaceutical, and other industries (Atichokudomchai *et al.*, 2001). The method for the manufacture of acid-thinned starch entails treating concentrated starch slurry (36–40 % solid) with mineral acid (HCl or H<sub>2</sub>SO<sub>4</sub>) at temperature below the gelatinization temperature for specific period depending on the desired viscosity or degree of conversion (Thirathumthavorn and Charoenrein, 2005). The mechanism of acid hydrolysis involves the attack of the glycosidic oxygen atom of the native starch by the hydroxonium ion and this result in cleavage and depolymerization. Acid hydrolysis of starch proceeds randomly, cleaving both  $\alpha$ -1, 4 and  $\alpha$ -1, 6 linkages and shortening the chain length with time. Alpha-1, 4 linkage and the amorphous regions containing  $\alpha$ -1, 6 linkages are more accessible to acid penetration and hydrolysis. Acid modification involves a two-stage attack on the starch granules. Acid attacks both amylase (AM) and amylopectin (AP) during the early stages of acid treatment but preferentially attacks the amorphous regions of the starch granule in the first stage and then attacks the more crystalline sections at slower rate (Wang and Wang, 2002).

#### **2.6.4 Studies on Modified Starches**

Native starches, irrespective of their source, are undesirable for many applications (Wang *et al.*, 1993). In order to improve on desirable functional properties, native starches are often modified. Modified starches have wide applications as binders, fillers, emulsion stabilizers, consistency modifiers and adhesives (Daramola and Osanyinlusi, 2006).

Modification of starch is an ongoing process as there are many possibilities. There is a huge market for the many new functional and value added properties resulting from these modifications (Kaur *et al.*, 2012)

Mitrevej *et al.*, (1996) characterized the compression behaviour of spray dried rice starch (SDRS) as well as pregelatinised starch (PS), and microcrystalline cellulose using Heckel analysis and SDRS was reported to have both good compactibility and flowability making it suitable for direct compression.

Okafor *et al.*, (2000) also reported a significant effect of modified starch on the drug release profile of tablets formulated while carrying out a study on modified starches used in direct compression.

Eichie and Okor (2002) have reported that acid treatment of cassava ( tapioca) starch rendered the starch more plastic and thus compressible.

Alebiowu and Itiola (2003) measured the effects of pregelatinization of native sorghum and plantain starches on the mechanical properties of paracetamol tablet formulations in comparison with corn starch BP. The tensile strength (TS) and brittle fraction index (BFI) were affected by pregelatinization of the starches.

Alebiowu and Itiola (2003) also reported that changing from native to pregelatinized starch disintegrants effected a decrease in disintegration time of tablets.

Adebowale and Lawal (2003) studied the functional properties and retrogradation behaviour of mucuna bean starch oxidized with sodium hypochlorite. They reported decrease in the pasting temperature, peak viscosity, breakdown viscosity, transition temperatures, gelatinization and retrogradation enthalpies upon oxidation.

Ofoefule *et al.*, (2004) studied the effects of physical ( pregelatinization) and chemical modification (acid hydrolysis) on the disintegration and dissolution attributes of *Tacca involucrata* starch. Pregelatinization conferred a better disintegration property on the starch than acid hydrolysis.

Daramola and Osanyinlusi (2006) have reported the effect of *Zingiber officinale* Roscoe belonging to same botanical family as *Cucurma longa* on cassava starch. The paper reports the effects of *Cucurma longa* grates on pasting and other physicochemical properties of cassava starch with and without lactic acid, with a view to using the active components in *Cucurma longa* grates as natural product modifying agents for non-fermented and fermented cassava starch.

Odeku *et al.*, (2008) investigated the material and tablet formation properties of thermally modified (by pregelatinization) forms of four *Dioscorea* starches. The results showed that the compressibility and flowability of the starches were improved by pregelatinization.

Recent studies by Han *et al.*, (2009) reported that different treatments affect the physicochemical properties of starch differently.

Recently, cola starch was isolated from *Cola nitida (rubra spp)* and characterized (Omojola *et al.*, 2011). Its physicochemical characterization showed high industrial potentials in the pharmaceutical, food and confectionary industries. The starch was then modified through acid hydrolysis; physicochemical properties were compared with that of the native starch and other acid thinned starches.

## CHAPTER THREE

### MATERIALS AND METHODS

#### 3.1 MATERIALS

##### 3.1.1 Chemicals and Reagents

- Cassava tubers (Kawo market, Kaduna state, Nigeria)
- Ludipress® (BASF, Germany)
- Starlac® (Roquette, France)
- Gelatin (M&B, England, UK)
- Lactose (BDH Chemicals LTD, Poole, England, UK)
- Stearic acid (TITAN BIOTEK, England, UK)
- Paracetamol powder (BDH Chemicals LTD, Poole, England, UK)
- Talc (BDH Chemicals LTD, Poole, England, UK)
- Xylene (SIGMA, Germany)
- Hydrochloric acid (MERCK, Germany)
- Ethanol (JHD, England, UK)
- Iodine crystals (BDH Chemicals LTD, Poole, England, UK)
- Ascorbic Acid powder (BDH Chemicals LTD, Poole, England, UK)

## **3.2 METHODS**

### **3.2.1 Collection and Identification of Cassava Tubers**

Cassava tubers were obtained from Kawo market, Kaduna state, Nigeria and were taken to the herbarium section of the Department of Biological Sciences, Ahmadu Bello University (A.B.U), Zaria, for identification. The tubers were allocated a specimen number of 4328.

### **3.2.2 Extraction of Cassava starch (Linus, 1995; Hasan *et al.*, 2014)**

Fresh tubers of cassava were washed and peeled, then cut into smaller pieces, washed and then grated. These were reduced to a fine pulp using a blender (Electric blender, model MJ – 176 NR, Matsushita Electric Industrial Co., Ltd, Osaka, Japan). The pulp was passed through a piece of calico cloth with sufficient distilled water. This was allowed to settle and the excess water decanted. The suspension of cassava starch was washed several times with 0.1 N NaOH, with excess alkali decanted each time, to neutralize the acidity of the starch. Then the suspension of starch in distilled water was then centrifuged. The tightly packed starch was then collected and allowed to dry in an oven at 40 °C. The dried starch was passed through 180 µm sieve for size reduction.

### **3.2.3 Preparation of acid modified starch**

Preparation of acid modified starch from cassava was done using the process described by the World Intellectual Property Organisation, WIPO (1997). A 36 % w/v aqueous suspension of the starch was made and poured into a stainless steel container. To this suspension, 45.4 ml of 6 N HCl was added drop wise with stirring. The mixture was heated for 24h at a temperature below 55° C over a water bath with a thermostat. After cooling, the acid modified starch product was separated from the reaction medium by means of

vacuum filtration and the supernatant decanted. The starch was washed in ratio 1:1 with water and then re-suspended in 400 ml water. The suspension was brought to pH of 6 with sodium hydroxide solution. The starch product was separated by means of vacuum filtration. The wet starch product was then suspended in 2 litres of ethanol and stirred for 30 min after which the starch was removed and dried in the oven at  $30\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$ .

### **3.3 PHYSICOCHEMICAL TESTS CARRIED OUT ON THE STARCH**

#### **a. Determination of organoleptic properties**

These include taste, odour, colour and powder texture.

#### **b. Ash value**

The remaining residue after the combustion of 2 g of starch in a silica dish at  $450\text{ }^{\circ}\text{C}$  was weighed. The percentage of ash was then calculated with reference to the starch.

#### **c. Identification Test for Starch**

Two drops of N/10 iodine solution were added to 10 ml of boiled and cooled aqueous starch solution. The solution was shaken. The colour of the mixture was observed and recorded.

#### **d. Determination of pH**

Two grams of starch was weighed and added to 100 ml of distilled water. This was shaken for 5 min. The pH of the supernatant liquid was determined using a pH meter (No. 378487, Eutech instruments, Singapore).

#### **e. Determination of solubility**

The following solvents were used: cold distilled water, hot distilled water, chloroform, acetone and ethanol. Two grams of starch was dispersed in about 10 ml each of the above solvents and kept for about 12 h. The clear supernatant was withdrawn and heated to dryness over a water bath. The weight of the residue relative to the volume of the solution was determined as the percentage solubility of starch in the solvent.

#### **f. Microscopy**

About 1 mg of starch was mounted on a slide, in glycerol. The size of the grains of starch was estimated using the calibrated eyepiece micrometer and the shape of the particles of starch were observed.

#### **g. Determination of amylose/amylopectin fraction**

This was carried out as described by Barry, (2007). 5 ml of 10 %  $\text{w/v}$  aqueous slurry of starch and 55 ml of 0.16 M sodium hydroxide was introduced into a flask and swirled gently until the suspension clears. After 5 min, 15 ml of 5 %  $\text{v/v}$  sodium hydroxide in 0.06 M hydrochloric acid was added and mixed well. The precipitate was harvested by centrifugation at 10,000 rpm for 15 min. The supernatant was stored in a separate flask and the deposit was washed by re-suspending it in 20 ml of 1 % sodium chloride and re-centrifuging after standing overnight. The original supernatant contains amylase that is precipitated by saturating it with 1- butanol and allowing it to stand for a few hours and collected by centrifugation at 5,000 rpm for 15 min. The precipitate was then dried in a Gallenkamp oven at 40 °C then weighed.

### **3.4 EVALUATION OF BASIC POWDER PROPERTIES OF ACID MODIFIED STARCH**

These tests will be carried out as described.

#### **3.4.1 Particle size analysis**

Test sieves ranging from 500, 250, 150, 90 and 75  $\mu\text{m}$  were arranged in a descending order. A 20 g quantity of starch powder was placed on the top sieve. Subsequently the nest of sieves was shaken for 15 min on the sieve shaker (Endecott, Serial No. 746,1 MK 11, England ). The weight of starch retained on each sieve was determined. The readings were taken in triplicate and the mean determined.

#### **3.4.2 Determination of true density**

An empty 50 ml pycnometer bottle was weighed (weight= $W$ ), then filled with xylene , taking care to wipe off excess. The weight of the filled bottle was taken ( $W_2$ ). A 2 g quantity of the starch sample was weighed ( $W_3$ ) and transferred into the pycnometer bottle. The excess solvent was wiped off before weighing the bottle again ( $W_4$ ). The true density  $\rho_t$  ( $\text{g}/\text{cm}^3$ ) was calculated using the equation:

$$\rho_t = \frac{(W_2 \times W_3)}{50(W_3 - W_4 + W_2 + W)} \dots\dots\dots(6)$$

#### **3.4.3 Flow rate**

Fifty (50) grams of the starch was poured into the funnel of the Erweka TA-3R flowameter (Erweka Apparatebau GmbH, Heusenstamm Kr. Offenbach/Main GDT, Germany). The apparatus was started and the time taken for the powder to flow through the orifice was

recorded. The flow rate, which is the quantity of material (in gram) that passes through the orifice in one second, was thus determined. The reading was taken in triplicate and the mean determined.

#### 3.4.4 Angle of repose

The static angle of repose (a) was measured according to the fixed funnel and free standing cone method and the tangent of the angle of repose (a) calculated using the equation:

$$\text{Tan } a = 2h/D \quad \dots\dots\dots(7)$$

h is the height of the heap of powder and D is the diameter of the base of the heap of powder.

#### 3.4.5 Bulk and Tapped densities

Ten gram quantity was placed in a 50 ml measuring cylinder and the volume  $V_o$  occupied by each of the samples was determined. After 500 taps, the occupied volumes,  $V_{500}$  were determined. The bulk and tapped densities were calculated as the ratio of weight to volume ( $V_o$  and  $V_{500}$ ) respectively.

Carrs index (CI) was determined using the equation below:

$$CI = (TD - BD/TD) \times 100\% \quad \dots\dots\dots(8)$$

CI is Carrs index, TD is tapped density and BD is bulk density.

#### 3.4.6 Powder porosity

This was derived from the values of the true density using the equation below:

$$\epsilon = 1 - BD/\rho_t \quad \dots\dots\dots(9)$$

BD is bulk density,  $\rho_t$  is the true density and  $\epsilon$  is the porosity.

### 3.4.7 Hydration capacity

A 1 g sample size each was placed in 4 individual 15 ml plastic centrifuge tubes; 10 ml distilled water was added before the tubes were stoppered. The contents were mixed on a vortex mixer for 2 min. They were then allowed to stand for 10 min then immediately centrifuged. The supernatant was carefully decanted before the sediment was weighed. The hydration capacity was taken as the ratio of the weight of the sediment to the dry sample weight

### 3.4.8 Swelling capacity

This was determined at the same time as the hydration capacity determination using the equation below:

$$S = (V2 - V1) / V1 \times 100 \% \dots\dots\dots(10)$$

S is the swelling capacity %, V2 is the volume of the hydration or swollen material and V1 is the tapped of the material before hydration.

### 3.4.9 Moisture sorption capacity

Two gram of starch was weighed and spread evenly over the surface of a petri dish of 70 mm size. It was then placed in a desiccator containing distilled water in its reservoir (RH = 100%) at room temperature. The weight gained by the exposed samples at the end of a 5-day period was recorded and the amount of water sorbed was calculated from the weight difference.

#### **3.4.10 Loss on drying /Moisture content**

Five gram of the starch sample was transferred into a petri dish and dried in an oven at 105 °C till a constant weight was obtained. The % moisture content was determined as the ratio of weight of the moisture loss to weight of sample, expressed as a percentage.

### **3.5 PREPARATION OF CO-PROCESSED EXCIPIENTS CONSISTING OF ACID HYDROLYZED STARCH- GELATIN- LACTOSE**

These procedures were carried out using co-drying method (Olowosulu *et al.*, 2011).

Five batches of suspensions were prepared from mixtures of acid modified starch, gelatin and lactose in different ratios of starch: gelatin: lactose 52.5:5:42.5; 42. 5:5:52.5; 32.5:5:62.5; 22.5:5:72.5 and 12.5:5:82.5. The required proportions of acid modified starch were dispersed in distilled water so as to obtain a final solid content of 40 % w/w. The required amount of gelatin and lactose were also added to distilled water and mixed with the starch slurries and stirred for 10 min continuously. The mixtures were then heated in a water bath at 55 °C for 15 min (below gelatinization temperature). The resultant materials were air dried on trays and further dried in a hot air oven (Gallenkamp Oven BS size three, England) at 40 °C for 48 h.

### **3.6 EVALUATION OF THE POWDER PROPERTIES OF THE PREPARED CO-PROCESSED EXCIPIENTS**

**3.6.1 This Will Be Done As Described In Section 3.4, Above. In Addition, The Following Tests Were Also Carried Out:**

#### **3.6.2 Fourier Transform Infrared (FTIR) Studies**

Fourier transform infrared (FTIR) spectra were recorded on a FTIR spectroscopy using the

instrument Nicolet iS10, Thermo Scientific (USA), in the frequency range of 400- 4000  $\text{cm}^{-1}$ . A 2.0 g of each individual sample as well as the mixture of drug and excipients were ground and mixed thoroughly with potassium bromide for 3 - 5mins in a mortar and pelletized using a barrel and bolts with spanners at a pressure of 1 ton/ $\text{cm}^2$ . The pellets were placed in light path and spectrum was obtained and reviewed for evidence of any interactions.

### **3.6.3 Differential Scanning Calorimetry (DSC) Studies**

Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan) was used for thermal analysis of drug and mixture of drug and excipients in a 1:1w/w ratio. Individual samples of drug and excipients were weighed to about 5mg in DSC aluminium pan. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50-300 °C. Heating rate of 20 °C $\text{min}^{-1}$  was used and the thermogram obtained was reviewed for evidence of any interactions ( Bozdag *et al.*, 2011)

### **3.6.4 Dilution Potential**

This is the amount of poorly compressible drug that can be satisfactorily compressed into a tablet with co-processed excipient. The drugs and the excipient were mixed in various ratios. They were then compressed at varying compression loads on a single punch Tableting Machine (Erweka Apparatebau West Germany) (Table 3.1). The crushing strengths of the compacts, were then determined.

### **3.6.5 Compaction Studies**

Compacts of each material weighing 500 mg were prepared by compressing them for 30 s with pre-determined loads (28.31; 56.62; 84.93; 113.25; 141.88; 169.88; 198.18 and 226.5

MN/m<sup>2</sup>) on a hydraulic hand press (Apex Hydraulic Presses, Apex Construction Limited, London WI and Dartford). Before each compression, the 10.5 mm die and flat faced punches were lubricated with 2 % w/v dispersion of magnesium stearate in ether-ethanol (1:1) solution. After ejection the compacts were stored in a dessicator for 24 h to allow for elastic recovery and hardening preventing false low yield values (Aulton, 2007). Their weights (*W*) and dimensions were then determined to within ± 1 mg and 0.01 mm respectively.

Heckel plots of  $\ln(1/1-D)$  versus applied pressure (*P*) and Kawakita plots of *P/C* versus *P* were used to evaluate the behaviour of the powders on compression.

### 3.6.6 Determination of tablet tensile strength

This is the stress needed to fracture a tablet by diametral compression. Tensile strength was determined using the equation stated below (Fell and Newton, 1970):

$$T = 2P/\pi Dt \quad \dots\dots\dots(11)$$

Where *P* is the load that causes tensile failure of a tablet of diameter, *D* and thickness, *t*. The mean fracture load values were used to calculate the values of *T* for the tablet formulations.

### 3.6.7 Determination of brittle fracture index (BFI):

This is a measure of the tablet tendency to laminate or cap during manufacture. It is given by the equation developed by Hiestand *et al.*, (1977).

$$BFI = 0.5 (T/T_0 - 1) \quad \dots\dots\dots(12)$$

Where  $T$  and  $T_0$  are the tensile strengths of tablets with and without a hole, respectively.

### **3.7 FORMULATION STUDIES**

Six batches of tablets were produced by direct compression (Table 3.1), three batches each for paracetamol and ascorbic acid tablets. The tablets were formulated using the co-processed excipient of filler/binder/disintegrant category: optimized batch (batch 4) of co-processed excipients StarGeLac (32.5: 5: 62.5). The mixture of the excipients and the drug was pre-blended in a mortar for 3 mins. The calculated amounts of magnesium stearate, talc (lubricant and glidant) and maize starch (exo-disintegrant) were then added; further blending was done for 3 mins. A single punch tableting machine (Erweka Apparatebau West Germany) using 12 mm concave-faced and 10.5 mm die and flat faced punches at varying compression loads. They were then compared with tablets formulated with commercial filler/binder excipients, Ludipress<sup>®</sup> and Starlac<sup>®</sup>.

**Table 3.1: Composition of Tablets Formulations**

Material (mg)	P1	P2	P3	A1	A2	A3
Paracetamol powder	250	250	250	-	-	-
Ascorbic acid powder	-	-	-	100	100	100
Co-processed excipient ( <i>StarGeLac</i> )	350	-	-	150	-	-
Co-processed excipient ( <i>Ludipress</i> ®)	-	350	-	-	150	-
Co-processed excipient ( <i>Starlac</i> ®)	-	-	350	-	-	150
Magnesium stearate	1	1	1	2	2	2
Talc	10	10	10	20	20	20
Maize starch	39	39	39	78	78	78
Total	650	650	650	350	350	350

Key:

P1, P2, P3- paracetamol tablet formulations

A1, A2, A3: ascorbic acid formulations

### 3.8 EVALUATION OF TABLET PROPERTIES:

#### a. Uniformity of weight

Twenty tablets from each batch were weighed using analytical balance (MSI-A, Electronic balance, USA).

The mean weights were calculated and the weight variation (% CV) calculated as:

$$\% \text{ CV} = \text{standard deviation} / \text{mean weight} \dots\dots\dots(13)$$

b. Crushing strength of tablets (CS)

Five tablets were selected at random from each batch. Their crushing strength was determined with a Monsanto hardness tester. The tablet was placed between the spindle and anvil of the hardness tester, adjusting the screw till the fit was snug. The screw was gradually tightened, applying pressure on the tablet until the tablet broke. The pressure that crushed the tablet in kilogram force (kgf) was read on the scale. The mean crushing strength for each batch was calculated.

c. Friability test

Ten tablets were dusted, weighed together and subjected to abrasion in a Roche friabilator at 25 rpm for 4 min. The tablets, after being dusted properly were weighed again collectively. The difference in weight was determined and expressed as % friability value.

d. Thickness and diameter measurement

The thickness and diameter of 5 tablets per batch was determined. The mean was calculated.

e. Disintegration time

This test was carried out using the BP (2002) method. The disintegration time of each batch of tablets was determined in distilled water that is thermostatically maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  using the Erweka disintegration test apparatus ( Type ZT3, No. 41728,

Germany). Six tablets were tested and the time taken for each of the tablets to disintegrate and pass through the mesh was recorded. The mean value was calculated.

f. Dissolution test

This test was carried out using the BP (2002) method.

One litre of 0.1 N Hydrochloric acid thermostatically maintained at  $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$  was used as the medium. The tablet was placed in the basket and the apparatus set at a rotational speed of 100 rpm. A 10 ml of sample was taken out after 10 min, filtered and 1 ml of filtrate diluted to 10 ml. The absorbance of the various resultant solutions were taken at the maximum wave length of 245 nm for paracetamol and 244 nm for ascorbic acid using a UV Spectrophotometer (Spectrum Lab 752, S. B Bran Scientific and Instrument Company, England). The absorbance was plotted against the various concentrations to obtain the calibration curve for paracetamol and ascorbic acid.

### **3.9 STATISTICAL ANALYSIS**

Statistical analysis was carried out to compare the crushing strengths and disintegration time of prepared co-processed excipient, StarGeLac with commercial co-processed excipients, Ludipress<sup>®</sup> and Starlac<sup>®</sup>, in paracetamol and ascorbic acid tablet formulations.

The student's t-test was used; at 95% confidence interval, probability values of  $p < 0.05$  were considered significant.

## CHAPTER FOUR

### RESULTS

#### 4.1 PRELIMINARY INVESTIGATION

##### 4.1.1 Organoleptic properties

Native cassava starch and acid hydrolyzed cassava starch were odourless, white in colour, fine textured and had bland taste. Table 4.1 presents the organoleptic properties of native cassava starch and acid hydrolyzed starch.

The percentage yield of native cassava starch from cassava tubers (*Mannihot esculenta* Crantz) was 14.8 % while that of acid hydrolyzed starch (after 24 hours) was 85 %.

**Table 4.1: Preliminary Investigation of Native Cassava Starch and Acid Hydrolyzed Cassava Starch.**

<b>Parameters</b>	<b>Native starch</b>	<b>Acid hydrolyzed starch</b>
Taste	Bland	Bland
Texture	Fine	Fine
Colour	White	White
Odour	None	None

#### **4.1.2 PHYSICO-CHEMICAL PROPERTIES OF NATIVE CASSAVA STARCH AND VARIOUS BATCHES OF ACID HYDROLYZED CASSAVA STARCH (AHS).**

Table 4.2 presents the physicochemical properties of native cassava starch and various batches of acid hydrolyzed cassava starch. From Table 4.2 it can be seen that the flow rate of cassava starch improved with hydrolysis. The flow rate increased in the order NCS < AHS-C6 < AHS-C12 < AHS-C18 < AHS-C24.

The values of bulk and tapped densities for native and modified cassava starches are also presented in table 4.2. From the values of bulk and tapped densities, Hausner's ratio and Carr's index were determined. The values of the bulk and tapped densities progressed thus: NCS < AHS-C6 < AHS-C12 < AHS-C18 < AHSC-24. The bulk density of a starch product describes its packing behaviour while the tapped density is indicative of the extent and rate of packing that will be undergone by the material during various operations involved in tableting.

Table 4.2 shows that modification of cassava starch by acid hydrolysis produced starch of better compressibility. The Hausner's ratio gives an insight into the degree of densification; the values in Table 4.2 also decreased with progression of hydrolysis.

Other properties like the angle of repose also improved with progression of acid hydrolysis.

**Table 4.2: Physico-chemical Properties of Native Cassava Starch and Various Batches of Acid Hydrolyzed Cassava Starch (AHS)**

Physico-chemical Parameters	Flow rate (g/ sec)	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
Native cassava starch (NCS)	0.9 (0.06)	38.7(0.03)	0.60(0.01)	0.95	36.84	1.58
AHS-C6	1.5 (0.04)	23.8 (0.02)	0.50 (0.04)	0.60 (0.03)	16.7	1.20
AHS-C12	2.4 (0.02)	20.5(0.01)	0.52 (0.03)	0.62 (0.08)	16.1	1.19
AHS-C18	3.5 (0.02)	16.8 (0.05)	0.55 (0.02)	0.65 (0.02)	15.3	1.18
AHS-C24	4.6 (0.08)	16.2 (0.04)	0.57 (.01)	0.67 (0.01)	14.9	1.17

Key:

- AHS-C6: Acid Hydrolyzed Cassava Starch after 6 h of hydrolysis
- AHS-C12: Acid Hydrolyzed Cassava Starch after 12 h of hydrolysis
- AHS-C18: Acid Hydrolyzed Cassava Starch after 18 h of hydrolysis
- AHS-C24: Acid Hydrolyzed Cassava Starch after 24 h of hydrolysis

### **4.1.3 COMPARISON OF THE PHYSICOCHEMICAL PROPERTIES OF NATIVE CASSAVA STARCH WITH ACID HYDROLYZED CASSAVA STARCH, AHS-24 (AFTER 24 H OF HYDROLYSIS).**

Table 4.3 captures the comparison of the physicochemical properties of native cassava starch with acid hydrolyzed cassava starch, AHS-24 (after 24 h of hydrolysis).

The results showed that the amylose/amylopectin content for native starch and acid-hydrolyzed cassava starch (AHS-24) were 29.0 % : 71.0% and 20.1 : 79.9% , respectively.

**Table 4.3: Physico-chemical Properties of Native Cassava Starch and Acid Hydrolyzed Cassava Starch (AHS-C24)**

<b>Physico chemical Parameters</b>	<b>Native cassava starch (NCS)</b>	<b>Acid-hydrolysed cassava starch (AHS-C24)</b>
Flow rate (g/ sec)	0.9(0.1)	4.60(0.05)
Angle of repose (°)	38.7 (0.04)	16.2(0.08)
Bulk density(g/ ml)	0.60 (0.02)	0.57(0.05)
Tapped density (g/ ml)	0.95(0.11)	0.67 (0.06)
Carrs index(%)	36.84	14.9
Hausner ratio	1.58	1.17
Particle density (g/ ml)	1.68	1.4
Swelling power (%)	1.3	1.9
Powder porosity (%)	64	45
Moisture content (%)	9.5	10
Moisture sorption capacity	25	27
Hydration capacity	2.4	2.37
Total Ash value (%)	90	89
Particle shape	spherical	spherical
Particle size (µm)	200.60	355.20
pH	5.6	5.8
Amylose fraction (%)	29.0	20.1
Amylopectin fraction (%)	71.0	79.9

## **4.2 INVESTIGATION OF TABLET PROPERTIES OF VARIOUS BATCHES OF ACID HYDROLYZED CASSAVA STARCH**

Five batches of pure compacts of native cassava starch and four different batches of acid hydrolyzed cassava starch were prepared by direct compression method. It was observed (Table 4.4) that the tablets have acceptable uniformity of weight with no tablet having greater than 5 % deviation in weight.

Acid modified starch had better friability values compared to native cassava starch as deduced from the crushing strength of the tablets. The crushing strength of a tablet, like its thickness, is a function of the die fill and compression force. In the ideal situation, at a constant die fill, the crushing strength values increase and thickness decreases as additional compression force is applied (Achor *et al*, 2010). All the tablets met the BP 2004 specification for disintegration for uncoated tablets, which is 15 min.

**Table 4.4: Comparison of Tablet Properties of Native Cassava Starch and Various Batches of Acid Hydrolyzed Starch:**

Tablet Properties	Weight (mg± SD)	Diameter (mm)	Thickness (mm)	Crushing Strength (Kgf)	Friability (%)	Disintegration time (min)
Native cassava starch	500±4	12.2(0.10)	5.05(0.20)	1.0 (0.04)	1.6(0.06)	0.12(0.14)
AHS-C6	500±5	12.20(0.02)	4.25(0.10)	1.9(0.48)	1.4(0.08)	0.33(0.22)
AHS-C12	500±5	12.14(0.12)	4.20(0.09)	4.2(0.20)	1.5(0.08)	1.06(0.2)
AHS-C18	500±3	12.13(0.09)	4.20(0.21)	4.5(0.44)	0.91(0.004)	1.16(0.15)
AHS-C24	500±3	12.09(0.10)	4.09(0.05)	5.3(0.40)	0.9(0.16)	2.10(0.2)

Key:

- AHS-C6: Acid Hydrolyzed Cassava Starch after 6 h of hydrolysis
- AHS-C12: Acid Hydrolyzed Cassava Starch after 12 h of hydrolysis
- AHS-C18: Acid Hydrolyzed Cassava Starch after 18 h of hydrolysis
- AHS-C24: Acid Hydrolyzed Cassava Starch after 24 h of hydrolysis

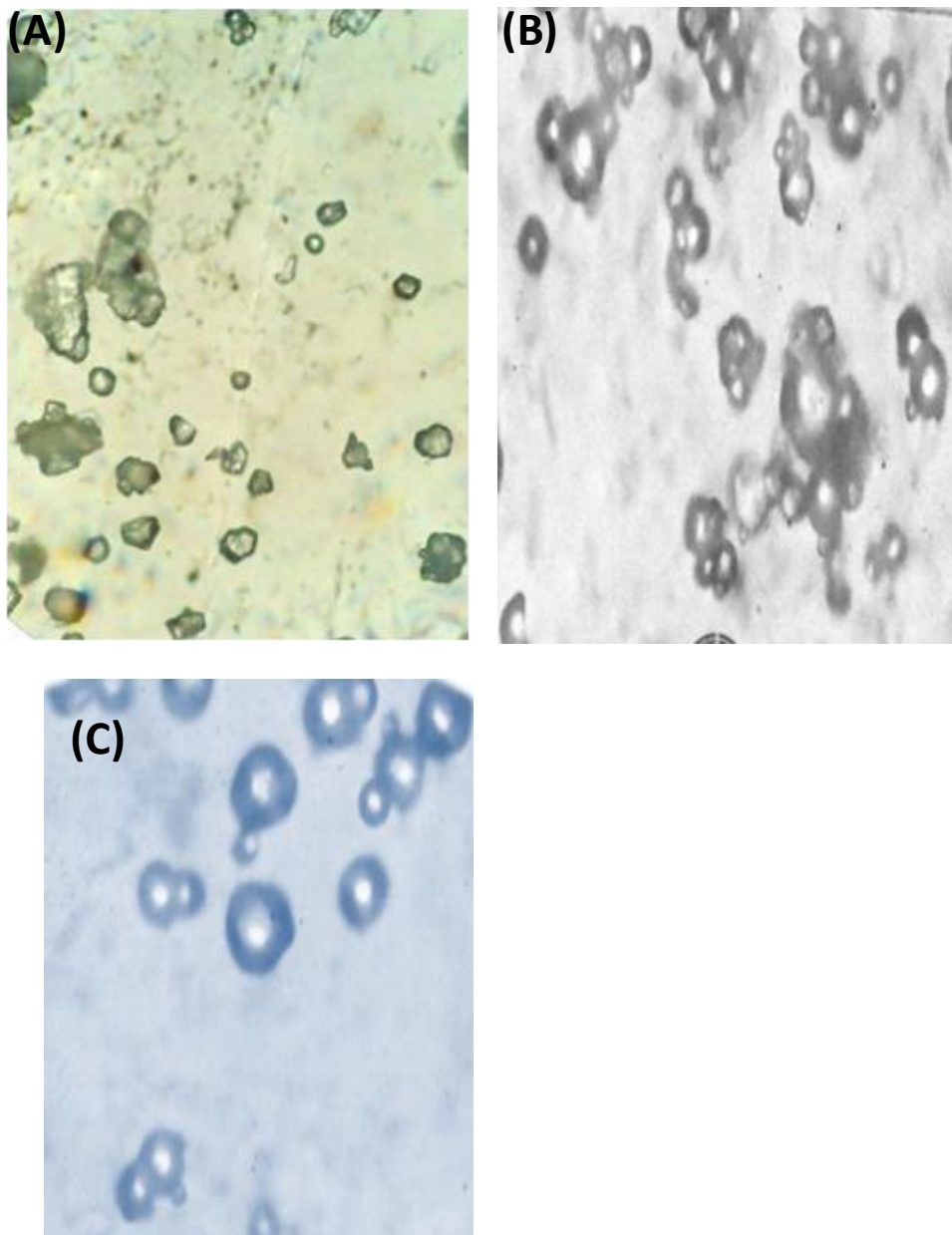


Figure 4.1: Photomicrographs of (A), Native Cassava Starch (X 400) ,(B) Hydrolyzed Cassava Starch (X 400) and (C) Co-processed Excipient, *StarGeLac* (X 400).

### **4.3 PHYSICOCHEMICAL PROPERTIES OF VARIOUS BATCHES OF CO-PROCESSED EXCIPIENTS**

Five batches of co-processed excipients (StarGeLac) were prepared using acid hydrolyzed cassava starch, gelatin and lactose. Results of comparison of the flow properties of the various batches showed that  $SGL\ 5 < SGL1 < SGL2 < SGL3 < SGL4$ .

This and other results obtained are shown in Table 4.5.

**Table 4.5: Physico-Chemical Properties of Various Batches of StarGeLac (SGL)**

Physical properties (SGL)	Flow rate (g/sec)	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
I	4.9(0.04)	33.6(0.23)	0.40(0.41)	0.50(0.29)	20.4	1.26
II	4.98(0.20)	32.6(0.21)	0.40(0.27)	0.43(0.08)	20.7	1.26
III	5.02(0.13)	29.7(0.16)	0.42(0.085)	0.45(0.07)	19.60	1.24
IV	5.08(0.25)	28.9(0.09)	0.44(0.18)	0.50(0.11)	16.60	1.19
V	4.15(0.05)	31.8(0.09)	0.42(0.09)	0.45(0.31)	23.08	1.30

Key:	AHS-C24(g)	Gelatin (g)	Lactose (g)
SGLI:	52.5	5	42.5
SGLII:	42.5	5	52.5
SGLIII:	32.5	5	62.5
SGLIV:	22.5	5	72.5
SGLV:	12.5	5	82.5

#### **4.4 PRELIMINARY INVESTIGATION OF THE TABLETING PROPERTIES OF VARIOUS BATCHES OF STARGELAC**

The compression and compaction characteristics of the various batches of co-processed excipients were studied by making compacts of them at pressure values ranging from 4.5 - 5.5 MT. The properties of the tablets were evaluated and the results obtained are shown on Table 4.6.

**Table 4.6: Tablet Properties of Various Batches of StarGeLac**

Properties	Average weight (mg)	Thickness (mm)	Diameter (mm)	Crushing strength (Kgf)	Friability (%)	Disintegration time (min)
SGL I	500	4.49(0.06)	12.1(0.01)	10(0.08)	0.3(0.02)	10.4(0.29)
SGL II	502(0.18)	4.51(0.08)	12.12(0.12)	10(0.08)	1.01(0.02)	6.38(0.15)
SGL III	497(0.20)	4.44(0.02)	12.0	8.6(0.09)	0.9(0.004)	6.5(0.09)
SGL IV	497(0.20)	4.45(0.06)	12.0	7.9(0.12)	0.8(0.009)	6.53(0.02)
SGL V	505(0.45)	4.69(0.15)	12.0	4.5(0.19)	1.33(0.08)	7.32 (0.06)

Key:

	AHSC-24(g)	Gelatin (g)	Lactose (g)
Batch I:	52.5	5	42.5
Batch II:	42.5	5	52.5
Batch III:	32.5	5	62.5
Batch IV:	22.5	5	72.5
Batch V:	12.5	5	82.5

#### **4.5 CHARACTERIZATION OF STARGELAC (SGL IV)**

Based on the preliminary investigation of the physicochemical and compression properties, batch IV of the co-processed excipient, StarGeLac, was subjected to further characterization. It is evident from Tables 4.5 and 4.6 that SGL batch IV exhibited better angle of repose, Carr's index and Hausner's ratio, which consequently resulted in better tableting properties that are indicated by crushing strength of 7.9 kgf and friability value of <1. Further characterization was thus carried out on SGL IV and the results are presented in Table 4.7.

The hydration and swelling capacities results showed that SGL IV is capable of absorbing at least two times its own weight of water. The physicochemical properties of co-processed excipient SGL IV were compared with those of the physical mixture of starch, gelatin and lactose, in the same proportion. The results are presented in Table 4.8. The results indicate that co-processed excipients StarGeLac IV (SGL IV) has better indices of flow than the physical mixture of the same components in the same proportion.

**Table 4.7: Physicochemical Properties of Co-Processed Excipient StarGeLac IV (SGL IV).**

Properties					
	Particle size (µm)	Particle density (g/ml)	Hydration capacity (%)	Swelling capacity	Moisture sorption capacity (%)
Values	235	1.36	2.3	1.69	27

**Table 4.8: Comparison of Physico-Chemical Properties of StarGeLac Batch IV (SGL IV) and Physical Mixture of Acid Hydrolyzed Starch: Gelatin: Lactose (PM-SGL)**

<b>Properties</b>	<b>Flow rate (g/sec)</b>	<b>Angle of repose (°)</b>	<b>Bulk density (g/ml)</b>	<b>Tapped density (g/ml)</b>	<b>Carr's index (%)</b>	<b>Hausner's ratio</b>
<b>SGL IV</b>	5.08	28.9	0.44	0.50	16.6	1.19
	(0.008)	(0.081)	(0.008)	(0.02)		
<b>PM-SGL</b>	5.89	33.9	0.40	0.43	20.7	1.26
	(0.016)	(0.16)	(0.028)	(0.012)		

Key:

SGL IV: StarGeLac Batch IV

PM-SGL: Physical Mixture of Acid Hydrolyzed Starch: Gelatin: Lactose (22.5: 5: 72.5)

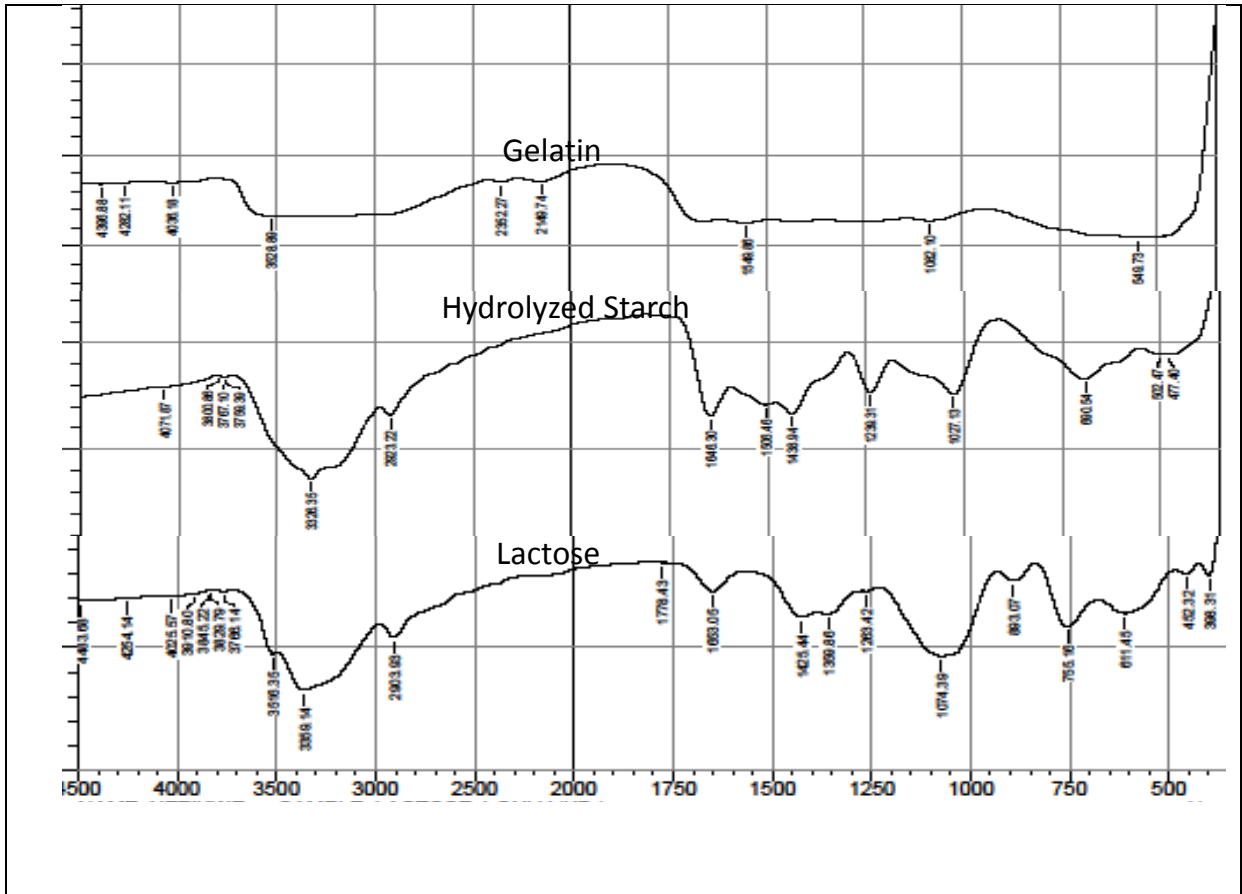


Figure 4.2: FTIR Spectra of Acid Hydrolyzed Cassava Starch, Gelatin and Lactose.

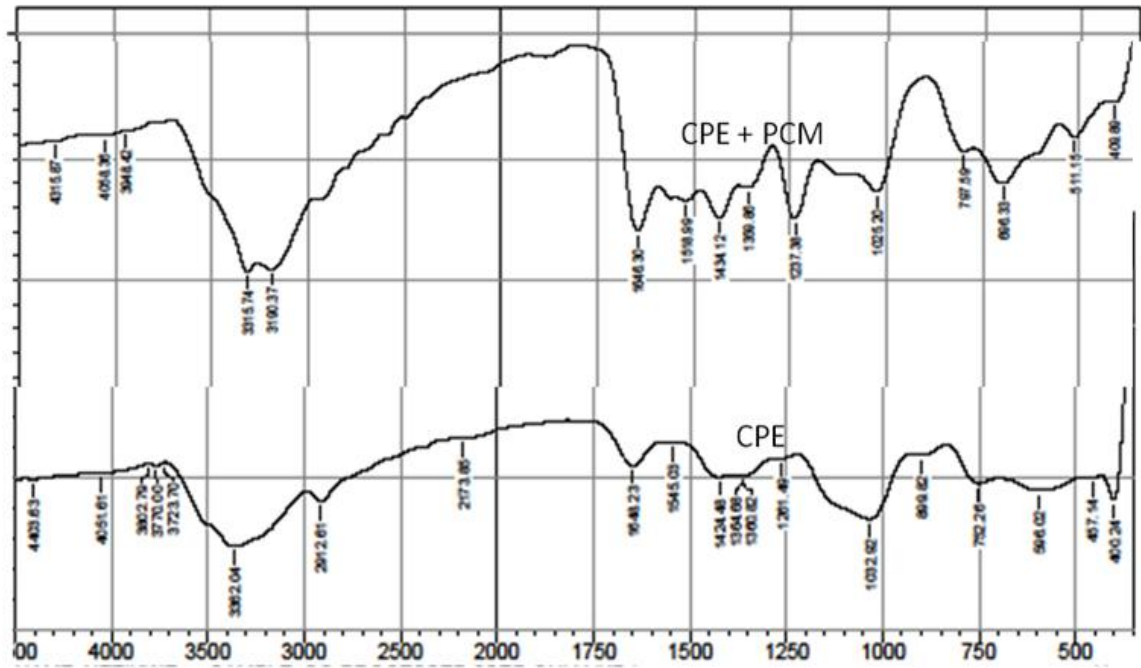


Figure 4.3: FTIR Spectra of Co-processed excipient (CPE), StarGeLac, and Co-processed Excipient, StarGeLac + Paracetamol (CPE + PCM)



Figure 4.4: FTIR Spectrum of Paracetamol

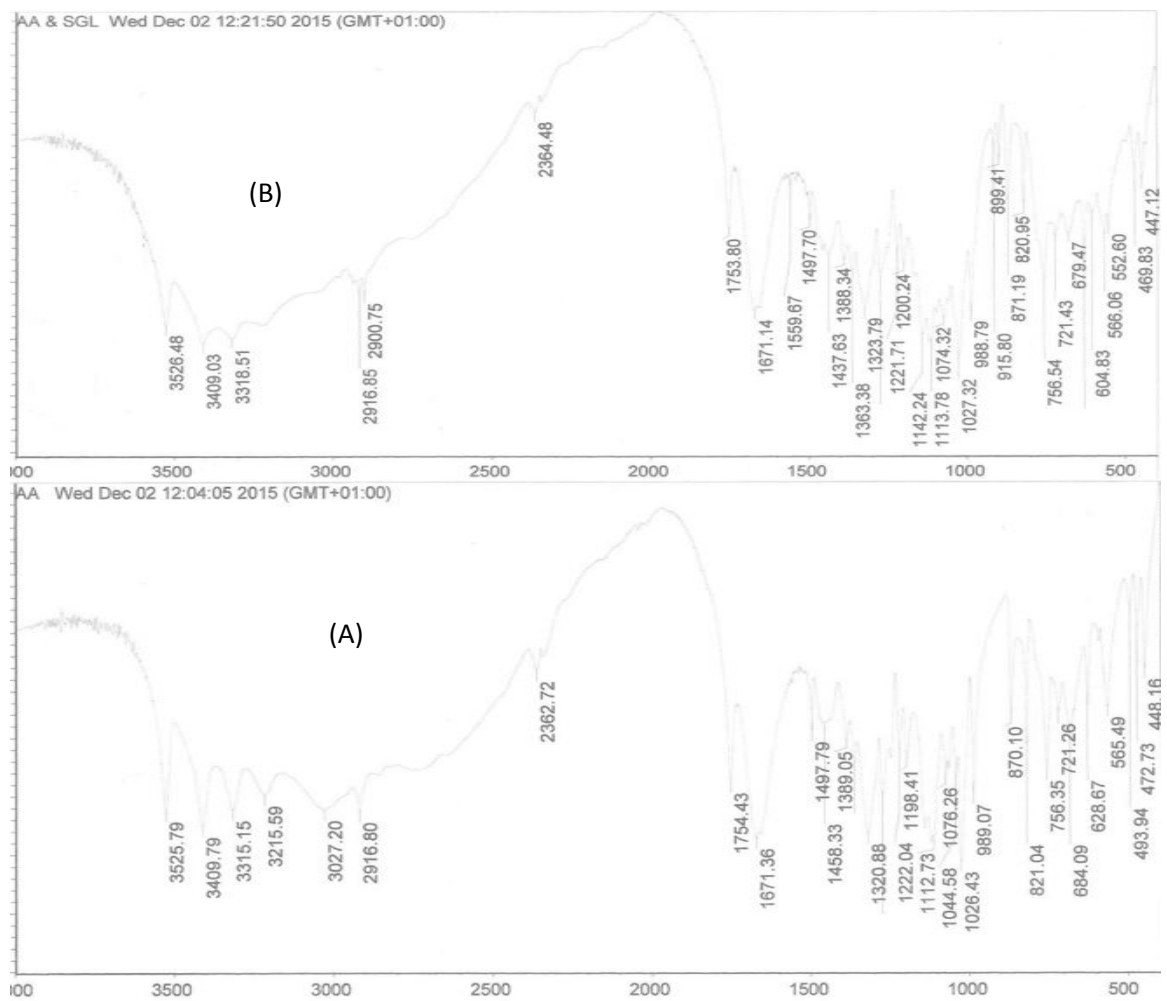
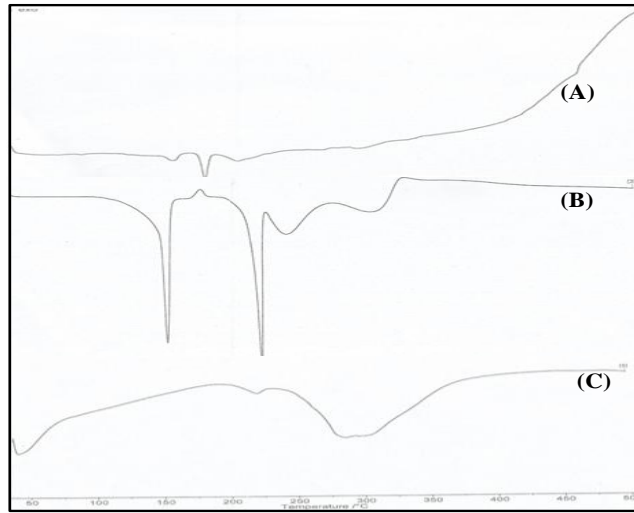
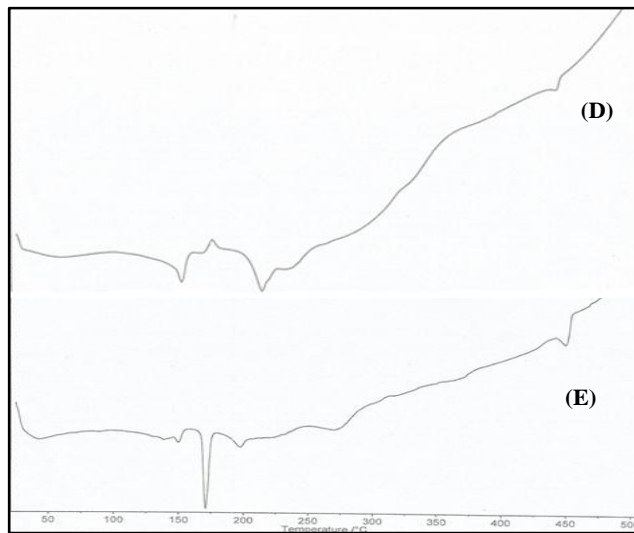


Figure 4.5: FTIR Spectra (A) Ascorbic acid and (B) Ascorbic acid and StarGeLac



1

Figure 4.6: DCS thermograms of (A) Acid hydrolyzed cassava starch (B) Lactose and (C) gelatin



30

Figure 4.7: DSC Thermograms of (D) StarGeLac (E) StarGeLac and paracetamol

#### **4.6 DILUTION POTENTIAL STUDY**

Paracetamol, a poor water soluble drug with high capping tendency (Lennartz and Mielck, 1998) and Ascorbic acid, a high dose water soluble drug that limits the quantity of the added excipients (Bajaj *et al.*, 2012) were used as model drugs in the evaluation of the dilution potential of the test co-processed excipient (SGL IV) .

The results showed that 40 % and 33.3% of paracetamol and ascorbic acid respectively compressed with StarGeLac (SGL IV) to give compacts of acceptable crushing strengths (Table 4.9). It was also observed that the crushing strengths of the compacts decreased with increase and decrease in drug and StarGeLac concentrations respectively. This is also illustrated in figure 4.8.

**Table 4.9: Dilution Potential of StarGeLac Using Paracetamol and Ascorbic acid as Model Drugs**

	Drug excipient ratio (D:E)	
	P	AA
SGL IV	40:60	33.3:66.7

Key:

SGL IV: Co-processed excipient; SGL IV: StarGeLac, batch IV; P: Paracetamol; AA: Ascorbic acid.

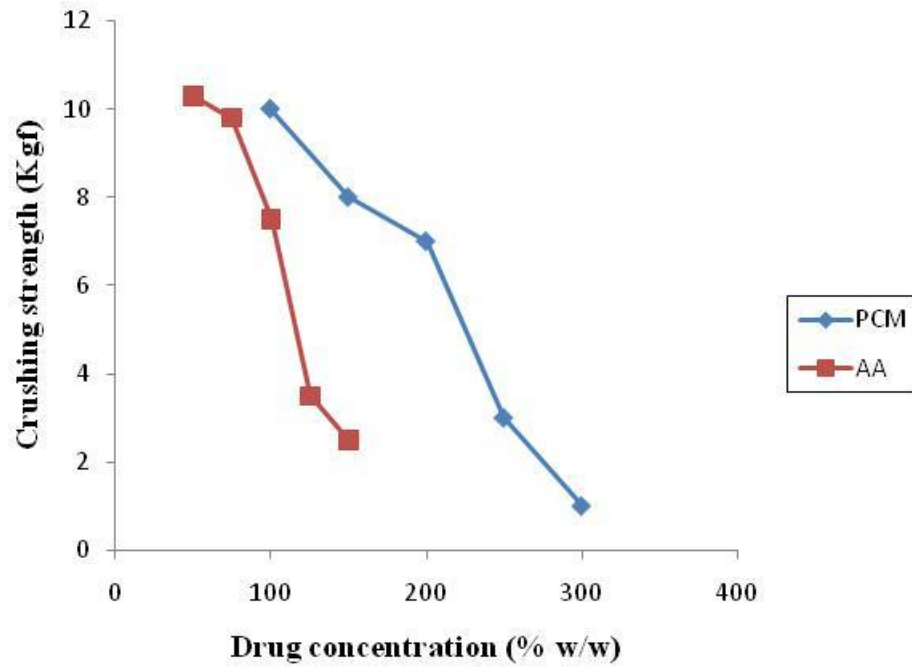


Figure 4.8: Graph of Crushing Strength (kgf) versus Drug Concentration (% w/w)

## **4.7 COMPACT ANALYSIS OF CO-PROCESSED EXCIPIENTS**

### **4.7.1 Heckel analysis**

The compression behavior of the co-processed excipient, StarGeLac (SGL IV) was characterized using the Heckel model (Heckel, 1961). It was compared with some commercial co-processed excipients. The values of the yield pressure,  $P_y$ ,  $D_A$ ,  $D_B$  and  $D_O$  are presented in Table 4.10.

Powder compaction is a volume reduction process (Heckel,1961) and the Heckel equation is based on the change in volume of a powder column during compression. The Heckel plots in Figure 4.9, thus gives a general impression of the densification of the powder column.

The mean yield pressures,  $P_y$ , were calculated from the linear portions of the plots and the intercept,  $A$ , was determined from the extrapolation of that region. The relative density values  $D_O$ ,  $D_A$  and  $D_B$  were also calculated. SGL IV had the highest value of  $P_y$ , followed by STL (Starlac) then LDP (Ludipress).

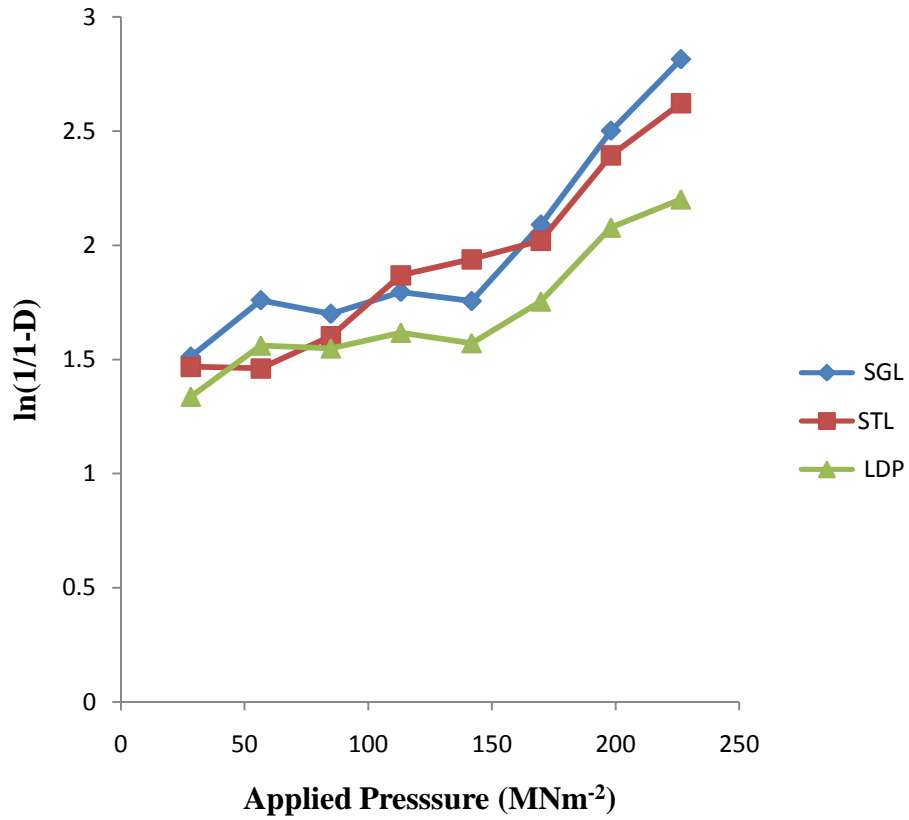


Figure 4.9: Heckel plot of  $\ln(1/1-D)$  versus applied pressure (MNm<sup>-2</sup>) for compacts prepared with StarGelac (SGL), Starlac<sup>®</sup> (STL) and Ludipress<sup>®</sup> (LDP).

**Table 4.10: Parameters Obtained From Heckel Plots (Heckel Constants)**

Materials	$P_y$	$D_A$	$D_B$	$D_O$
SGL IV	298.30	0.73	0.31	0.42
STL	241.12	0.75	0.36	0.37
LDP	231.51	0.76	0.37	0.39

**Key:**

SGL IV: Co-processed excipient, StarGeLac, batch IV;

STL: Starlac<sup>®</sup>;LDP: Ludipress<sup>®</sup> $P_y$ : yield pressure $D_A$ : total degree of densification at zero and low pressures $D_B$ : particle rearrangement phase in early compression stages $D_O$ : degree of initial packing in the die

#### 4.7.2 Kawakita Analysis

The Kawakita equation (Kawakita and Ludde, 1971) describes the relationship between the volume reduction of a powder column and the applied pressure. Figure 4.10 shows Kawakita plots for StarGeLac, Starlac<sup>®</sup> and Ludipress<sup>®</sup>; a linear relationship was obtained at all compression pressures. Values of 'a' and 'ab' were calculated from the slope and intercept of the plots respectively.  $P_k$  values were calculated from the reciprocal of b while  $D_1$  values, which are the initial relative densities of the materials, were obtained from the reciprocal of b. These are presented on Table 4.11.

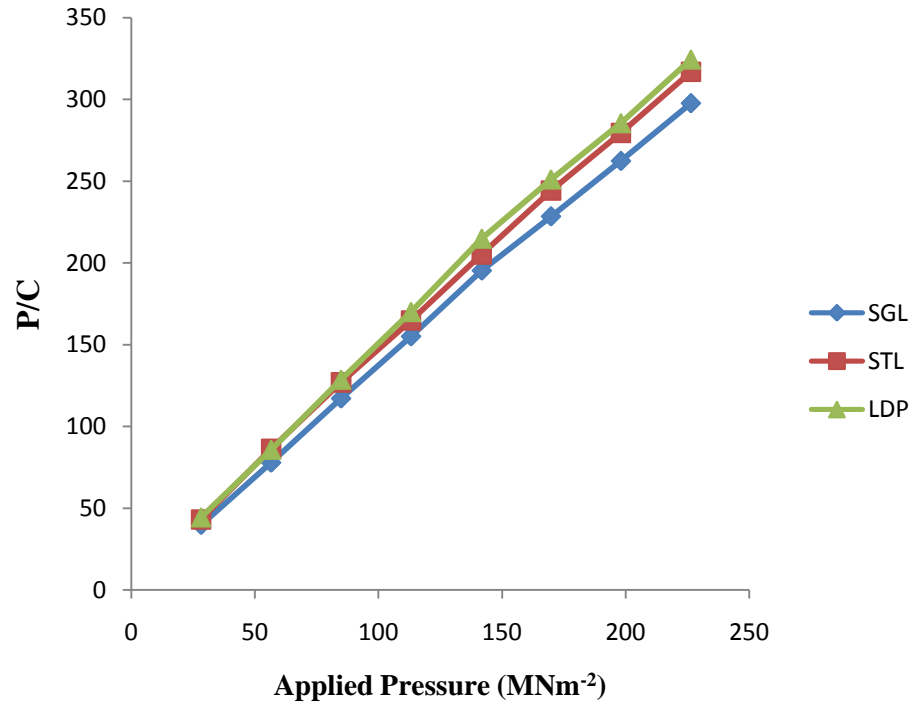


Figure 4.10: Kawakita Plots of P/C Versus Applied Pressure, P(MNm<sup>-2</sup>) for Compacts Prepared With StarGeLac (SGL), Starlac<sup>®</sup> (STL) and Ludipress<sup>®</sup> (LDP).

**Table 4.11: Parameters Obtained From Kawakita plots**

Materials	$P_k$	$D_1$	a	b
SGL IV	4.2354	0.2331	0.7668	0.2361
STL	5.7724	0.2733	0.7266	0.1732
LDP	5.2986	0.2942	0.7057	0.1887

Key:

SGL IV: Co-processed excipient StarGeLac, batch IV;

STL: Starlac<sup>®</sup>;

LDP: Ludipress<sup>®</sup>

#### **4.8 MECHANICAL PROPERTIES OF STARGELAC AND SOME COMMERCIAL DC EXCIPIENTS**

The results (Table 4.12) show that SGL4 produced tablets of acceptable crushing strength.

The results also show that tablets prepared with SGL4 as well as Starlac<sup>®</sup> and Ludipress<sup>®</sup> exhibited low tendency to fracture.

**Table 4.12: Tensile Strength (T) and Brittle Fracture Index (BFI) of Compacts**

	T (MNm <sup>2</sup> )	BFI
SGL	0.4	0.35
STL	0.2	0.05
LDP	0.3	0.1

Key:

SGL IV: Compacts prepared with Co-processed excipient StarGeLac, batch IV;

STL: Compacts prepared with Starlac<sup>®</sup>;

LDP: Compacts prepared with Ludipress<sup>®</sup>

#### **4.9 ANALYSES OF TABLETS FORMULATED WITH CO-PROCESSED EXCIPIENTS AND MODEL DRUGS**

The results of the tests carried out on the tablets formulated with Co-processed excipients (StarGeLac, Starlac and Ludipress) and Model Drugs are presented on Table 4.13.

All the tablets exhibited uniform weight with low standard deviation values. The diameters of the tablets were found to be just above 12 mm for paracetamol tablets and 8 mm for ascorbic acid tablets; the thickness was found to be between 5.12 and 5.5 mm.

The crushing strengths of all the tablets were found to be below 8 Kgf, with the rank order of SGL-P> LDP-P> STL-P for paracetamol tablets and LDP-AA> SGL-AA> STL-AA for ascorbic acid tablets. The friability of all formulations was found to be less than 1% which is indicative of the durability of the tablets. All the tablets however met the BP 2004 specification for disintegration for uncoated tablets, which is 15 minutes.

**Table 4.13: Tableting Properties Of Tablets Formulated With Stargelac, Ome Commercial Co-Processed Excipients And Model Drugs**

Properties	Thickn ess (mm)	Diam eter (mm)	weig ht (mg)	Crushi ng strengt h (Kgf)	Friabil ity (%)	Disinteg ration time (min)	Dissolu tion time (% drug release in 45 min)	T <sub>50%</sub> (min)	Drug content (%)
<b>SGL-P</b>	5.33 (0.02)	12.1 (0.01)	649 (0.02)	7.5 (0.05)	0.9 (0.06)	3.5 (0.02)	70 (0.03)	10 (0.001)	101 (0.02)
<b>STL-P</b>	5.12 (0.06)	12.0	652 (0.04)	6.0 (0.01)	0.8 (0.04)	1.4 (0.03)	76 (0.02)	10 (0.01)	105 (0.03)
<b>LDP-P</b>	5.20 (0.04)	12.1 (0.02)	655 (0.06)	6.5 (0.01)	0.75 (0.02)	1.0 (0.02)	78 (0.05)	10 (0.02)	105 (0.01)
<b>SGL-AA</b>	5.40 (0.02)	8.1 (0.02)	360 (0.04)	5.7 (0.02)	0.85 (0.01)	2.0 (0.01)	70 (0.03)	10 (0.01)	101 (0.01)
<b>STL-AA</b>	5.50 (0.04)	8.09 (0.01)	345 (0.04)	6.0 (0.03)	0.9 (0.01)	1.0 (0.04)	71 (0.01)	10 (0.01)	102.6 (0.02)
<b>LDP-AA</b>	5.45 (0.02)	8.10 (0.02)	35 (0.01)	6.9 (0.02)	0.9 (0.02)	0.9 (0.04)	75 (0.02)	10 (0.06)	104.6 (0.08)

Key:

SGL-P: StarGeLac : paracetamol

STL-P: Starlac ® : paracetamol

LDP-P: Ludipress® : paracetamol

SGL-AA: StarGeLac : ascorbic acid

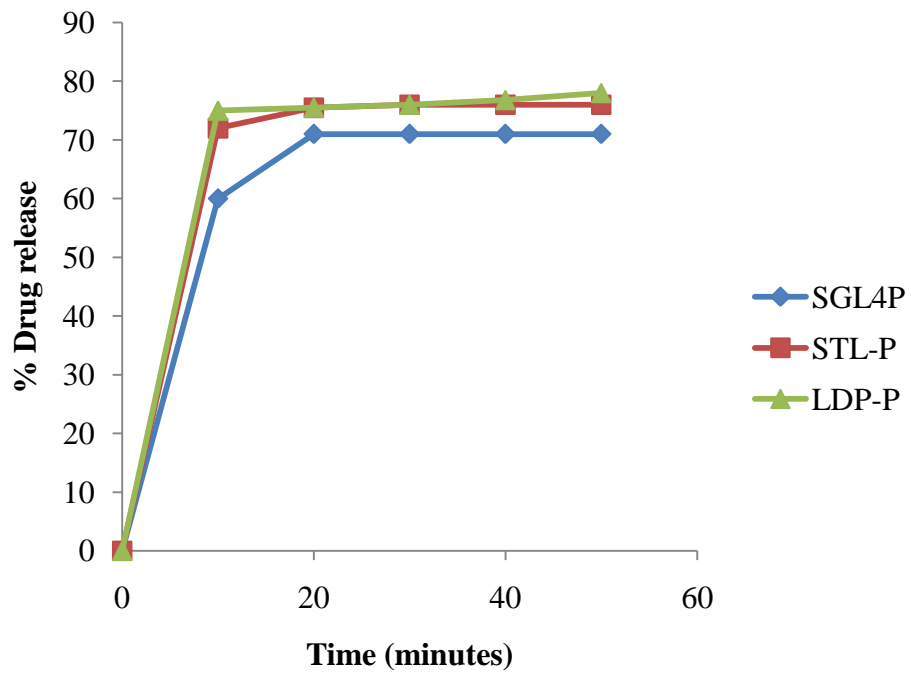
STL-AA: Starlac ® : ascorbic acid

LDP-AA: Ludipress® : ascorbic acid

#### **4.10 DISSOLUTION STUDIES**

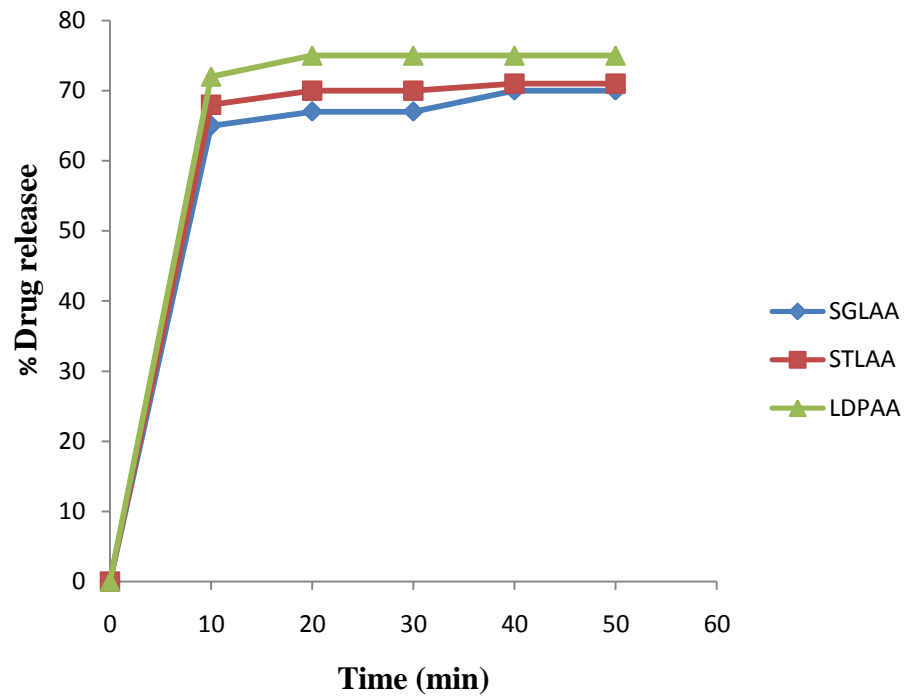
This was carried out for tablets containing the model drugs. The  $T_{50\%}$  which is the time taken for 50% of the drug to be released and the % drug content was determined for all batches of tablets.

Figure 4.11a and 4.11b illustrate the paracetamol and ascorbic dissolution profiles from tablets prepared with StarGeLac, Starlac ® and Ludipress ®



Key:  
SGL-P: Paracetamol tablets prepared with co-processed excipient, StarGeLac  
STL-P: Paracetamol tablets prepared with Starlac ®  
LDP-P: Paracetamol tablets prepared with Ludipress®

Figure 4.11a: Graph of Percentage drug release against time (min) for paracetamol tablet formulations (SGL-P, STL-P and LDP-P)



Key:  
 SGL-AA: Ascorbic acid tablets prepared with co-processed excipient, StarGeLac  
 STL-AA: Ascorbic acid tablets prepared with Starlac®  
 LDP-AA: Ascorbic acid tablets prepared with Ludipress®

Figure 4.11b: Graph of Percentage drug release against time (min) for ascorbic acid tablet formulations (SGL-AA, STL-AA and LDP-AA)

## CHAPTER FIVE

### DISCUSSION

#### 5.1 PRELIMINARY INVESTIGATION

##### 5.1.1 Organoleptic Properties of Native and Acid-hydrolyzed Cassava Starches

The native and acid-hydrolyzed cassava starches were both white in colour, fine textured with characteristic bland taste. The native starch gave the characteristic blue-black colouration with iodine. Amylose in starch is responsible for this colouration in the presence of iodine. The iodine molecule slips into the amylose coil, giving this characteristic colour (Knutson, 1986); this complied with BP (2002) specification. These results are presented in Table 4.1.

##### 5.1.2 Physico-chemical Properties of Native Cassava Starch and Various Batches of Acid Hydrolyzed Cassava Starch (AHS)

Acid hydrolyzed starch has better flow properties than native starch (Ocheja, 2000). The flow rate increased in the order NCS < AHS-C6 < AHS-C12 < AHS-C18 < AHSC-24. The improvement in flow is reflected by the increase in particle size which is noticed after 24 h of exposure to the acid during hydrolysis. Increase in particle size results in better flow because there will be less friction between particles (Ocheja, 2000). Other preliminary studies like determination of bulk and tapped densities as well as Carr's index and Hausner's ratio, were carried out to select the best batch out of the five batches of hydrolyzed starch.

The Bulk density of a starch product describes its packing behaviour while the tapped density is indicative of the extent and rate of packing that will be undergone by the

material during various operations involved in tableting. Carr (1965) stated that values of 5-10, 12-16, 18-21 and 23-28 represent flow that is excellent, good, fair and poor, respectively. It can thus be seen that native starch with Carr's index of 36.84 % has poor flow and that the flow improved with increase in exposure time with AHSC-24 having Carr's index of 14.9 %. Also Hausner's ratio for native starch was 1.5, significantly higher than 1.2 and this also indicates poor flow. Hydrolyzed starch however showed improvement with increase in hydrolysis time with AHSC-24 having Hausner's ratio of 1.17. The angle of repose, another index of flowability, follows the same pattern. It can be seen from the results that the angle of repose decreased with increase in the time of hydrolysis. It has been reported that the angle of repose is affected by the cohesiveness of the powder; if the powder is cohesive the angle of repose will be high and if the powder is non-cohesive or adhesive the angle of repose will be low (Bhimte and Tayade, 2007).

It is thus evident from Table 4.2 that the period or time of hydrolysis is significant in the acid modification of starch and affects the basic properties of starch accordingly. This finding is supported by earlier work by Neelam *et al.*, (2012), who reported increase in progression of some physical properties of starch as hydrolysis proceeded. The susceptibility of starch granules to hydrolysis depends on factors that include its method of preparation and the nature of the starch (Dona *et al.*, 2010). Also, Soto *et al.* (2012) reported that the amylose portion is found in greater proportion in starch from cereals than in starch from tubers; this agrees with the results that showed that the amylose/ amylopectin content for native and hydrolyzed cassava starches were 29.0 % : 71.0% and 20.1 : 79.9% , respectively. The amylose and amylopectin ratio provide distinctive characteristics specific to each type of starch which affect their functional properties

(Aboubakar *et al.*, 2007). The results showed that the amylose/ amylopectin content for native and hydrolysed cassava starches were 29.0 % : 71.0% and 20.1 : 79.9% , respectively. A significant reduction in amylose content was observed after 24 h of hydrolysis. It has been reported that increase in hydrolysis reaction time results in increase in the crystallinity of the starch and a decrease in the amylose content (Atichokudomchai *et al.*, 2000).

It has been found that starches with higher amylose content are more resistant to hydrolysis (Absar *et al.*, 2009). Results of further tests carried out on starch, after hydrolysis for 24hours, are presented in Table 4.4. Hydrolyzed starch had slightly higher moisture content and moisture sorption capacity compared to native starch .This could be because they were dried under similar conditions thus giving rise to the same amounts of total solids in both starches. It has been reported that the moisture content of starch is usually related to a large extent to the type of starch and the methods and condition of drying (Shildneck and Smith, 1967; Neelam *et al.*, 2012).

Increased swelling power of hydrolyzed starch is also indicative of better disintegrant property compared with native starch (Okafor, 1990).

Hydrolyzed starch and native starch had similar pH values, 5.8 and 5.6, respectively. Total ash values were also similar, 89 % for hydrolyzed starch and 90 % native starch. The flow of hydrolyzed starch is also significantly improved, 4.60 g/ sec, compared to native starch, which is, 0.9 g / sec. This property is significant because a free flowing powder results in uniform die fill, less weight and uniformity of content variations.

## 5.2 INVESTIGATION OF TABLET PROPERTIES OF NATIVE CASSAVA STARCH AND VARIOUS BATCHES OF ACID HYDROLYZED STARCH

It can be seen from the results that the effect of period or time of hydrolysis on modified starch is significant in the properties of their respective compacts. The thickness and friability values of the tablets reduced with increase in hydrolysis time. This means that the degree cohesiveness of the powders reduced with progressing hydrolysis resulting in more compact tablets with lower friability as is deduced from the increasing crushing strengths. The disintegration time also increased with a reduction in powder cohesiveness which translated into a commensurate decrease in compact porosity. Earlier work by Okafor (1990) also documents the improved disintegrant property of hydrolyzed cassava starch.

Figures 4.1 and 4.2 show the photomicrographs of native and hydrolyzed cassava starch at x 400 magnification. Native cassava starch particles were small angular polyhedral; hydrolyzed starch particles were spherical. Particle size is one of the important properties that govern flow of powders. Larger particles flow better than smaller particles because particulate function is more of surface phenomenon by generation of resistance to flow. Small particles, have large surface area thus have more surface energy to attract with one another and tend to adhere together and have more resistance to flow (Ohwoavworhua *et al.*, 2007). Large particle size is thus desired because large particles have small surface area and hence small surface activity.

Hasan *et al.*, (2012) however also reported that particle size is not the only characteristic that is involved in the flow of powders, other characteristics of excipients such as densities and moisture content may also affect flow properties of powder.

### **5.3 PRELIMINARY INVESTIGATION OF THE PHYSICO-CHEMICAL PROPERTIES OF VARIOUS BATCHES OF CO-PROCESSED EXCIPIENTS**

The value of Carr's index between 5-15 and 15-20 indicates excellent and good flowability, respectively. Values greater than 21 indicate poor flow (Carr, 1965). Batches SGL I and SGL II had Carr's index of >20, indicating poor compression characteristics.

The unsatisfactory flow of batches SGL I and SGL II may be due to the fines of a higher percentage. The results revealed that the Carr's index value was inversely proportional to quantity or proportion of lactose.

The angle of repose also presented in the rank order: SGL I > SGL II > SGL V > SGL IV > SGL III. The slight increases in SGL IV and SGL V could be attributed to increased quantities of lactose, which is a fine powder. Hausner's ratio also progressed in the same order as the Carr's compressibility index, with values being inversely proportional to the quantity or proportion of lactose in StarGeLac.

Based on the evaluation of these basic powder properties, SGL IV was selected as the best performing batch.

### **5.4 PRELIMINARY INVESTIGATION OF THE TABLET PROPERTIES OF VARIOUS BATCHES OF CO-PROCESSED EXCIPIENT**

On evaluation of the tableting properties of various batches of StarGeLac, results obtained (Table 4.6) further support the emergence of SGL IV as the optimum batch of StarGeLac.

The results showed that the pure compacts of SGL IV placebo tablets gave acceptable uniformity of weight with no tablet deviating by > 5% of the mean weight. The weights of the tablets varied from 497 to 505 mg.

The crushing strengths of the prepared tablets varied from 7.9 – 10 Kgf with tablets having higher quantity of hydrolyzed cassava starch (batches SGL I and SGL II) showing more hardness; SGL I also records the highest disintegration time. The friability of SGL III and SGL IV blends the formulations was found to be less than 1.0%; resistance to weight loss indicates the tablets ability to withstand abrasion in handling, packaging. Friability declined with increase in tablet crushing strength, except for batch V. The low crushing strength and high friability of batch V could be attributed to the relatively poor binding properties of lactose (Bolhuis and Chowan, 1996), which has a higher percentage in batch 5.

The excipients blend SGL IV showed acceptable crushing strength and friability. The results indicate also however that all the other tablets disintegrated within 15 min, consistent with the recommended maximum of the British Pharmacopoeia (2004) for uncoated tablets. For these reasons SGL IV was chosen for further characterization.

#### **5.5 CHARACTERIZATION OF CO-PROCESSED EXCIPIENT STARGELAC (SGL IV).**

The physico-chemical properties of SGL IV are shown in Table 4.7. The hydration capacity of SGL IV is 2.3 %. The hydration capacity of a material represents the water absorbed by the particle or particle surface (Ohwoavworhua *et al.*, 2007). The smaller the particle size, the larger the surface area for the absorption of water; co-processing of acid hydrolyzed starch with gelatin and lactose resulted in powder particles of larger size (235 µm) and the particle of acid-hydrolyzed starch (200.6 µm). Also, the moisture sorption capacity is the measure of the sensitivity to moisture of a material and reflects the relative physical stability of the tablets formulated with the material when stored under humid

conditions (Ohwoavworhwa *et al.*, 2010). The results show that the moisture sorption capacity of SGL IV is 27 %. The swelling capacity which reflects increase in volume of the material showed that of SGL IV to be 1.69. This suggests that SGL IV has some disintegrant property and if incorporated in tablet formulation, would probably aid tablet disintegration by two mechanisms: capillary or wicking and swelling (Hasan *et al.*, 2012). On comparison with the physical mixture of the single excipients, the results (Table 4.8) illustrate an increase in flow properties of co-processed StarGeLac, as reflected by a flow rate 5.89 g/ sec, for the former and 5.08 g/ sec, for the latter respectively. The corresponding angles of repose also are 28.9° and 33.9° respectively. The compressibility indices as reflected in the table are: 16.6 % and 20.7 % respectively. All these results indicate improvement in both flow property and compressibility of StarGeLac after co-processing when compared with the physical mixture of the same single excipients in the same ratio. This is because of the impregnation of the particles of the co-processed excipients into the matrices of each other, which reduces the rough particle surfaces thus creating a near optimal size distribution, causing better flow (Ajay *et al.*, 2012). The powder and tableting properties of StarGeLac were also compared with Starlac<sup>®</sup> (alpha-lactose monohydrate 85 %, native maize starch 15 %) and Ludipress<sup>®</sup>. (lactose 93 %, kollidon 30 3.5%, kollidon CL (crospovidone) 3.5 %). StarGeLac had lower density values than Starlac<sup>®</sup> and Ludipress<sup>®</sup> which in turn had better flow rate than StarGeLac. They also had comparable angles of repose, with StarGeLac having a slightly higher value. Starlac<sup>®</sup> was observed to have higher Carr's index and Hausner's ratio. These properties are also reflected in the placebo tablets ; the crushing strength values of Starlac<sup>®</sup> and Ludipress<sup>®</sup> were lower than StarGeLac which could be due to the combined binding action of

hydrolyzed starch and gelatin. Attempts have been made, in earlier works, to combine two materials in order to obtain a mixture with improved compaction behavior and functionality as a binder (Larhrib and Wells, 1998). The acceptable flow rate of all three materials allowed for compacts of acceptable weights, thickness and diameter. Friability values were also all under acceptable limit of 1 %. The disintegration time of Starlac<sup>®</sup> and Ludipress<sup>®</sup> were high. Starlac<sup>®</sup> contains co-spray dried maize starch and lactose, giving it synergistic functional performance hence the fast disintegration. Ludipress<sup>®</sup> also contains a super-disintegrant, kollidon 30, which facilitates disintegration. The higher disintegration time of StarGeLac is a carryover effect of the combined binding action of gelatin and starch resulting in higher mechanical strength.

## **5.6 FTIR Study**

FTIR studies are displayed in Figure 4.2- 4.5. The presence of Infra Red (IR) frequencies between 3500 – 3100 cm<sup>-1</sup> (due to the N – H stretch of the amine group) in gelatin and lactose, which also appear in the co-processed excipient StarGeLac, indicate the absence of change in the functional group (Kemp, 1991) which implies that no excipient – excipient reaction took place between the daughter excipients. Subsequently, the presence of IR frequencies between 1670 – 1640 cm<sup>-1</sup> (as a result of a stretch in the C=O functional group) in both spectra of ascorbic acid alone : ascorbic acid with StarGeLac and frequencies between 3500 – 3200cm<sup>-1</sup> in both spectra of paracetamol alone : paracetamol with StarGeLac (as a result of the hydrogen bonded O-H stretch) are also indicative of the absence of excipient – drug interaction (Kemp, 1991).

## **5.7 DSC**

The physical properties of the co-processed excipient were measured as a function of temperature by subjecting it to a controlled temperature program using DSC. The information regarding the effects of storage at elevated temperatures that were obtained by the thermograms generated indicated the absence of any interaction as the thermograms of mixtures (co-processed excipient) show patterns corresponding to those of the individual components.

## **5.8 DILUTION POTENTIAL STUDY**

Dilution potential can be defined as the amount of active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipient (Gohel and Jogani, 2005). Paracetamol and ascorbic acid were used for this study. It was observed from the results (Table 4.9) that the crushing strengths of the tablets decreased with increase in the concentration of paracetamol and ascorbic acid. This could be caused by the poor compressibility and elastic recovery of the drugs (Lennartz and Mielck, 1998); The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient (Gohel and Jogani, 2005). The results showed that 40 % and 33.3% of paracetamol and ascorbic acid respectively compressed with StarGeLac (SGL IV) to give compacts of acceptable crushing strengths. Hydrolyzed starch, gelatin and lactose physical mixture did not yield satisfactory tablets even with the same percentage of drugs. This result shows that agglomerates of SGL IV exhibited higher compressibility and better binding property than the physical mixture.

## 5.9 COMPACT ANALYSIS OF CO-PROCESSED EXCIPIENT

### 5.9.1 Heckel Analysis

The shape of the Heckel plots obtained (Figure 4.5) shows an initial curve typical of type B plot. The rank order of SGL IV > STL > LDP was observed for mean yield pressure,  $P_y$  (Table 4.10). This implies that the onset of plastic deformation was fastest in LDP compacts. High  $P_y$  is indicative of higher yield strength, requiring higher forces of compaction to initiate deformation (Adeoye and Alebiowu, 2014). The  $D_A$  values represent the total degree of packing achieved at zero and low pressures and follow the rank order LDP > STL > SGL IV. The particulate rearrangement phase in the early compression stages is represented by  $D_B$ . The  $D_B$  is also highest for LDP compacts suggesting more fragmentation at low pressure. The values for  $D_O$  did not follow any particular trend; the highest value was observed for SGL IV.

### 5.9.2 Kawakita Analysis

Figure 4.6 shows representative Kawakita plots for SGL IV, STL and LDP. A linear relationship was obtained at all compression pressures. The  $D_I$  value which is the measurement of the packed initial relative density of the material with application of pressure (Podczek and Sharma, 1996) was observed to be highest for LDP. The  $P_k$  value, which is an inverse measurement of plastic deformation occurring during the compression process (Bakre and Abimbola, 2013), was observed to be lowest for SGL IV; this could also be potentiated by gelatin, an amorphous binder, also being plastically deformable (Mattson, 2000); But the highest amount of total plastic deformation, which gave the best packing (Bakre and Abimbola, 2013), was exhibited by LDP, as evidenced by the lowest value of  $a$ . Bakre and Abimbola, 2013, have reported that formulations prepared by direct

compression underwent plastic deformation more rapidly than those prepared by wet granulation.

#### **5.10 MECHANICAL PROPERTIES OF STARGELAC AND SOME COMMERCIAL DIRECT COMPRESSION EXCIPIENTS**

Tensile strength is a method of measuring the mechanical strength of tablets. It is the force required to break a tablet in a diametrical compression test and is used to evaluate tableting performance of materials and gives an insight into the brittle fracture tendency of tablets prepared from the materials. Brittle fracture index (BFI) is the measure of the tablet tendency to laminate or cap during manufacture (Uhumwangho *et al.*, 2006).

The results (Table 4.12) show that tablets prepared with SGL IV exhibited acceptable crushing strength. This can be as a result of the absence of entrapped air or low density regions in the tablets, which shows that there was even consolidation of the tablets during compaction (Okor, 2005). Tablets prepared with SGL IV as well as Starlac<sup>®</sup> and Ludipress<sup>®</sup> also exhibited low tendency to fracture since the BFI values fall well below the maximal fracture tendency, which is 1 (Okor, 2005). A low BFI is desirable for minimization of capping and lamination during tablet production. However the desirable effect on T, tensile strength, largely depends on the intended use of the tablets (Odeku *et al.*, 2008). Also, there appears to be a relationship between  $P_k$  value and the T, tensile strength of tablets. Low  $P_k$  values of tablets have been shown to be responsible for high T values as higher total plastic deformation would lead to more contact points for interparticulate bonding (Odeku *et al.*, 2008).

## 5.11 ANALYSIS OF TABLETS FORMULATED WITH CO-PROCESSED EXCIPIENT AND MODEL DRUGS

From the results shown in Table 4.13, it can be concluded that the agglomerates of SGL IV, STL and LDP exhibited satisfactory tableting characteristics with the selected model drugs. The average weight of tablets was between 649 -655 mg for paracetamol and 345-360 mg for ascorbic acid. All tablets exhibited uniform weight with acceptable standard deviation values. The diameters and thickness of the tablets showed little variation. The same trend was observed with the friability for tablets of both model drugs. The requirement for tablets friability is below 1 % (Banker and Rhodes, 1995). The crushing strength was within acceptable range of 4 -7 Kgf (Tsige and Alexander, 1993). The ANOVA analysis also showed that there is no significant difference at  $p$  value  $\geq 0.05$  between the crushing strengths of the three batches of paracetamol tablets. Using Duncan homogenous Subset and Mean plot the result showed that little strength is required to crush STL-P than LDP-P, while high energy strength will be required to crush SGL-P. Comparing each sample to the other; Bonferroni analysis showed that there is no significant difference when comparing each of the samples to another at  $\geq 0.05$  P value.

Similarly, there is also no significant difference at  $p$  value  $\geq 0.05$  between the crushing strengths of the three batches of ascorbic Acid tablets. Results of application of Duncan homogenous Subset and Mean plot showed that lower force is required to crush STL-AA than SGL-AA, while higher force will be required to crush LDP-AA. Comparing each sample to the other; Bonferroni analysis showed that there is no significant difference when comparing each of the samples to another at  $\geq 0.05$  P value.

The requirement for disintegration time is 15 minutes for uncoated tablets (BP 2004). Here all the batches exhibited disintegration time below the stated limit though disintegration times for StarGeLac were higher than for Starlac ® and Ludipress ®.

The probable reasons for quicker disintegration may be attributed to the presence of a superdisintegrant, i.e. Kollidon CL (crospovidone) in Ludipress ® as well as due to presence of an adjuvant, modified maize starch, in Starlac ®, which facilitates the disintegration process. The ANOVA analysis revealed that there is a significant difference at  $p \text{ value} \geq 0.05$  between the disintegration times of the three batches of paracetamol tablet samples; but on application of Duncan homogenous Subset and Mean plot, the result showed that SGL-P will disintegrate faster than STL-P followed by LDP-P. While comparing each sample to the other Bonferroni analysis showed that there is a significant difference when comparing each of the samples to another at  $\geq 0.05$  P value. On analysis of the disintegration times of the ascorbic acid tablets, the ANOVA analysis showed that there is a significant difference at  $p \text{ value} \geq 0.05$  between the disintegration times of the three batches of ascorbic acid tablets. Using Duncan homogenous Subset and Mean plot, the result showed that the time taken by STL-AA to disintegrate will be less and so disintegration is faster than that of LDP-AA, followed by SGL AA. Comparing each ascorbic acid tablet sample to the other; Bonferroni analysis showed that there is a significant difference when comparing the time take for SGL-AA to disintegrate to both LDP-AA and STL-AA but there is no significant difference while comparing STL-AA and LDP-AA at  $\geq 0.05$  P value.

## 5.12 DISSOLUTION STUDIES

Dissolution rate of the drug from the primary particles of the tablet is an important factor in drug absorption and for many formulations is the rate-limiting step. Dissolution rate is indicative of the availability of a drug from the tablet.

This was carried out for tablets containing the model drugs. The  $T_{50\%}$  which is the time taken for 50 % of the drug to be released was 10 min for both paracetamol and ascorbic acid tablet batches. It has been recorded that binder type, binder quantity and method of incorporation of the binder affect tablet properties such as dissolution rate (Zhang *et al.*, 2005). Differing reports exist about formulations containing gelatin as binder (Singh *et al.*, 2002). A swollen, very thin, tough and rubbery water insoluble membrane known as a pellicle is formed, which act as a barrier and can restrict the release of the drug. In a study conducted by Asker *et al.*, (1981); Singh *et al.*, (2002), increase in both disintegration and dissolution time was observed in prednisolone tablets containing gelatin as binder. Kumar, (2015), has also reported formation of a dense matrix around drug particles by binder mucilage, providing more barriers for the drug particles to escape before dissolution.

However, at 45 minutes the percentage of drug released for all tablets was above 70 %. All the batches of tablets passed the dissolution test for tablets which specifies that at least 70 % of the drug should be in solution after 45 min (British Pharmacopoeia, 2002).

The results showed that the release of ascorbic acid with StarGeLac was faster than that of paracetamol (Figures 4.8a and 4.8b). This could be because of the solubility of ascorbic acid. The fastest rate release of both drugs is from Ludipress® (LDP-P & LDP-AA). This agrees with the disintegration times of the tablets for which tablets prepared with Ludipress also exhibited the fastest times.

## CHAPTER SIX

### SUMMARY, CONCLUSION AND RECOMMENDATIONS

#### 6.1 SUMMARY

In this study, a direct compression co-excipient StarGeLac was designed and developed. Acid hydrolyzed cassava starch and lactose in different ratios were dispersed with a fixed proportion of gelatin and the co-processed excipient was prepared using the co-drying method. Hydrolysis of native cassava starch resulted in improved physicochemical properties because the results showed better flow rate, angle of repose, Carr's index, Hausner's ratio and swelling capacity compared to the native starch. It was also seen from the results that the effect of period or time of hydrolysis on modified starch is significant as the degree of cohesiveness of the powders reduced with progressing hydrolysis resulting in more compact tablets.

The initial batches of co-excipients that were developed were evaluated for their physicochemical and tableting properties. The results of the preliminary investigation showed that batch 4 (SGL IV) of the prepared co-processed excipient had superior physicochemical properties when compared with other batches. Also, placebo tablets prepared with SGL4 exhibited acceptable crushing strength and friability. The co-processed excipient StarGeLac (SGL IV) containing acid-hydrolysed starch, gelatin and lactose in the ratio 22.5: 5: 72.5 was chosen for further evaluation. The properties of StarGeLac determined include: hydration capacity, FTIR study, DSC, Heckel and Kawakita analyses, dilution potential, tensile strength and brittle fracture tendency. The hydration and swelling capacities results showed that SGL IV is capable of absorbing at least two times its own weight of water. The FTIR spectra and DSC thermograms showed

that the prepared co-processed excipient did not undergo any form of chemical changes; plots of SGL IV, Starlac<sup>®</sup> and Ludipress<sup>®</sup> based formulations obtained from Heckel and Kawakita equations showed that StarGeLac consolidates by plastic deformation but that the onset is slower (higher  $P_y$  value) and shows total plastic deformation (lower  $P_k$  value) when compared with the other commercial co-processed excipients. Dilution potential studies revealed that that 40 % and 33.3% of paracetamol and ascorbic acid respectively compressed with StarGeLac (SGL4) to give compacts of acceptable crushing strengths. Acid-hydrolysed starch, gelatin and lactose physical mixture did not yield satisfactory tablets even with the same percentage of drugs. Assessment of mechanical properties also exhibited compacts of sufficient mechanical strength and high brittle fracture tendency.

The tableting properties of StarGeLac were evaluated by using paracetamol, a poorly soluble and compressible drug and ascorbic acid, a water soluble drug, as model drugs. The performance of StarGeLac in the formulations was then compared with that of StarLac<sup>®</sup> and Ludipress<sup>®</sup> based formulations. Robust tablets of paracetamol and ascorbic acid were prepared using StarGeLac and were comparable to those prepared with StarLac<sup>®</sup> and Ludipress<sup>®</sup>. Paracetamol tablets prepared with StarGeLac had higher crushing strength and disintegration time than the ascorbic acid counterpart but both paracetamol and ascorbic acid tablets prepared with the commercial co-processed excipients had faster disintegration times.

Finally, the obtained results reveal that acid hydrolysis impacts positively on the physicochemical properties of cassava starch and that acid hydrolyzed cassava starch, gelatin and lactose can be considered for use, as a multifunctional excipient, in the filler-binder-disintegrant category, in direct compression tableting.

## **6.2 CONCLUSION**

The rate of acid hydrolysis is directly proportional to exposure time and the flow and tablet properties of cassava starch were improved by modification through acid hydrolysis rendering it suitable for use as a direct compression excipient. Co-processing of acid hydrolyzed cassava starch, gelatin and lactose yielded a multifunctional three-component direct compression excipient, StarGeLac, with suitable powder, mechanical and tablet properties. StarGeLac produced tablets of paracetamol and ascorbic acid of acceptable tablet properties and is comparable to commercially available direct compression excipients.

## **6.3 RECOMMENDATIONS**

- Co-processed excipients containing hydrolyzed starch, gelatin and lactose can be developed and used to impart mechanical strength to the formulation of bi-layer tablets.
- StarGeLac can be further developed for use in direct compression tableting by modification of the lactose portion by spray drying.

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## I

Particle size distribution of native and hydrolyzed starches

Particle size ( $\mu$ )	weight retained (g)				
	NS	AHSC6	AHSC12	AHSC18	AHSC24
500	1.8	2.21	2.62	2.61	2.90
250	3.5	3.15	4.15	4.54	4.25
150	1.84	1.25	1.58	1.62	1.82
125	1.60	0.9	1.2	1.36	1.38
90	6.68	1.26	1.24	1.12	1.56
75	2.68	3.2	3.8	4.68	5.82

## II

**Preparation of Batches of Co-Processed Excipient, Stargelac (SGL) Containing various Ratios Of Hydrolyzed Starch, Gelatin And Lactose**

Batches of co-processed excipient (STARGELAC)					
	SGL1	SGL2	SGL3	SGL4	SGL5
Hydrolysed starch (g)	52.5	42.5	32.5	22.5	12.5
Gelatin (g)	5	5	5	5	5
Lactose (g)	42.5	52.5	62.5	72.5	82.5

### III

#### Dilution potential of SGL4 using paracetamol as model drug

	Batches				
	I	II	III	IV	V
Paracetamol (mg)	100	150	200	250	300
SGL4 (mg)	400	350	300	250	200
Total weight	500	500	500	500	500
Crushing strength (Kgf)	10	8	7	3	1

### IV

#### Dilution potential of SGL4 using ascorbic acid as model drug

	Batches				
	I	II	III	IV	V
Ascorbic acid (mg)	50	75	100	125	150
SGL4 (mg)	200	175	200	125	100
Total weight	250	250	250	250	250
Crushing strength (Kgf)	10.3	9.8	7.5	3.5	2.5

#### IV.

Particle size distribution of StarGeLac (SGL4)

<b>Particle size (<math>\mu</math>)</b>	<b>weight retained (g) SGL4</b>
500	0.21
250	1.25
150	4.34
125	4.29
90	4.81
75	8.2

## V. Statistical Data (ANOVA)

### DISINTEGRATION TIME OF PARACETAMOL

#### One way Descriptive

Disintegration Time of Paracetamol

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Between-Component Variance
					Lower Bound	Upper Bound			
LDP	6	43.5000	7.34166	2.99722	35.7954	51.2046	35.00	55.00	
STL	6	35.0000	3.68782	1.50555	31.1299	38.8701	30.00	40.00	
SGL	6	25.5000	3.83406	1.56525	21.4764	29.5236	19.00	30.00	
Total	18	34.6667	9.02285	2.12671	30.1797	39.1536	19.00	55.00	
Fixed Model			5.23450	1.23378	32.0369	37.2964			
Random Effects				5.19882	12.2979	57.0354			76.51667

#### Test of Homogeneity of Variances

Disintegration Time of Paracetamol

Levene Statistic	df1	df2	Sig.
2.464	2	15	.119

#### ANOVA

Disintegration Time of Paracetamol

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	973.000	2	486.500	17.755	.000
Within Groups	411.000	15	27.400		
Total	1384.000	17			

#### Robust Tests of Equality of Means

Disintegration Time of Paracetamol

	Statistic <sup>a</sup>	df1	df2	Sig.
Welch	16.788	2	9.491	.001
Brown-Forsythe	17.755	2	10.218	.000

a. Asymptotically F distributed.

**Post Hoc Tests**

**Multiple Comparisons**

Dependent Variable: Disintegration Time of Paracetamol

	(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
	Disintegration Time	Disintegration Time				Lower Bound	Upper Bound
Bonferroni	LDP	STL	8.50000*	3.02214	.039	.3591	16.6409
		SGL	18.00000*	3.02214	.000	9.8591	26.1409
	STL	LDP	-8.50000*	3.02214	.039	-16.6409	-.3591
		SGL	9.50000*	3.02214	.020	1.3591	17.6409
	SGL	LDP	-18.00000*	3.02214	.000	-26.1409	-9.8591
		STL	-9.50000*	3.02214	.020	-17.6409	-1.3591

\*. The mean difference is significant at the 0.05 level.

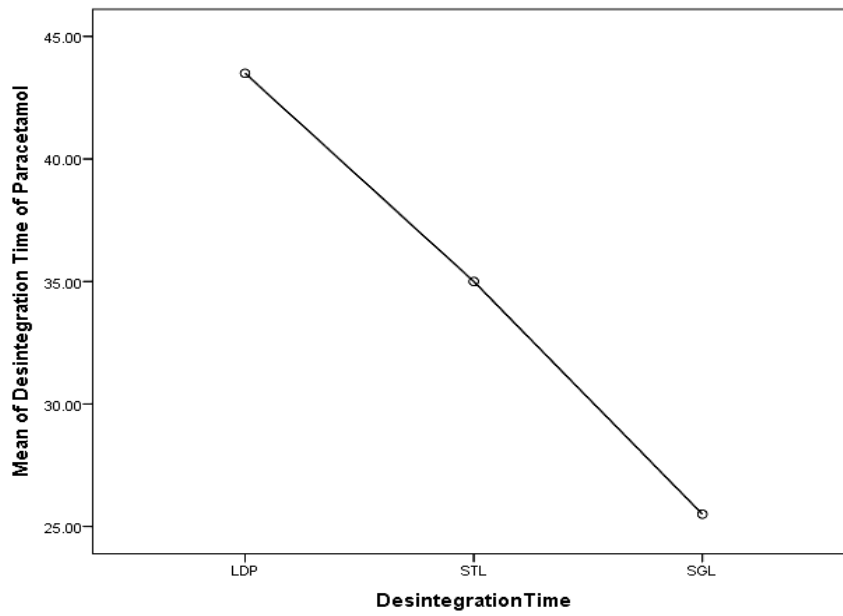
**Homogeneous Subsets**

**Disintegration Time of Paracetamol**

	DisintegrationTime	N	Subset for alpha = 0.05		
			1	2	3
Duncan <sup>a</sup>	SGL	6	25.5000		
	STL	6		35.0000	
	LDP	6			43.5000
	Sig.		1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 6.000.



Mean Plots of Disintegration times of the three batches of Paracetamol Tablets (SGL-P, STL-P and LDP-P)

Crushing Strength of Paracetamol

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Between-Component Variance
					Lower Bound	Upper Bound			
LDP	6	7.8333	.40825	.16667	7.4049	8.2618	7.00	8.00	
STL	6	7.4167	.91742	.37454	6.4539	8.3794	6.00	8.00	
SGL	6	8.3333	1.36626	.55777	6.8995	9.7671	6.00	10.00	
Total	18	7.8611	.99714	.23503	7.3652	8.3570	6.00	10.00	
Fixed Model			.97895	.23074	7.3693	8.3529			
Random Effects				.26498	6.7210	9.0012			.05093

**TEST OF HOMOGENEITY OF VARIANCES**

Crushing Strength of Paracetamol

Levene Statistic	df1	df2	Sig.
2.876	2	15	.088

**ANOVA**

Crushing Strength of Paracetamol

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.528	2	1.264	1.319	.297
Within Groups	14.375	15	.958		
Total	16.903	17			

## ROBUST TESTS OF EQUALITY OF MEANS

Crushing Strength of Paracetamol

	Statistic <sup>a</sup>	df1	df2	Sig.
Welch	.925	2	8.170	.434
Brown-Forsythe	1.319	2	9.792	.311

a. Asymptotically F distributed.

### Post Hoc Tests

#### Multiple Comparisons

Dependent Variable: Crushing Strength of Paracetamol

	(I) Crushing Strength	(J) Crushing Strength	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Bonferroni	LDP	STL	.41667	.56519	1.000	-1.1058	1.9392
		SGL	-.50000	.56519	1.000	-2.0225	1.0225
	STL	LDP	-.41667	.56519	1.000	-1.9392	1.1058
		SGL	-.91667	.56519	.377	-2.4392	.6058
	SGL	LDP	.50000	.56519	1.000	-1.0225	2.0225
		STL	.91667	.56519	.377	-.6058	2.4392

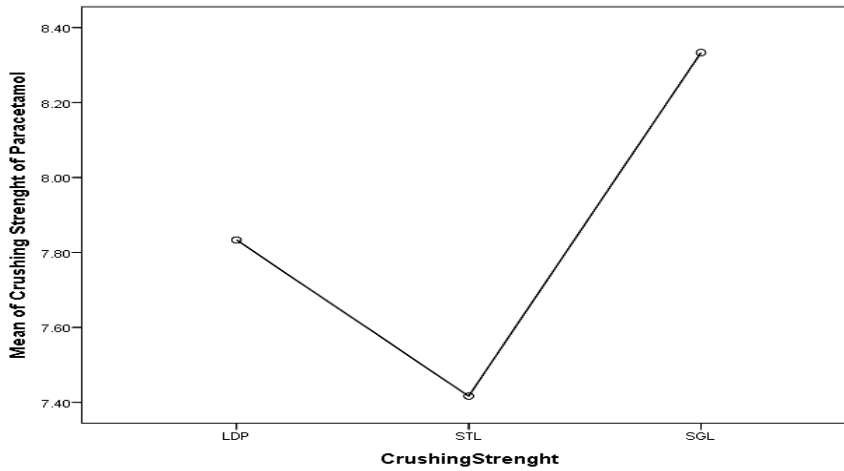
### Homogeneous Subsets

#### CRUSHING STRENGTH OF PARACETAMOL

	Crushing Strength	N	Subset for alpha = 0.05
			1
Duncan <sup>a</sup>	STL	6	7.4167
	LDP	6	7.8333
	SGL	6	8.3333
	Sig.		.144

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 6.000.



Mean Plots of crushing strengths of the three batches of Paracetamol Tablets (SGL-P, STL-P and LDP-P)

### DISINTEGRATION TIME OF ASCORBIC ACID

#### One way Descriptive

Disintegration Time of Ascorbic Acid

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Between - Component Variance
					Lower Bound	Upper Bound			
LDP	6	110.000	10.48809	4.28174	98.9934	121.0066	100.00	130.00	
STL	6	104.500	17.53568	7.15891	86.0974	122.9026	80.00	122.00	
SGL	6	252.500	31.89828	13.02242	219.0248	285.9752	200.00	295.00	
Total	18	155.6667	73.42703	17.30692	119.1523	192.1811	80.00	295.00	
Fixed Model			21.87083	5.15500	144.6790	166.6543			
Random Effects				48.44269	-52.7654	364.0987			6960.36111

**Test of Homogeneity of Variances**

Disintegration Time of Ascorbic Acid

Levene Statistic	df1	df2	Sig.
2.186	2	15	.147

**ANOVA**

Disintegration Time of Ascorbic Acid

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	84481.000	2	42240.500	88.308	.000
Within Groups	7175.000	15	478.333		
Total	91656.000	17			

**Robust Tests of Equality of Means**

Disintegration Time of Ascorbic Acid

	Statistic <sup>a</sup>	df1	df2	Sig.
Welch	52.769	2	8.712	.000
Brown-Forsythe	88.308	2	9.016	.000

a. Asymptotically F distributed.

**Post Hoc Tests**

**Multiple Comparisons**

Dependent Variable: Disintegration Time of Ascorbic Acid

	(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
	Ascorbic Acid	Ascorbic Acid				Lower Bound	Upper Bound
Bonferro ni	LDP	STL	5.50000	12.62713	1.000	-28.5142	39.5142
		SGL	-142.50000*	12.62713	.000	-176.5142	-108.4858
	STL	LDP	-5.50000	12.62713	1.000	-39.5142	28.5142
		SGL	-148.00000*	12.62713	.000	-182.0142	-113.9858
	SGL	LDP	142.50000*	12.62713	.000	108.4858	176.5142
		STL	148.00000*	12.62713	.000	113.9858	182.0142

\*. The mean difference is significant at the 0.05 level.

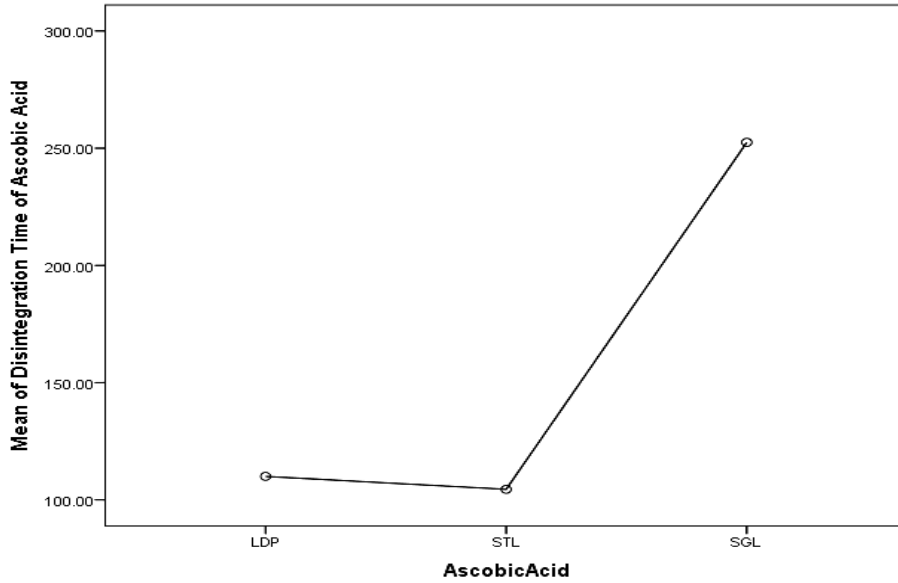
**Homogeneous Subsets**

**Disintegration Time of Ascorbic Acid**

	Ascorbic Acid	N	Subset for alpha = 0.05	
			1	2
Duncan <sup>a</sup>	STL	6	104.5000	
	LDP	6	110.0000	
	SGL	6		252.5000
	Sig.		.669	1.000

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 6.000.



Mean Plots of Disintegration times of the three batches of Ascorbic Acid Tablets (SGL-AA, STL-AA and LDP-AA)

### CRUSHING STRENGTH OF ASCORBIC ACID

#### One way Descriptive

#### Crushing Strength of Ascorbic Acid

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Between-Component Variance
					Lower Bound	Upper Bound			
LDP	6	7.0833	1.68572	.68819	5.3143	8.8524	5.00	9.50	
STL	6	5.3333	1.36626	.55777	3.8995	6.7671	4.00	8.00	
SGL	6	6.0833	1.11430	.45491	4.9139	7.2527	5.00	8.00	
Total	18	6.1667	1.51463	.35700	5.4135	6.9199	4.00	9.50	
Fixed Model			1.40831	.33194	5.4592	6.8742			
Random Effects				.50690	3.9857	8.3477			.44028

**Test of Homogeneity of Variances**

Crushing Strength of Ascorbic Acid

Levene Statistic	df1	df2	Sig.
1.123	2	15	.351

**ANOVA**

Crushing Strength of Ascorbic Acid

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	9.250	2	4.625	2.332	.131
Within Groups	29.750	15	1.983		
Total	39.000	17			

**Robust Tests of Equality of Means**

Crushing Strength of Ascorbic Acid

	Statistic <sup>a</sup>	df1	df2	Sig.
Welch	1.830	2	9.735	.212
Brown-Forsythe	2.332	2	13.511	.135

a. Asymptotically F distributed.

**Post Hoc Tests**

**Multiple Comparisons**

Dependent Variable: Crushing Strength of Ascorbic Acid

	(I) Ascorbic Acid	(J) Ascorbic Acid	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Bonferro ni	LDP	STL	1.75000	.81309	.144	-.4402	3.9402
		SGL	1.00000	.81309	.713	-1.1902	3.1902
	STL	LDP	-1.75000	.81309	.144	-3.9402	.4402
		SGL	-.75000	.81309	1.000	-2.9402	1.4402
	SGL	LDP	-1.00000	.81309	.713	-3.1902	1.1902
		STL	.75000	.81309	1.000	-1.4402	2.9402

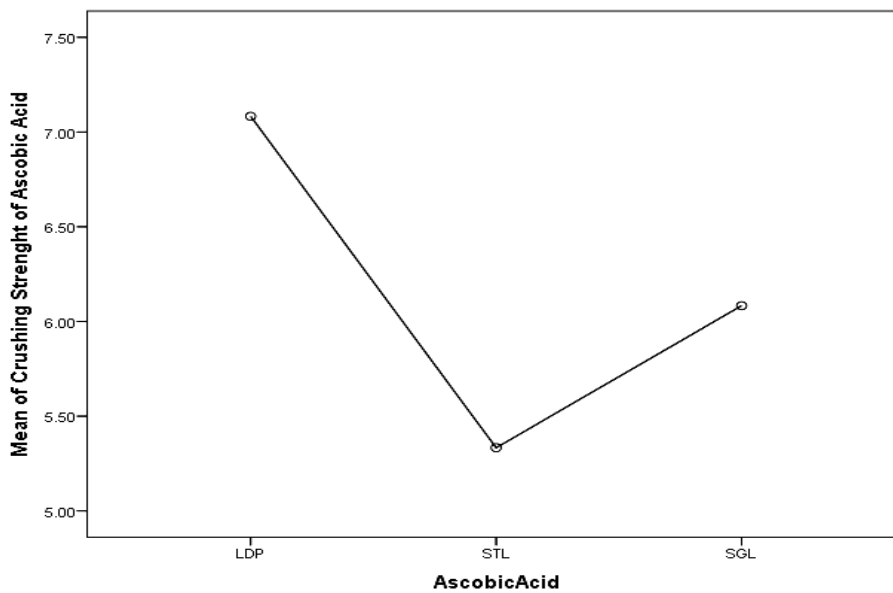
### Homogeneous Subsets

#### Crushing Strength of Ascorbic Acid

	Ascorbic Acid	N	Subset for alpha = 0.05
			1
Duncan <sup>a</sup>	STL	6	5.3333
	SGL	6	6.0833
	LDP	6	7.0833
	Sig.		.058

Means for groups in homogeneous subsets are displayed.

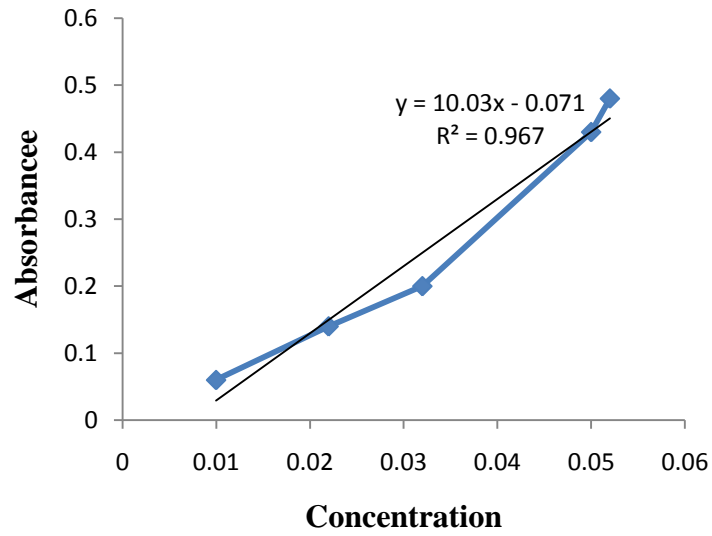
a. Uses Harmonic Mean Sample Size = 6.000.



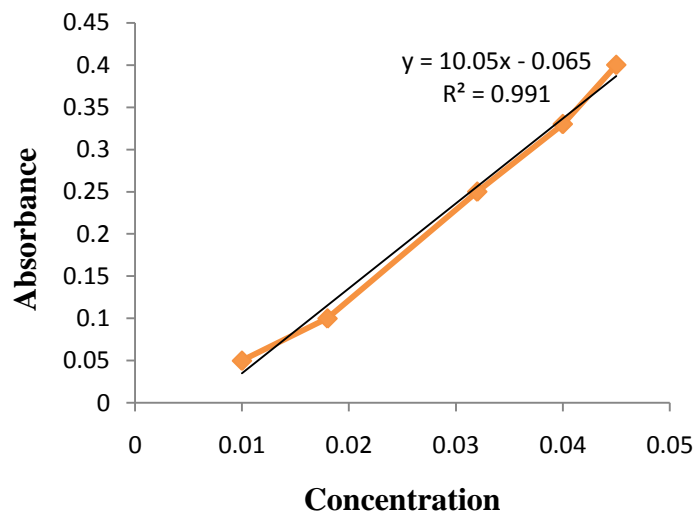
Figures 4.10a and 4.10b: Mean Plots of crushing strengths of the three batches of Ascorbic Acid Tablets (SGL-AA, STL-AA and LDP-AA)

## VI. Beer Lambert Plots

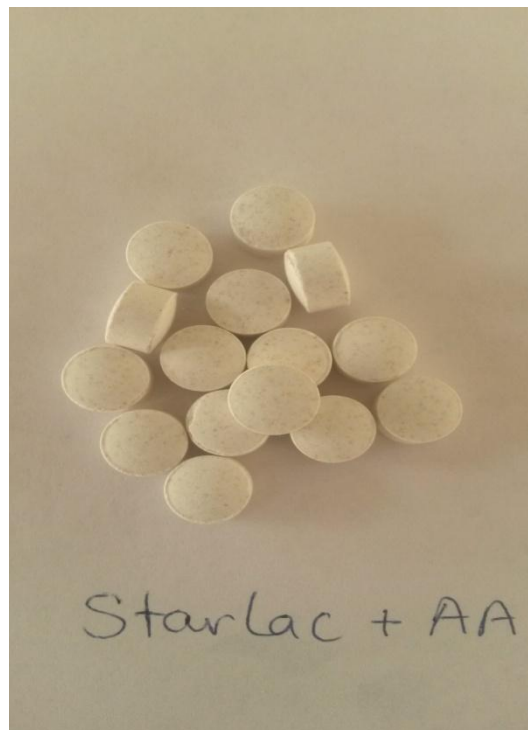
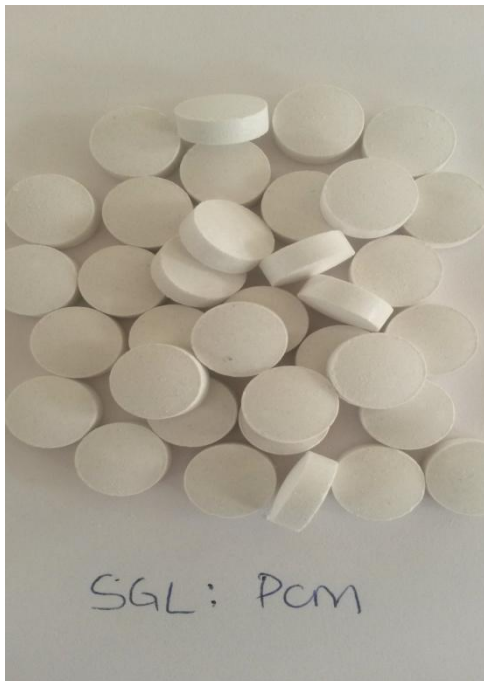
### SGL-P

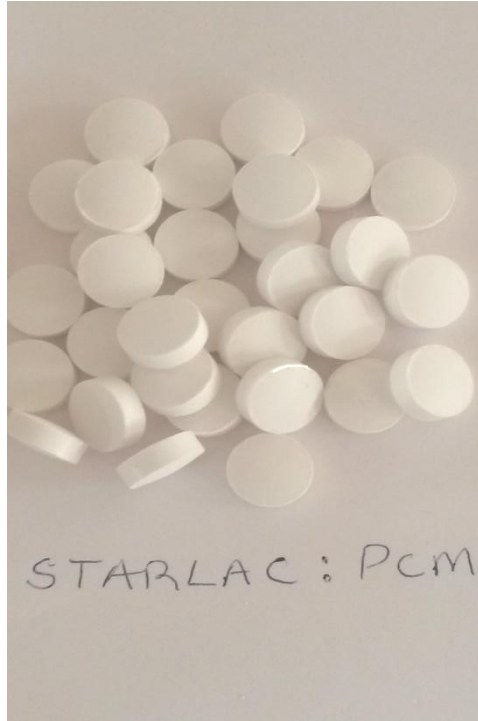


### SGL-AA

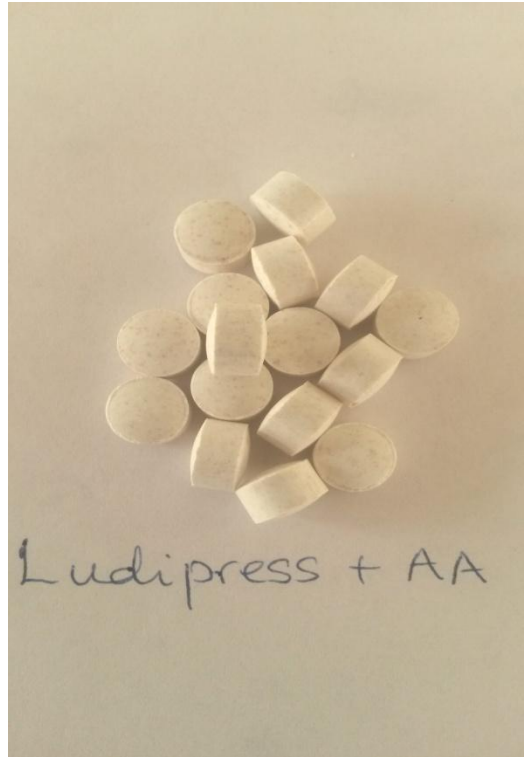


VI. Pictures of Tablets

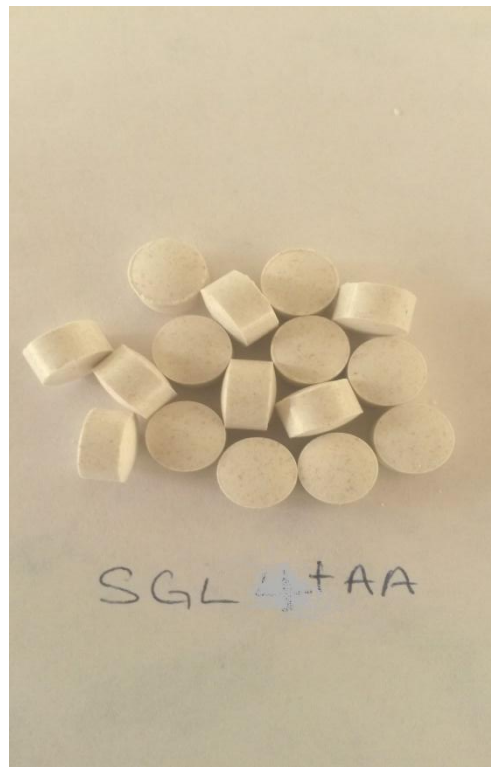




STARLAC : PCM



Ludipress + AA



SGL + AA