ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

PREPARATION AND CHARACTERIZATION OF RETROGRADED CASSAVA STARCH AND ITS EVALUATION AS DIRECTLY COMPRESSIBLE EXCIPIENT

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A Thesis Submitted to School of Graduate Studies, Addis Ababa University, School of Pharmacy, Department of Pharmaceutics and Social Pharmacy, in Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmaceutics

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Acronyms

BP:	British Pharmacopoeia
CI:	Carr's Index
EPHARM:	Ethiopian Pharmaceutical Share Company
HR:	Hausner Ratio
RH:	Relative Humidity
RS:	Retrograded Starch
SD:	Standard Deviation
SP:	Swelling Power
USP/NF:	United States Pharmacopoeia/National Formulary

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Abstract

Starch is a semi-crystalline biopolymer that serves as a carbohydrate reserve in many plants, including cereals, roots, tubers, seeds, and fruits. Starch granules can vary in shape, size, structure, and chemical composition, depending on the origin of the starch. In recent years among polysaccharides, starch is receiving utmost attention due to its usefulness in different industrial products. Unprocessed native starches are structurally weak and functionally restricted for application in pharmaceutical, food and non-food technologies. Modifications are necessary to create a range of functionality. Modification can be, physical, chemical or enzymatic.

Starch was isolated from Cassava (*Manihot esculenta*), gelatinized in the presence of water then allowed for retrogradation. Some of the physicochemical properties of the retrograded cassava starch such as densities, flow, swelling power, solubility, moisture sorption were determined and compared to those of native cassava starch and Starch 1500®. Compactability was determined through volume reduction of the powder under tapping for Kawakita analysis and volume reduction mechanism under compression pressure for Heckel plot. The comparative direct compressibility and magnesium stearate sensitivity of these starches in tablet formulations were also studied and the resulting tablets were evaluated for their physico-mechanical properties.

The results of flow and compactability studies of the retrograded starch powder (angle of repose, Carr's index (CI) and Hausner ratio (HR), and Kawakita analysis) indicate that retrogradation improved both flow and compactability of the modified cassava starch. Retrograded cassava starch showed angle of repose below 30, CI below 16, HR below 1.25, and flow rate of 8.23 ± 0.227 (g/s). In moisture sorption study, retrograded cassava starch exhibited relatively higher moisture sorption pattern than the native form. Retrogradation also increased the swelling power of the native cassava starch. The small "a" values of the Kawakita constant (indicating good fluidity) supported the fact that modification of the starch improves the powder flowability. Heckel plot was used as assessment parameter where the P_y, D_0, D_A, D_B variables were investigated. Retrograded cassava starch depicted lower P_y value than Starch 1500® owing to a higher plastic deformation. Retrograded cassava starch showed higher sensitivity to magnesium stearate than starch 1500®.

From the foregoing it can be concluded that retrograded cassava starch has the potential to be used as an alternative directly compressible excipient as it exhibits good flow and compaction properties.

Keywords: Cassava Starch; Retrogradation; Directly Compressible Excipient; Magnesium Stearate Sensitivity.

1. INTRODUCTION

1.1. Starch

Nature has chosen the starch granule as an almost universal form for packaging and storing carbohydrate in green plants. In granule form, starch is semi-crystalline, water-insoluble and dense. It is hydrated to only a small degree, so that a large amount of carbohydrate is stored in a small volume. In spite of the insolubility of starch, it is adequately convertible to sugar by the enzymes of plant metabolism. Also, raw starch granules are digested by innumerable predators ranging from bacteria and molds to higher animals and man (Moorthy 2004; Mishra and Rai, 2006). Starch represents an important part of many agricultural products like legumes (bean, pea, and faba), cereals (wheat, corn, and rice) and tubers (potato and tapioca) (Marques *et al.*, 2006).

Native starch granules are composed of two types of alpha-glucans, linear amylose (an α-1,4 polymer) and amylopectin (a branched polymer) consisting of short linear α-1, 4 polymer chains linked to each other by α-1, 6 linkages, which represent approximately 98-99% of the dry weight (Jayakody *et al.*, 2005; Onitilo *et al.*, 2007). The ratio of the two polysaccharides varies according to the botanical origin of the starch (Jacobson *et al.*, 1997). The basic chemical formula of the starch molecule is $(C_6H_{10}O_5)_n$. These two components form a semi-crystalline structure in the starch granules, which consist of crystalline lamellae (ordered, tightly packed of parallel glucan chains) and amorphous lamellae (less ordered regions) (Oates, 1997). Starches of different origins have different degrees of crystallinity (range about 15-45 %) (Zobel, 1988).

Amylose is mainly linear molecule of α-(1-4)-linked glucose residues with a small fraction of α-(1-6)-linkages (Fig. 1.1). It makes up a minor fraction of starch granule where it generally accounts for 20-30% of the total starch (Boudries *et al.*, 2009). There are also a number of natural waxy mutants for example, barley, maize, wheat and rice, with starch containing little or no amylose (Morrison *et al.*, 1984).

Amylopectin is the major constituent of starch and consists of large, highly branched molecules. It is composed of linear α-(1-4)-linked glucouse chains connected by α-(1-6)-linkages (Fig. 1.1). The outer and inner chains of amylopectin are designated as A-, B-, C-chains (Peat *et al.*,1952). A polymorph crystallize in an orthogonal unit cell with slightly distorted hexagonal packing and

8 water molecules per unit cell, whereas the B polymorph crystallizes in a hexagonal unit cell with a more open hexagonal packing and 36 water molecules per unit cell. The C polymorphic structure is a mixture of A and B unit cells and, therefore, is considered to be intermediate between A and B forms in packing density and structure (Sarko and Wu, 1978; Bogracheva *et al*., 2002). The ratio of A- to B- chains is a parameter used when characterizing the structures of different amylopectins (Hizukuri, 1996).

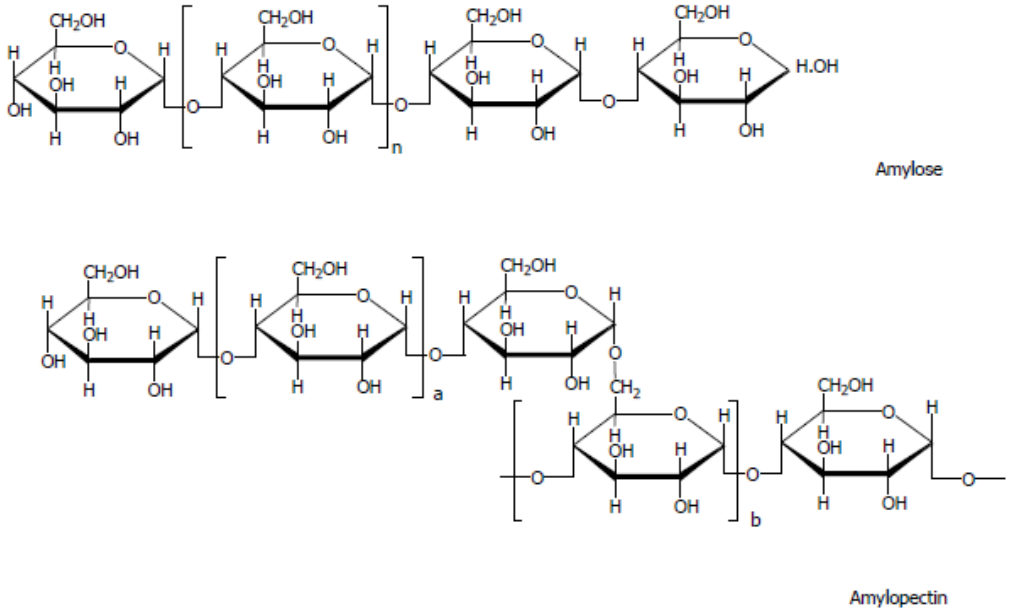

Figure 1.1: Structure of linear amylose and branched amylopectin molecules (adapted from Tester *et al*., 2004).

Each structure plays a critical role in the ultimate functionality of the native starch and its derivatives. The amylose/amylopectin ratios of starches can be genetically manipulated and offer a significant opportunity for the researcher with certain crops. Viscosity, shear resistance, gelatinization, textures, solubility, tackiness, gel stability, cold swelling and retrogradation are all functions of their amylose/amylopectin ratio (Martin and Smith, 1995; Boudries *et al*., 2009). The physical properties of starch are not only affected by amylose/amylopectin ratios but also by other components of the starch granules such as lipids and phosphorylated glucose residues (Morrison *et al*., 1984; Jane *et al*., 1996).

Starch is not only a staple food in human and animal diets; it is also widely used as a raw material in the food industry, as well as in paper, textile, and carpets, as binder and adhesives, as absorbents and as encapsulates bone replacement implants, bone cements, drug delivery systems, and tissue engineering scaffolds (Satyam *et al*., 2010; Neelam *et al*., 2012). The awareness of environmental issues has led to an increase interest in renewable and degradable materials. The use of starch in plastics and packaging, products that were formerly made out of petroleum-based raw materials, is gaining more interest (Slattery *et al*., 2000).

Starch can be used either in its native form or after chemical or physical modification. The usefulness of native or modified starch is based on its functional properties, which may include: adhesivness, cold-swelling properties, specific viscosity, freeze-thaw stability, processing tolerance, gel texture and film-forming properties (Aime *et al*., 2001). Starch is widely used in the production of pharmaceuticals because of its relative inertness, wide availability, low cost and high functionality. These uses are mainly due to its adhesive, thickening, gelling, swelling and film forming properties (Michaud, 2002).

The main starch sources on a global basis are maize, wheat, potato and cassava. Maize is the most important starch source and as much as 12% of the world production of maize is used for starch production. Potato and wheat starch makes up only a few percent of the total world production, though in Europe these starches are of great importance (De Baere, 1999). For centuries tropical starches (such as cassava, arrowroot, sago, taro, sweet potato or yam) have served as staple foods for millions of people, throughout the hot and humid regions of the world (Zhi-fen *et al*., 2008).

1.2. Cassava Plant and its Starch

1.2.1. Cassava Plant

Cassava is a woody shrub (Fig.1.2a) of the spurge family, native to South America. It is extensively cultivated as an annual crop in tropical and subtropical regions for its edible starchy tuberous root (Fig. 1.2b), a major source of carbohydrates. Cassava (*Manihot esculenta*) is one of the leading food and feed plants of the world (Onitilo *et al*., 2007).It is also one of the most common food crops grown and consumed in many parts of Africa. West Africa and the adjoining Congo basin, tropical South America and South and Southeast Asia are responsible for most of

global cassava production. Nigeria is the world's largest producer of cassava, while Thailand is the largest exporter of dried cassava (Paulos *et al*., 2009; Adejumo *et al*., 2011; Shiihii *et al*., 2011). Cassava is cultivated throughout western and southern parts of Ethiopia, particularly in Gamo Gofa, Illubabor and Wollega regions (Paulos *et al*., 2009). The crop grows well in various soil types and can withstand drought. It is an important famine reserve crop in countries with unreliable rainfall. It can be planted alone or in association with many other crops, like maize, groundnuts, vegetables, and rice (Onitilo *et al*., 2007).

Cassava tubers (Fig. 1.2b) are rich in carbohydrates, mainly starch are a major source of energy (Adejumo, 2011). Cassava roots contain significant amounts of calcium, phosphorus and vitamin C. However, they are poor in protein and other nutrients. Cassava is classified as either sweet or bitter. Like other roots and tubers, both bitter and sweet varieties of cassava contain ant-nutritional factors and toxins, with the bitter varieties containing much larger amounts. They must be properly prepared before consumption, as improper preparation of cassava can leave enough residual cyanide to cause acute cyanide intoxication, goiters, and even ataxia or partial paralysis.

(a) (b)

Figure 1.2: (a) Cassava plant (picture by Gabriel, T.) and (b) Cassava root (picture by Hailu, T.)

1.2.2. Cassava Starch

Starches are now made in many countries from many different starchy raw materials, such as wheat, barley, maize, rice, sweet potatoes, cassava, sago palm and waxy maize. Although they have similar chemical reactions and are usually interchangeable, starches from different sources have different granular structures which affect their physical properties. Unlike other tuber starches, extraction of starch from cassava is simple and the isolated starch is pure white in color and relatively free from other chemical impurities (Tetchi *et al*., 2007).

Starch granules in storage tissues can vary in shape, size and composition. The shape and size of the granules depends on the source, which allows one to identify the botanical source of the starch by microscopic examination (Narayana *et al*., 2002). Cassava starch granules are spherical in shape, exhibiting normal particle size distribution (12.71 μm to 14.34 μm) and A type crystallinity. The proximate composition of the starches on dry weight basis were found to be 0.001 - 0.01% protein, 0.08 - 0.11% fat, 0.03 - 0.1% ash, and 85.7% - 87.5% starch (Hoover 2001; Paulos *et al*., 2009).

The flour produced from the cassava plant, which on account of its low content of non-carbohydrate constituents might well be called a starch, is known in world trade as tapioca flour. It is used directly, made into a group of baked or gelatinized products or manufactured into glucose, dextrins and other products. Cassava starch has many remarkable properties such as high paste viscosity, high paste clarity and freeze-thaw stability which are advantageous to many industries (Tetchi *et al*., 2007). However, it also has negative characteristics such as long texture (high cohesiveness), sensitivity to shear, high temperature and low pH, which makes it undesirable for some specific uses. To extend its usefulness cassava starch has often been modified (Nabeshima and Grossmann, 2001).

1.3. Starch Modification

Pharmaceutical grade starch can be obtained from various sources depending on the ease of extraction, abundance of the material in any particular location as well as cost (Moorthy and Rajasekharan, 2006). However, unprocessed native starches are structurally too weak and

functionally too restricted for application in pharmaceutical, food and non-food technologies. Modifications are necessary to create a range of functionality**.**

To meet the demanding technological needs of today, the properties of starch are modified by a variety of modification methods. Starch modification is aimed at correcting one or some of the above mentioned shortcomings, which will enhance its versatility and satisfy consumer demand (Tharanathan, 2005; Singh *et al*., 2010). Starch modification can be achieved by chemical, physical, enzymatic methods as well as genetically. Starch modification can be introduced by altering the structure including the hydrogen bonding in a controlled manner to enhance and extend their application in industrial prospective (Singh *et al*., 2010; Neelam *et al*., 2012).

1.3.1. Chemical Modification

Chemical modification is the most common type of starch modification. It is the treatment of native starch with small amounts of approved chemical reagents. Chemical modification of starch changes the functionality of the starch. The chemistry involved in the modification of starch is quite straightforward and involves primarily reactions associated with the hydroxyl groups of the starch polymer (Tharanathan, 2005; Assen *et al*., 2011). Side chains can be introduced into the starch molecules through chemical reactions between the hydroxyl groups and functional groups. The side chains interrupt the hydrogen bonds between the hydroxyl groups of starch and destroy the granular semi crystalline structure of natural starch. Derivatization via ether or ester formation, oxidation of the hydroxyl groups to carbonyl or carboxylic groups, and hydrolysis of glycosidic bonds are some of the major mechanisms of chemical modification (Tomasik and Schilling, 2004).

1.3.2. Physical Modification

Physical modification involves physical treatment of starch granules thermally or by other physical means to impart certain needed properties or correct one or more shortcomings associated with native starch (Xie *et al*., 2005). Physical modification of starch is mainly applied to change the granular structure and convert native starch into cold water-soluble starch or small-crystallite starch. These set of techniques are generally given more preference as these do not involve any chemical treatment that can be harmful for human use (Teresa and Silva, 2011).

A large number of physical methods are available today. These include: heat-moisture treatment, annealing (Hoover and Vasanthan, 1994; Bhattacharyya *et al*., 2004; Pukkahuta *et al*., 2007), ultra high pressure treatment, osmotic-pressure treatment, thermal inhibition, gelatinization and retrogradation (Karim *et al*., 2000; Nabeshima and Grossmann, 2001; Ratnayake and Jackson, 2009).

1.3.3. Enzymatic Modification

This involves the exposure of starch suspensions to a number of enzymes primarily hydrolyzing enzymes that tend to produce highly functional derivatives. Origin of this technique can be dated back to the times when glucose syrup or high fructose corn syrup was produced (Kavlani *et al*., 2012). The enzymes amylomaltases (α-1,4-α-1,4 glucosyltransferases) found in eukarya, bacteria and archea representatives, breaks an α-1,4 bond between two glucose units to subsequently make a novel α-1,4 bond producing a modified starch that can be used in food stuffs, cosmetics, pharmaceutics, detergents, adhesives and drilling fluids. It is also a good source of plant-derived substitute for gelatin except that it forms a turbid gel whereas gelatin gels are transparent. Starch modified with amylase enzyme produces derivative with good adhesion property and mainly used in coating the food with colorant (Akhilesh *et al*., 2010).

1.3.4. Genetic Modification

These sets of techniques involve transgenic technology that targets the enzymes involved in starch biosynthesis thus avail the advantage over environmentally hazardous post-harvest chemical or enzymatic modifications. Genetic modifications can be carried out by the traditional plant breeding technique or through biotechnology. Amylose-free starch, high amylose starch and altered amylopectin structure are some of the most common genetic modification (Kavlani *et al*., 2012).

1.4. Retrograded Starch

1.4.1. Retrogradation of Starch

The retrogradation process is defined as the linking of starch chains into ordered crystalline structures. When starch is heated in the presence of water and subsequently cooled, the disrupted amylose and amylopectin chains can gradually re-associate into a different ordered structure in a

process termed retrogradation. Starch granules heated in excess water starts swelling as the water is absorbed by the granules. Past a certain state, the phenomenon is irreversible and undergoes an order-disorder phase transition called gelatinization over a temperature range characteristic of the starch source. This phase transition is a non-equilibrium process associated with the diffusion of water into the granule, hydration and swelling of the starch granules, uptake of heat, loss of crystallinity, and amylose leaching (Hoover, 1995; Liu *et al*., 2009). On cooling, the starch chains (amylose and amylopectin) in the gelatinized paste associate, leading to the formation of a more ordered structure. These molecular interactions are termed collectively "retrogradation" and the resulting starch thus produced is known as resistant starch that demonstratesresistance to digestibility by amylase enzymes (Hoover, 1995; Sandhu and Singh, 2007). Starch retrogradation is usually accompanied by a series of physical changes such as increased viscosity and turbidity of pastes, gel formation, exudation of water and increased degree of crystallinity with the appearance of B-typecrystalline polymorphs (Hoover *et al*., 2010).

The components of starch, amylopectin and amylose, have different roles in retrogradation. The linear fraction of starch is particularly susceptible to retrogradation while amylopectin being the branched fraction of starch is, slowly retrogradable. During retrogradation, amylose forms double-helical associations of 40-70 glucose units whereas amylopectin crystallization occurs by re-association of the outermost short branches (Singh *et al*., 2005). Much evidence suggests that changes in the amylopectin are the main cause for what we call retrogradation because they are responsible for all long-term rheological and structural changes. The amylose, however, is responsible for the short-term changes (Gudmundsson, 1994). Extent of retrogradation and the nature of crystallite formed may be affected by the origin of starch **(**Fechner *et al*., 2005), amylose content, length of amylopectin end chains (Bao *et al*., 2007) density of paste, physical or chemical modification (Lawal, 2008), as well as by paste storage condition (Singh *et al*., 2005).

Retrogradation is an ongoing process, which initially involves rapid re-crystallization of amylose molecules followed by a slow re-crystallization of amylopectin molecules. Amylose retrogradation determines the initial hardness of a starch gel and the stickiness and digestibility of processed foods. The long-term development of gel structure and crystallinity of processed

starch, which are involved in the staling of bread and cakes, are considered to be due to retrogradation of amylopectin (BeMiller, 2003; Fadda *et al*., 2014).

1.5. Compression of Powders

Compression refers to a reduction in the bulk volume of materials as a result of displacement of the gaseous phase. Stages involved in the bulk reduction of powdered solids are shown in Fig. 1.3. At the onset of the compression process, when the powder is filled into the die cavity, and prior to the entrance of the upper punch into the die cavity, the only forces that exist between the particles are those that are related to the packing characteristics of the particles, the density of the particles and the total mass of the material filled into the die (Fig. 1.3(I)). The packing characteristics of the powder mass will be determined by the packing characteristics of the individual particles (Cunningham *et al.*, 2004).

When external mechanical forces are applied to a powder mass, there is usually a reduction in volume due to closer packing of the powder particles, and in most cases, this is the main mechanism of initial volume reduction. The early stages of compaction are characterized by particle rearrangement; break down of the stable arches of particles, and deformation or breaking of the granules for agglomerated powders **(**Fig. 1.3(II)). Further densification during compaction takes place due to mechanical interactions at the contact between neighboring particles, rearrangement of particles becomes more difficult and further compression leads to some type of particle deformation (Fig. 1.3(III)). The natures of these interactions, which range from fragmentation to plastic deformation of the particles, depend on the mechanical properties of the powder material (Gonul *et al*., 2000; Cunningham *et al*., 2004). If on removal of the load, the deformation is to a large extent reversible, i.e. it behaves like rubber, then the deformation is said to be elastic (Fig 1.3(IV a)). All solids undergo elastic deformation when subjected to external forces. With several pharmaceutical materials such as acetylsalicylic acid, elasticdeformation becomes the predominant mechanism of compression within the range of maximum forceencountered in practice. In other groups of powdered solids, an elastic limit is reached, and loads above this level result in deformation not immediately reversible on the removal of the applied force. Bulk volume reduction in these cases results from plastic deformation and/or viscous flow of particles, (Fig 1.3(IV b)) which are squeezed into the remaining void spaces, resembling the behavior of modelling clay. This mechanism predominates in materials in which

theshear strength is less than the tensile or breaking strength (Armstrong, 1989; Gonul *et al*., 2000).

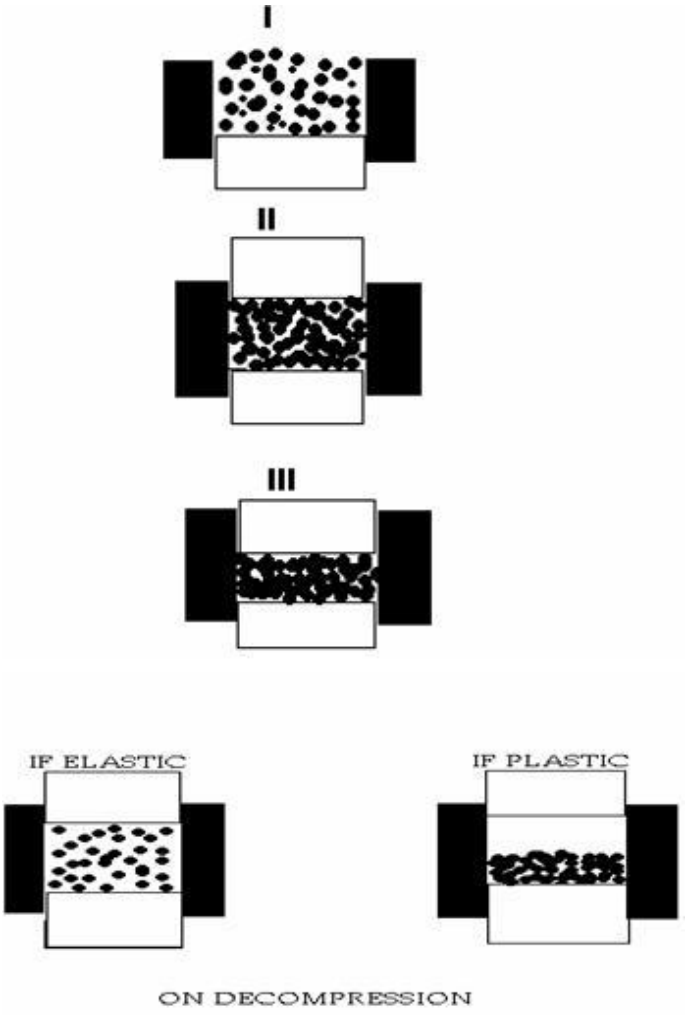

Figure 1.3: Schematic presentation of stages involved in compression (I - III) and decompression (IV)

Conversely, in materials in which the shear strength is greater than the tensile strength, particles may be preferentially fractured, and the smaller fragments then help to fill up the adjacent air spaces. This is most likely to occur with hard, brittle particles and is known as brittle fracture; sucrose behaves in this manner. The ability of a material to deform in a particular manner depends on the lattice structure; in particular whether weakly bonded lattice planes are inherently present. Brittle fracture creates clean surfaces that are brought in intimate contact by applied load.

1.5.1. Tablet Preparation by Direct Compression

Tablets are the most preferred dosage forms because they can be accurately dosed and provide good patient compliance, they are easy for companies to manufacture, and they can be produced at a relatively low cost. This popularity of tablets coupled with an increased understanding of the physics of compression and of manufacturing process variables have matured the manufacture of tablets as a science in its own right. Tablets are manufactured by using tablet compression machines. Tableting process was introduced in the early 1840s and since then numerous changes have taken place, apart from changes in tablet manufacturing, including the establishment of stringent regulatory requirements for the materials that should be used, the establishment of stability requirements, and the development of high-performance tableting machines (Mir *et al*., 2008; Meeus, 2011).

The tableting, mixture that is going to be compressed can be prepared by either of the three techniques- wet granulation, dry granulation or direct compression. Each of the individual technique mentioned above has its own advantages and disadvantages (Olowosulu *et al*., 2011; Meeus, 2011; Wang *et al*., 2010). But the invention of direct compression had increased the production of tablets enormously all over the world due to its advantages over the other two techniques. Cost effectiveness, stability, faster dissolution and less wear and tear of punches are among the advantages of direct compression (Bushra *et al*., 2003; Dokala and Pallavi, 2013). Whereas segregation, low dilution potential, lubricant sensitivity, and cost are claimed as the major disadvantages of the method (Jivraj *et al*., 2000; Dokala and Pallavi, 2013; Rojas *et al*., 2013).

Direct compression method involves simple blending of active pharmaceutical ingredient (API) with other ingredients and direct compaction of the resultant mixture by applying pressure (via an upper and a lower punch) to materials held in a die cavity (Mullarney *et al*., 2003; Izuagie *et al*., 2012). Although simple in terms of unit processes involved, the direct-compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physicomechanical properties required for the development of a robust

direct compression manufacturing process, which can bescaled-up from laboratory to production scale smoothly (Rojas *et al*., 2013; York, 1992; Zhang *et al*., 2003).

1.5.2. Requirements of Directly Compressible Adjuvant

In order to determine the suitability of an excipient for direct compression its functional properties must be assessed. The directly compressible adjuvant should be free flowing. Flowability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of ±5%. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and inaccurate filling (Gohel and Jogani, 2005; Gauhar *et al*., 2011; Chaudhari and Patil, 2012)**.**

The most important functional property is compactibility, which is related to the deformation mechanism that occurs when a pressure is applied to bind particles together to form a compact (Rojas *et al*., 2013). For example, brittle-deforming materials fragment during compaction, easing the formation of a large bonding area. On the other hand, ductile materials show plastic deformation and deform by dislocation of the crystals along slip-planes, forming hard compacts (Jivraj *et al*., 2000; Akram *et al*., 2011)**.**

The dilution potential is another crucial property in a direct compression excipient. It is defined as the minimum amount of excipient needed in the blend with an active ingredient to form tablets of adequate compactibility and friability (<1%). A directly compressible adjuvant should have high dilution potential so that the final dosage form has a minimum possible weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient (Apeji *et al*., 2011; Rojas *et al*., 2013).

Powder flow is another important factor to assess in a directly compressible agent. In order to enhance flow, lubricating excipients are employed. Currently, magnesium stearate is the most widely used lubricant. It eases the compaction process by reducing wall friction during tablet ejection, improves flowability, bulk and tap densities, compressibility and reduces the adhesion

of the powder to metal surfaces (Riepma *et al*., 1993). Since it is hydrophobic, the formation of an external film on the blended particles could reduce surface wettability, decreasing dissolution rates and prolonging disintegration times. Magnesium stearate could also weaken the bonding of the powder mixture by creating an interface on the surface which could reduce particle binding (Kushner and Moore, 2010). These effects could be aggravated by increasing the amount of magnesium stearate and mixing time and by using mainly plastic-deforming materials. Therefore, the sensitivity to magnesium stearate has been used to characterize the consolidation properties of excipients. Fragmenting materials could be less sensitive to magnesium stearate because of the creation of lubricant free surfaces during compression. In contrast, plastically deforming materials suffer from a high lubricant sensitivity, since the lubricant film is not destroyed during consolidation, because crystal-plane slipping maintains a continuous lubricant matrix over the particles (Bolhuis *et al*., 1999).

A directly compressible adjuvant should be capable of being reworked without loss of flow or compressibility. On recompression, the adjuvant should exhibit satisfactory tableting characteristics. The adjuvant should remain unchanged chemically and physically (Zhang *et al*., 2003; Dokala and Pallavi, 2013)**.**

A wide range of materials from various sources have been developed and marketed as directly compressible vehicles such as lactose, starch, cellulose derivatives, inorganic substances, polyalcohol, and sugar-based materials. Furthermore, many grades of existing excipients such as spray dried lactose, microcrystalline cellulose (MCC), granular dicalcium phosphate, crospovidone and pregelatinized starch have been introduced in the market (Gohel and Jogani, 2005; Olowosulu *et al*., 2011)**.**

1.5.3. Starches in Tablet Formulations

In today's pharmaceutical industry, excipients must have more functional properties than being just inert fillers. Excipients are now essential parts of the drug delivery system in pharmaceutical tablets. They are generally used as diluent, binder, disintegrant, gliding agent, lubricant or release control agent. At a time when synthetic polymers and animal-based products are creating some concerns amongst users, the need for natural excipients that are safe and versatile becomes more

acute. Starch is one of the most traditional excipients used for solid dosage formulations. Depending on the application, starch acts as a diluent, disintegrant or binder. Native starch is a classic tablet disintegrant whereas pregelatinized starch is often used as a binder (Olayemi *et al*., 2008). Starch also offers a wide range of possibilities and can be one of the preferred functional excipients of the future. It can undergo a wide range of physical or chemical modifications in order to modify its properties. The specific advantages brought by special starches can be better illustrated by examples, softening it for fast disintegration. Pregelatinized or cold water soluble starches act as strong binders resulting in stronger, but also slower, disintegrating tablets (Jivraj *et al*., 2000; Michaud, 2002).

1.6. The Present Study

The pharmaceutical industries are always in high demand of new excipient with the desired set of functionalities. These days, modified starches are playing a major role in pharmaceutical factories. Many kinds of starch from different source have been modified and their possible applications in the pharmaceutical sector have been studied. Many papers are written on evaluating the nature of starch before its gelatinization temperature as a pre-gelatinized starch. However, the properties of starch after its gelatinization temperature have not been studied so far. Hence, in this study cassava starch was gelatinized, allowed to retrograde and evaluated for its application as a direct compressible excipient. Starch 1500®, partially pre-gelatinized starch was used as a standard against which retrograded cassava starch was compared.

1.7. Objectives

1.7.1. General Objective

To evaluate retrograded cassava starch as direct compressible diluent.

1.7.2. Specific Objectives

- To prepare retrograded cassava starch;
- To characterize some of the physicochemical properties of retrograded cassava starch powder;
- To evaluate retrograded cassava starch as a direct compressible excipient in tablets against Starch 1500®.

2. MATERIALS AND METHODS

2.1. Materials

Cassava was purchased from the local cassava cultivating farmers (Wollyta zone, around Sawla area). Sodium metabisulphite (Guangzhou Jinhaunda Chemical Reagent Co. Ltd, China), Starch 1500® (Colorcon, France) were kindly donated by the Ethiopian Pharmaceutical Share Company (EPHARM). Saturated solution of sodium chloride (NaCl) (LABMERK chemicals PVT.LTD, India), NaOH (LOBA CHEMIE PVT.LTD, India) and Magnesium stearate (BDH Chemicals Ltd, England) were used as received.

2.2. Methods

2.2.1. Cassava Starch Extraction

Starch was isolated from cassava according to the method described elsewhere (Gebre-Mariam and Schmidt, 1996). The cassava tuber was peeled and chopped to pieces to facilitate extraction. The chopped cassava tuber was suspended in enough amount of distilled water containing 0.075% w/v of sodium metabisulphite. After the mixture was allowed to settle, its supernatant was decanted. The sedimented starch slurry was repeatedly washed with distilled water containing 0.075% w/v of sodium metabisulphite until the supernatant became translucent. The material was then passed through fine muslin to remove cell debris and the translucent suspension was collected, filtered and allowed to settle. The resulting starch was dried in air at room temperature.

2.2.2. Retrogradation of Cassava Starch

Retrograded cassava starches were prepared by modifications and combinations of the methods described elsewhere (Chung *et al*., 2006; Liu *et al*., 2007). Aqueous slurry of starch with 1:3 starch to water ratio was prepared in a glass jar. The slurry was heated in a water bath (70 ^{o}C) for 4 min to prevent the phase separation during autoclaving. Then the starch paste was autoclaved at 100 ^{o}C for 10 min to gelatinize the starch. The gelatinized starch was sealed and retrograded by storing at 4 ^{0}C for eight days. Then, the starch gel was dried for 12 h in an oven at 60 ^{o}C. The dried products were grinded and sieved through 224 µm before testing.

2.2.3. Characterization of Retrograded Starch

2.2.3.1. Particle Size Determination

Granule size and size distribution and the specific surface area of the starch sample were measured with Malvern Mastersizer laser diffraction spectrometer (Malvern Instruments Ltd. Malvern, UK) using absolute ethanol as dispersion medium. Volume and surface weighted means as well as particle size distributions were determined (Gebre-Mariam and Schmidt, 1998). Determinations were done in triplicate and results are given as mean and standard deviation.

2.2.3.2. Density and Density Related Properties

True density

The true densities of native starch, retrograded starch and Starch 1500® were determined with a pycnometer using toluene as the displacement fluid, according to the methods described elsewhere (Shiihii *et al*., 2011). An empty 50 ml pycnometer bottle was weighed (W), then filled with toluene and the excess was wiped off. The filled bottle was weighed a second time (W_1). A 2g quantity of sample was weighed (W_2) and quantitatively transferred into the pycnometer bottle. Then, sufficient amount of toluene was added to wash down and overlay the sample. After a few min, the sedimented starch was stirred with a small glass-stirring rod to release entrapped air, the sample equilibrated for a few min. When evolution of air bubbles through the supernatant toluene layer had stopped, the stirrer was removed and rinsed into the pycnometer with toluene. The excess solvent was wiped off and the bottle was weighed again (W_3). The true density (g/ml) was calculated with Eq. 2.1. Determinations were done in triplicate.

$$\text{True Density} = \frac{W2}{[(W1 + W2) - W3]} \times SG \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Eq. 2.1}$$

Where W_1 = weight (g) of the pycnometer filled with toluene, W_2 = weight (g) of sample, W_3 = weight (g) of pycnometer plus sample plus toluene, and SG = specific gravity of toluene (g/ml).

Bulk density

The bulk densities of native cassava starch, retrograded starch and Starch 1500® powder were determined by pouring 30 g of sample powder through a funnel into a 250 ml glass measuring

cylinder. The measuring cylinder was then lightly tapped to collect down all the powder from the wall of the measuring cylinder. Then, the volume occupied by the sample powder was read directly from the measuring cylinder and used to calculate the bulk density as g/ml using Eq. 2.2. Determinations were done in triplicate.

$$\text{Bulk Density } (\rho_b) = \frac{m}{V_b} \quad \text{..... Eq. 2.2}$$

Where m is the weight of the powder and V_b is bulk volume.

Tapped Density

Tapped density of each sample was determined by automatically tapping 30g of sample powder 500 times using tapped densitometer (ERWEKA (SVM) Germany). The volume reading from the measuring cylinder was used to calculate the tapped density as g/ml using Eq. 2.3. Determinations were done in triplicate.

$$\text{Tapped Density } (\rho_t) = \frac{m}{V_t} \quad \text{..... Eq. 2.3}$$

Where m is the weight of the powder and V_t is the tapped volume.

The Hausner ratio (HR) and Carr's index (CI) were used as measurement of interparticle friction and the potential powder arch, respectively. They are also used to estimate the flow properties of powders. HR was calculated as the ratio of tapped density to the respective bulk density using Eq. 2.4 and the CI was expressed as a percentage using Eq. 2.5.

$$HR = \frac{\rho t}{\rho b} \quad \text{..... Eq. 2.4}$$

$$CI = \frac{\rho t - \rho b}{\rho t} * 100 \quad \text{..... Eq. 2.5}$$

2.2.3.3. Flow Rate and Angle of Repose

The flow properties were evaluated by standard funnel method. A funnel was mounted on a laboratory stand at a height of 10 cm from the bench. 30 g of starch was poured into the funnel with the tip closed. The tip-plug was removed and the starch was allowed to pass through the orifice, the height and diameter of the starch heap were measured. As the starch was allowed to pass through the orifice, the time taken was recorded. The angle of repose and flow rate were calculated using Eq.2.6 and Eq.2.7, respectively. Determinations were done in triplicate.

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r) \quad \text{..... Eq. 2.6}$$

Where h is the height and r is the radius of the starch powder pile

$$\text{Flow Rate} = \frac{m}{t} \quad \text{..... Eq. 2.7}$$

Where m is the mass in gram and t is time in second.

2.2.3.4. Kawakita Analysis

Powder compression was studied using the degree of volume reduction. The method described by Zhang et al (2003) was employed. 30 g of starch powder was poured into a graduated measuring cylinder. The measuring cylinder containing the sample powder was automatically tapped using tapped densitometer (ERWEKA, Germany) 5, 10, 20, 30, 40, 50, 75, 100, 300, 400 and 500 times. After every tap, the reduction in volume was read. The relationship between the degree of volume reduction of the powder column and the applied pressure is described using Kawakita equation (Eq. 2.8). The experiment was done in triplicate.

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \quad \text{..... Eq. 2.8}$$

Where N is the number of taps and ‘a’ and ‘b’ are constants. The constants of the Kawakita equation were calculated from the slope and intercept of the line from the graph of N/C versus N. The constants of Kawakita equation can be used to estimate the flow and cohesive properties of powders. Constant ‘a’ describes the degree of volume reduction at the limit of tapping and is called compactibility; *1/b* is considered to be a constant related to cohesion, or the amount of

time it takes to achieve the final packing stage and is called cohesiveness, *C* being the degree of volume reduction during the tapping treatment and is calculated using Eq. 2.9.

$$C = \frac{(V_o - V_N)}{V_o} \quad \text{..... Eq. 2.9}$$

Where V_o is the loose volume of the powder column before tapping and V_N is the volume of the powder column after a certain number of taps (N).

2.2.3.5. Determination of Moisture Content

Moisture content of starch powder was determined by gravimetric method (Olayemi *et al*., 2008) in triplicate. 2 g of each powder sample was spread into weighed, dried Petri dish and heated in an oven (Kottermann® 2711, Germany) at a temperature of 130 °C for about 2 h. Then, the sample was weighed and the results were used to determine the moisture content using Eq. 2.10.

$$\% \text{ Moisture content} = \left[\frac{W_i - W_f}{W_i}\right] \times 100 \quad \text{..... Eq. 2.10}$$

Where W_i and W_f are the weights of sample powder before and after drying, respectively

2.2.3.6. Determination of Moisture Sorption Pattern

The moisture sorption properties of the starches were investigated gravimetrically based on a method described elsewhere (Olayemi *et al*., 2008; Odeku and Picker-Freyer 2009a) in triplicate. In this, the samples were weighed before and after storage at room temperature under 20%, 40%, 60%, 75%, and 100% relative humidity (RH) conditions. These RH conditions were achieved in desiccators by using proper saturated salt solutions. Native starch, retrograded starch and Starch 1500® powder samples were pre-dried in an oven for 2 h at 130 ºC. Two grams of the pre-dried starches were placed on dried and weighed Petri-dish and transferred to a particular RH chamber. Samples were equilibrated for four weeks at room temperature. Then, the weights of the starches were recorded and the moisture uptake of each sample was calculated as the weight difference of the starches before and after equilibration in a given RH and expressed as percent moisture uptake.

2.2.3.7. Determination of Swelling Power and Solubility

Swelling power was determined by dispersing 0.5 g of starch samples in 10 ml of distilled water in apre-weighed centrifuge tubes. The slurries were heated in a thermostatically controlled water bath at 20, 37, 50, 65, 75 and 85 ^{o}C for 30 min with shaking every 5 min to keep the starch granules suspended. The heated slurries were then cooled to room temperature and centrifuged at 300 rpm for 15 min to separate gel and supernatant. The supernatant was decanted carefully into a Petri-dish and dried in an oven for 2h at 130 °C. Weight of the residue (W_1) was determined and the water solubility index was calculated from the amount of dried solids recovered by evaporating the supernatant and expressed as gram dried solids per 100 g of sample on dry weight basis. The percent solubility (% S) was calculated using equation Eq. 2.11. The precipitates obtained were weighed (W_2) and used to calculate the swelling power (SP) of the starches using Eq. 2.10 (Mweta *et al*., 2008; Chitedze, 2012). All determinations were done in triplicate.

$$SP = \frac{W2*100}{W3*(100-S)} \quad \text{..... Eq. 2.10}$$

$$S\ (\%) = \frac{W1}{W3} * 100 \quad \text{..... Eq. 2.11}$$

Where W_1 is the weight (g) of soluble material in the supernatant, and W_2 is the weight (g) of precipitate.

2.2.4. Tablet Preparation

The compaction properties and lubricant sensitivity of the native cassava starch, retrograded cassava starch and Starch 1500® were evaluated according to the method described elsewhere (Jagtap *et al*., 2012). Each sample of starch was mixed with variable proportions of magnesium stearate ranging from 0 to 2% (w/w) for a period of 3 min using Turbula mixer (Willy A. Bachofen AG, Turbula2TF, Basel, Switzerland) at 45 rpm. Each blend was then compressed into tablets with a single-station instrumented tablet press (Korsch EK0, XP1, K0010288, KORSCH AG, Germany) using flat faced punches and a die of 10 mm diameter at fixed compression pressure (20 ± 0.5 KN) to produce 400 mg tablet. The tablets were kept for 24 h at room

temperature in glass containers before their properties were evaluated. The tablets obtained were tested for appearance, hardness, friability and disintegration time.

2.2.5. Tablet Evaluation

2.2.5.1. Tablet Weight and Thickness

Ten tablets from each batch were randomly selected and weighed individually. Ten tablets from each batch were also selected at random and the thickness of the tablets measured accurately using a caliper.

2.2.5.2. Friability

Ten tablets from each batch were randomly selected and lightly dusted with a soft brush. The ten tablets were weighed on an analytical balance and the reading recorded. The ten tablets were then placed in a friabilitor (ERWEKA®, Germany) for four min at 25 revolutions per min. The tablets were lightly dusted and only the intact tablets were weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss.

2.2.5.3. Crushing Strength

Ten tablets were taken from each batch and the crushing strength of each tablet was determined using Schleuniger hardness tester (Geschenk der, Switzerland). Each tablet was placed between the platens and the crushing strength (in Newton) that just caused the tablet to break was recorded and the average hardness of three determinations was taken.

2.2.5.4. Tensile Strength

The radial tensile strength of the tablets was determined according to the method described elsewhere (Odeku and Akinwande, 2012) at room temperature using the data obtained from crushing strength, diameter, and thickness of the tablets according to the equation (Eq. 2.12).

$$\sigma_x = \frac{2F}{\pi DT} \quad \text{Eq. 2.12}$$

Where σ_x is the tensile strength, F is the force required to break the tablet (N), D is the diameter of the tablet (mm), and T is the tablet thickness (mm).

2.2.5.5. Heckel Plot

The Heckel plot provides an indication of the ability of granules to undergo volume reduction, i.e. compressibility. The Heckel equation relates the relative density, D, of a powder bed during compression to the applied pressure, P, which provides information on the mechanism of powder consolidation during compact formation (Muazu *et al*., 2009). The Heckel equation is written as follows:

$$\ln [1 / (1 - D)] = KP + A \quad \text{Eq. 2.13}$$

The slope of the straight line portion (K) is the reciprocal of the material's mean yield pressure (P_y). From the value of the intercept A, the relative density (D_A) can be calculated using the following equation:

$$D_A = 1 - e^{A} \quad \text{Eq. 2.14}$$

The powder's relative density at the point at which the applied pressure equals zero (D_0) describes the initial rearrangement phase of densification as a result of die filling. The relative density D_B describes the phase of rearrangement at low pressures and is the difference between D_A and D_0:

$$D_B = D_A - D_0 \quad \text{Eq.2.15}$$

The Heckel analysis was made using tablets prepared at compaction force 5, 10, 15, 20, 25 and 30 KN in a single-station instrumented tablet press using 10 mm flat faces punches. At every pressure applied, the diameter and height of the tablets were measured and used to calculate the Heckel parameters. All determinations were done in triplicate.

2.2.5.6. Disintegration Time

The disintegration times of six tablets were determined in triplicate according to USP30/NF 25 specification (2007) in distilled water at 37 °C ± 2 °C using a disintegration testing apparatus (CALEVA, G.B. Caleva Ltd., UK). The time taken for all the tablets to disintegrate and pass through the wire mesh was recorded.

2.2.5.7. Statistical Analysis

The results generated were subjected to statistical analysis to compare the properties of the retrograded cassava and Starch 1500® using Analysis of Variance (ANOVA) with statistical software Origin 7 (OriginLab ™ Corporation, USA). At 95% confidence interval, p values less than or equal to 0.05 were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Preliminary Study

Factors like moisture content, temperature, temperature holding time and time of storage affect the outcome of the resulting starch. To be able to select the appropriate modification method which resulted in enhanced properties than the native cassava starch the effects of each was first studied.

To see the effect of one factor all other factors were controlled during modification and compression force and weight of the tablet prepared during tableting were kept constant. Table 3.1., shows the effect of water to starch ratio, temperature, temperature holding time and storage time of modification with regards to flow modified starch powder and crushing strength tablets.

Tablet 3.1: Effect of water to starch ratio, temperature, temperature holding time and storage time of modification on flow of the modified powder and crushing strength of its tablets.

	Ratio	**Flow Rate (gm/s)** (±SD)	**Angle of Repose** (±SD)	**Crushing Strength (N)** (±SD)	**Friability (%)** (±SD)
Effect of water to starch ratio	40:60	5.16 ± 0.23	28.34 ± 0.19	63.32 ± 2.01	1.06 ± 3.03
	50:50	6.03 ± 0.19	28.93 ± 0.29	83.91 ± 2.03	0.70 ± 3.03
	60:40	7.76 ± 0.11	24.57 ± 0.21	125.62 ± 3.40	0.21 ± 0.03
	70:30	8.32 ± 0.23	26.27 ± 0.30	198.22 ± 3.08	0.09 ± 0.01
	Temperature (ºC)				
Effect of temperature	80	6.36 ± 0.24	29.32 ± 0.63	93.36 ± 4.07	1.30 ± 0.01
	90	6.34 ± 0.31	28.53 ± 0.71	123.32 ± 3.23	0.60 ± 0.02
	100	8.23 ± 0.22	26.28 ± 0.98	196.42 ± 3.03	0.09 ± 0.01
	110	8.23 ± 0.34	26.33 ± 0.95	198.26 ± 2.04	0.09 ± 0.02
	120	8.22 ± 0.23	26.27 ± 0.80	198.22 ± 3.08	0.09 ± 0.01
	Time (min)				
Effect of temperature holding time	5	7.21 ± 0.14	21.63 ± 1.15	147.43 ± 2.81	0.13 ± 3.03
	10	8.32 ± 0.23	26.27 ± 0.30	198.22 ± 3.08	0.09 ± 0.02
	15	8.32 ± 0.24	26.27 ± 0.31	198.12 ± 3.09	0.09 ± 0.02
	20	8.32 ± 0.25	26.27 ± 0.32	198.20 ± 3.10	0.09 ± 0.01
	Day				
Effect of storage time	1	6.32 ± 0.21	28.62 ± 1.16	98.22 ± 2.81	0.43 ± 0.03
	4	7.76 ± 0.22	27.71 ± 1.06	154.40 ± 2.11	0.17 ± 0.02
	8	8.32 ± 0.23	26.27 ± 0.30	198.22 ±3.08	0.09 ± 0.01
	12	8.32 ± 0.24	26.26 ± 0.41	198.20 ± 4.06	0.09 ± 0.01

It was observed that as the water to starch ratio of modification increased the resulting starch showed improvement in flow, an increase in crushing strength and a decrease in tablet friability. The experiment showed that as the temperature of modification increased the flow of the resulting powders increased, the crushing strength increased and the friability decreased. However, as the temperature of modification increased beyond 100 ^{o}C the powder showed no difference in flow and crushing strength. To see the effect of moisture storage time during modification samples were stored for 1 day, 4 days, 8 days and 12 days. The result indicated that, flow of the powder and crushing strength of the tablets increased until the 8th day. However, modified starch stored for 12 days showed similar result as the 8th day powder.

The objective of the preliminary study is to select the method that is the water to starch ratio, temperature and time combinations that can result in enhanced flow of the modified powder, and a directly compressible tablet with the desirable crushing strength and friability within the requirement (that is less than 1%).

3.2. Particle Size and Distribution

Starch granule shape, surface, size and size distribution are important factors that influence functional properties of starch such as gel clarity, swelling power, water binding capacity and solubility (Singh *et al*., 2003). Generally, the starch granule size may range from 1 to 110 µm (Hoover, 2001; Moorthy, 2002). The volumetric particle size and size distribution of native cassava starch, retrograded cassava starch and Starch 1500® are shown in Fig. 3.1. - 3.3.

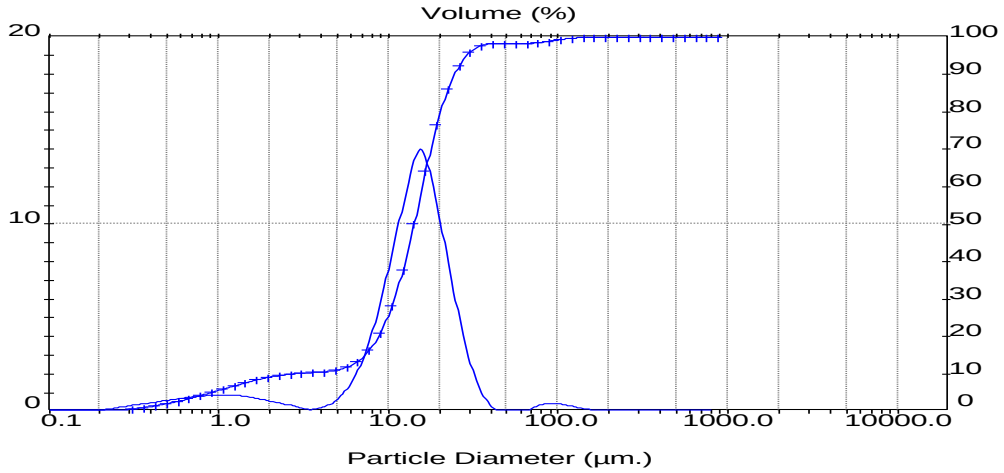

Figure 3.1: Particle size distribution of Native cassava starch

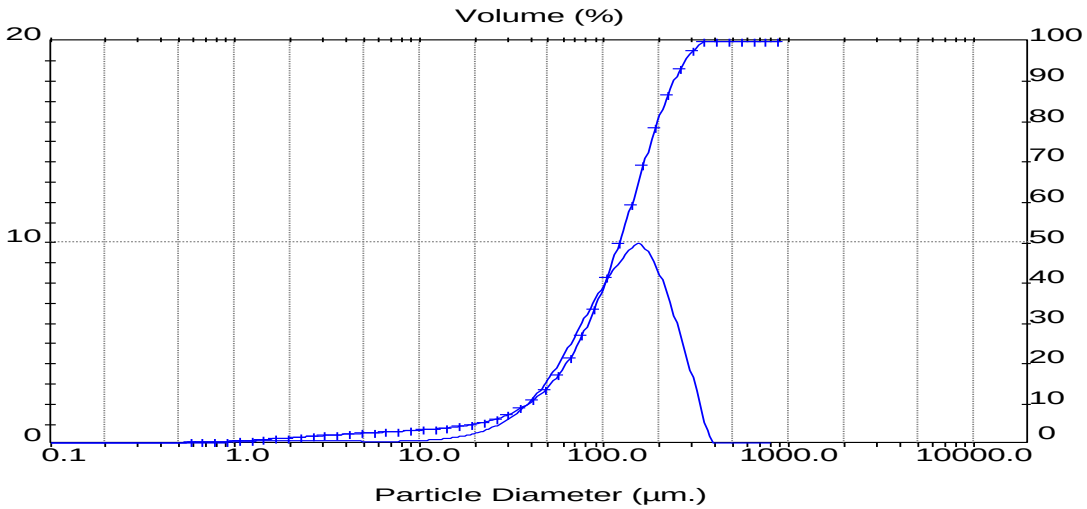

Figure 3.2: Particle size distribution of retrograded cassava starch

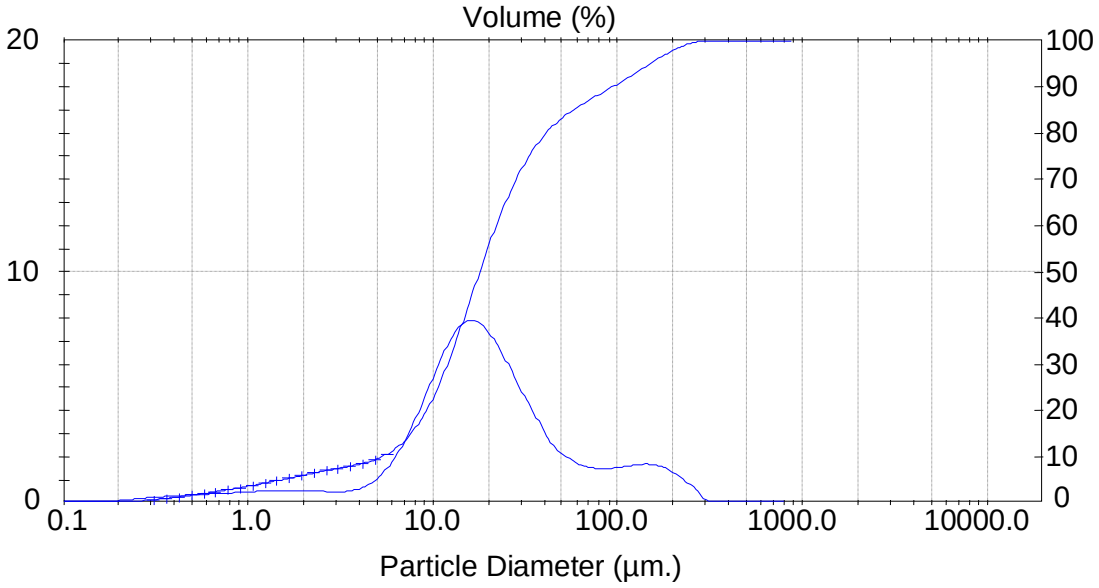

Figure 3.3: Particle size distribution of Starch 1500®

From the above result, it is evident that retrograded cassava starch has higher mean volumetric particle size than the native cassava starch and Starch 1500®. Retrograded cassava starch exhibited volumetric particle sizes of 130.58 µm while Starch 1500® and native cassava starch showed volumetric particle size of 30.04 µm and 15.79 µm, respectively. The retrograded cassava starch displayed larger particle size than the respective native starch which might have resulted from particle aggregation. Because of this high particle size, retrograded cassava starch has a lower specific surface area.

The particle size and surface area of starch can affect the disintegration, flow and tableting properties. It was shown that rice starch which has very small particle size has better compactability than corn and potato starch. However, rice starch exhibited poor flowability caused by its fine particle size (Singh *et al*., 2006). This poor flow properties, which is characterized by low bulk densities, retarded or impeded formation of a lubricant film during mixing. Since retrograded cassava starch has large particle size, it is expected to show a good flowability as compared to native starch.

3.3. Powder Properties of Starches

Powder properties are important in solid dosage forms. The properties are determined by a combination of powder characteristics. The flow properties of powders are critical for effective use of the powder in direct compression. The flowability of a powder is defined as the ability of the powder to flow in a desired manner in a specific piece of equipment. A powder property such as flow is affected by the surface condition of the constituent particles. The two fundamental forces that can affect powder flow are cohesion and friction. Cohesion is the mutual attraction and resistance to separation of contacting powder particles of identical material. Friction is the resistance exerted by one particle against the motion of another particle at the points of contact. Frictional forces act at a tangent to the surface of the contact point (Hiestand, 1966). The flow of a powder plays a very important role in powder technology. It is involved in several processes like blending, powder transfer, tableting, encapsulation etc. Hence, the flow behavior of a powder can decisively affect the quality of the product (Prakash *et al.*, 2011). Good flow property minimizes weight variations in tablet production by ensuring uniformity in die fill (Bare *et al*., 2011) whereas, poor flow can cause bridging, arching, surging, and enhanced movement of particles in the die cavity.

There are few simple acceptable tests to evaluate the flowability of a powder essential in determining the suitability of a material as a direct compression excipient. These include angle of repose, HR and Carr's percent compressibility which are considered as indirect measurements of powder flowability. And also flow rate of the powder as a direct measurement (Odeku and Picker-Freyer, 2009b). Some of the powder properties of native cassava starch, retrograded cassava starch and Starch 1500® are presented in Table 3.2.

Flow rate is one of the simplest & direct methods to determine powder flow and is affected by particle and process related effects. As described by Laovachirasuwan *et al* (2010), particle effects are due to particle shape, size and density, whereas process effects consist out of orifice diameter, hopper width, height of powder bed and hopper wall angle. Flow rate is important during direct compression, especially in multiple-station tablet press (Laovachirasuwan *et al*., 2010). From Table 3.2, the flow rate rank order for the powders tested was as follows: Starch 1500® > retrograded cassava starch > native starch (no flow was recorded for native starch due to its poor flowability). The differences observed in the flow rate of the starches could be due to the difference in particle size which affects the packing properties of the powder particles.

The true density of retrograded cassava starch (1.56 ± 0.023 g/ml) was higher than that of native cassava starch (1.42 ± 0.052 g/ml) and Starch 1500® (1.49 ± 0.038 g/ml) ($P < 0.05$). This might be due to the particle size difference of the three starches since particles size affects the packing arrangement of molecules and true density is principally correlated with the packing arrangement of molecules in crystalline materials. Many other factors can influence powders density and its measurement. These factors vary depending upon the type polymorph, crystallinity and water content (Ohwoavworhua and Osinowo, 2010; Mîinea *et al*., 2011).

High angle of repose is indicative of poor flow while the Hausner ratio is indicative of interparticle friction; the Carr's index (CI) shows the capacity of a material to diminish in volume. As the value of these indices increases, the flow of the powder decreases. In general, however, HR greater than 1.25 indicates poor flow; CI below 16% indicates good flowability while values above 35% indicate cohesiveness (Staniforth, 1996). CI is affected by the particle shape, surface characteristics, particle size, size distribution and the packing configuration adopted by the powder during the bulk densities determination. Therefore, a low CI would imply a good initial packing arrangement, with less volume of voids. From Table 3.2, the values obtained for bulk and tapped densities of starch powders are significantly different. The value recorded for retrograded cassava starch are higher than those of Starch 1500® and native cassava starch indicating that retrograded cassava starch has a better packing behavior compared to the two starches. This is likely to affect the degree of consolidation of formulations containing these materials as filler-binder during compression, with retrograded cassava starch ensuring a greater

degree of consolidation (Vromans *et al*., 1985; Rojas *et al*., 2013). Evaluation of powder densification behavior upon tapping was performed through calculating HR and CI for all powder samples. According to the results of Hausner ratio, retrograded cassava starch and Starch 1500® gave good flow characteristics whereas native cassava starch exhibited poor flow. The result was consistent with the lower Carr's compressibility index of retrograded cassava starch and Starch 1500®, showing that retrograded starch exhibits higher compressibility than the native starch. Thus, the flow indices as assessed by indirect methods showed that the retrograded powders were free flowing. Retrogradationof cassava starch improved the flow property of native starch significantly as indicated by CI below 16, HR below 1.25, flow rate of 8.23 ± 0.227 (g/s) and angle of repose below 30.

Optimal moisture content in the pharmaceutical formulations is very important since it affects the flowability of powder, compressibility/compactibility, hardness of granules and tablets, die-wall friction and stability (physical, chemical and microbial). Moisture increases the compact strength by increasing the tensile strength of the powder bed, by decreasing the density variation within the tablets, and by recrystallization. The reduction of tablet density variation was ascribed to the lubrication of the die wall, which allows more of the applied force to be transmitted through the compact onto the lower punch (Bare *et al*., 2011). Absorbed water also decreases particles' surface energy and subsequently decreases tablets' adhesion to the die wall. Any water expressed duringcompaction also functions as a low-viscosity lubricant (Ngwuluka *et al*., 2010**).** The moisture content of dry starch varies from 6 - 16%, depending on the process used for drying the starch and season of collection. The maximum moisture content recommended for safe storage of starch is 13% (Moorthy, 2002). In this study, retrograded cassava starch (11.8 ± 0.288) exhibited relatively higher moisture content than native cassava starch (9.93 ± 0.178) and Starch 1500® (9.47 ± 0.371).

3.4. Moisture Sorption Pattern

Water content can be an issue for tablet's physical, chemical and microbial stability. Hygroscopic excipients could be useful to absorb water away from water sensitive drugs such as acetylsalicylic acid. Thus; it can improve chemical stability due to hydrolysis. On the other hand, increased water sorption could affect the chemical stability, microbial stability, flow

properties,compaction, hardness, and dissolution rate of dosage forms of pharmaceuticals (Hiestand, 1966; Nokhodchi, 2005). Moisture sorption has been attributed to intra- and intermolecular hydrogen bonding of water with the hydroxyl groups of the starch molecule (Paulos *et al.*, 2009)**.** Thisproperty is a measure of moisture sensitivity of material and its knowledge is necessary wherecontrolledpowder flow or compaction is critical. Moisture modifies the flow and mechanical properties of many powders including starches which have been classified as a moderately hygroscopic material (Gebre-Mariam and Schmidt, 1996)**.** The moisture sorption profiles of native cassava starch, retrograded cassava starch and Starch 1500® have been determined in various humidity chambers (20, 40, 60, 75 and 100% RH) for four weeks and the results are depicted in Fig. 3.4.

Table 3.2: Some powder properties of native cassava starch, retrograded cassava starch and Starch 1500®.

Powder Properties	Native CS (±SD)	Retrograded CS (±SD)	Starch1500® (±SD)
Moisture Content (%)	9.93 ± 0.178	11.8 ± 0.288	9.47 ± 0.371
True density (g/ml)	1.42 ± 0.052	1.56 ± 0.023	1.49 ± 0.038
Bulk density (g/ml)	0.59 ± 0.003	0.70 ± 0.007	0.63 ± 0.007
Tapped density (g/ml)	0.67 ± 0.004	0.77 ± 0.022	0.71 ± 0.004
Carr's Index (%)	15.96 ± 0.068	8.05 ± 0.553	10.91 ± 0.473
Hausner ratio	1.33 ± 0.000	1.08 ± 0.042	1.12 ± 0.005
Angle of repose (degree)	*	26.28 ± 0.982	23.83 ± 0.574
Flow rate (g/sec)	*	8.23 ± 0.227	9.79 ± 0.496

Mean ± SD (n = 3), CS: Cassava starch

* Values could not be determined

Generally, moisture sorption of all the starches gradually increased as the RH increased from 20% to 80% and then the moisture sorption increased significantly at 100% RH. This shows that there was a gradual saturation of the monomolecular layer of the polymer powder beds and at 100% RH, saturation of monomolecular layer and subsequent diffusion of excess moisture (absorption) into bulk powder bed increased the water uptake significantly (Young and Nelson, 1967). The crystalline portion of starches does not absorb water and the extent of water absorption is proportional to the amount of amorphous portion present (Achor *et al.*, 2010). From

Fig. 3.4, it can be seen that the retrograded cassava starch showed relatively higher moisture sorption pattern than its unmodified form. This could be attributed to a decrease in crystalline portion of the starches after retrogradation.

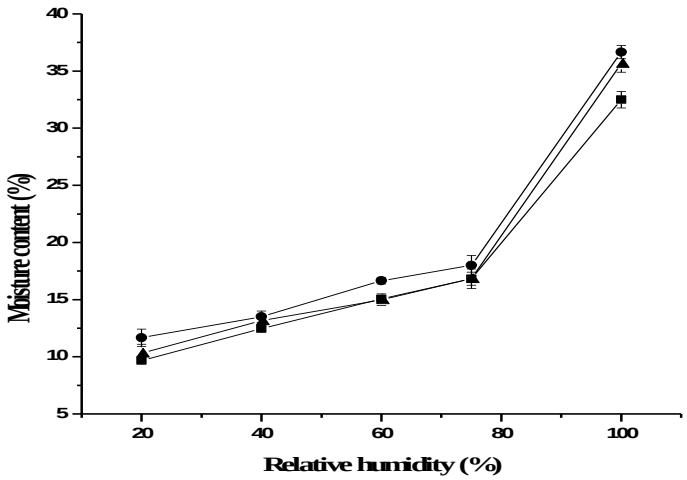

Figure 3.4: Moisture sorption patterns of native cassava starch (—■—), retrograded cassava starch (—●—) and Starch 1500® (—▲—) at room temperature.

3.5. Solubility and Swelling Power

The swelling power of starch has been reported to depend on water holding capacity of starch molecules by hydrogen bonding (Sandhu and Singh, 2007). Hydrogen bonds stabilize the structure of the double helices in crystallites. When starch is heated in excess water, the crystalline structure is disrupted (due to breakage of hydrogen bonds) and water molecules are linked by hydrogen bonding to the exposed OH groups of amylose and amylopectin. This causes an increase in granule swelling and solubility (Tester and Karkalas, 1996).

The solubility and swelling power of native cassava starch, retrograded cassava starch and Starch 1500® at temperatures ranging between 25 °C and 85 °C are depicted in Fig. 3.5 and 3.6, respectively. As expected, the swelling power and solubility of the starch increased with temperature. The swelling power of retrograded cassava starch was found to increase considerably from 7.081 - 13.76 g/g and the retrograded cassava starch solubility also increased

from 2.0 - 8.1% with increasing temperature from 20 °C to 85 °C. Retrograded cassava starch has shown higher swelling power almost at all temperature (20 °C - 85 °C) points in comparison with native cassava starch and Starch 1500®. At 85 °C native starch showed the highest swelling power (21.63 g/g). The degree of swelling depends on the bonding forces within the granules of a starch. Thus, highly associated starch granules with an extensive and strongly bonded micellar structure should display relatively greater resistance towards swelling. Accordingly, the granules of retrograded cassava starch must exhibit lower bond strength than both native cassava starch and Starch 1500®. According to the results, retrogradation enhances starch swelling power at low temperature.

Swelling power and solubility provide evidence of the strength of interaction between starch chains within the amorphous and crystalline domains. The degree of this interaction could be determined by amylose-amylopectin ratio, chain length, molecular weight distribution and length

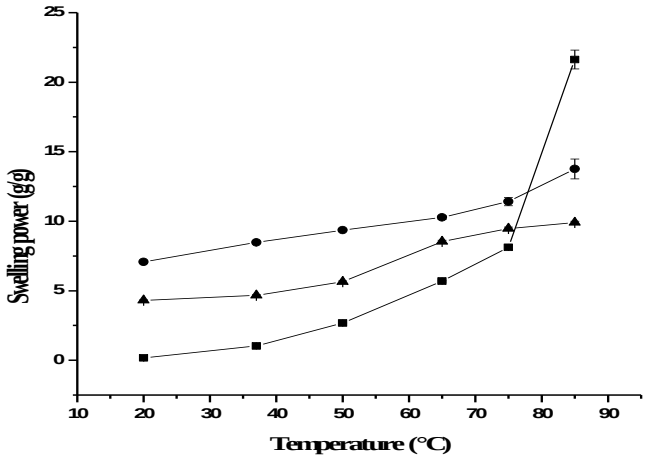

Figure 3.5: Swelling power of native cassava starch (—■—), retrograded cassava starch (—●—) and Starch 1500® (—▲—) at different temperatures.

of branching (Moorthy, 2002; Sandhu and Singh, 2007). It has been indicated that starch granules with low amylose content being less rigid, swell freely when heated. The starch

granules with higher amylose content, on the other hand, being better reinforced and thus more rigid, probably swell less freely (Tester and Morrison, 1990).

Solubility of starch depends on a number of factors such as source, inter-associative forces, swelling power, presence of other components, etc. As can be seen from the solubility profiles of the starch samples at different temperatures (Fig. 3.6), moderate solubility values were found for modified starch. Retrograded cassava starch showed almost similar solubility profile with native cassava starch at 20 °C, then retrograded starch showed lower solubility profile compared to native cassava starch and Starch 1500®.

From the solubility profile, Starch 1500® exhibited the highest solubility and retrograded cassava starch showed the lowest profile. The decrease in solubility of retrograded starch indicates that there is lower dispersion of retrograded starch in aqueous systems. And application of heat and excess water could not fully disrupt (due to breakage of hydrogen bonds) the crystalline structure creating less exposed OH groups. The high solubility of Starch 1500® might be due to the loss of granular structure and release of amylose as the amylose molecules are preferentially solubilized and leached from the swollen starch granules (Alam and Hasnain, 2009).

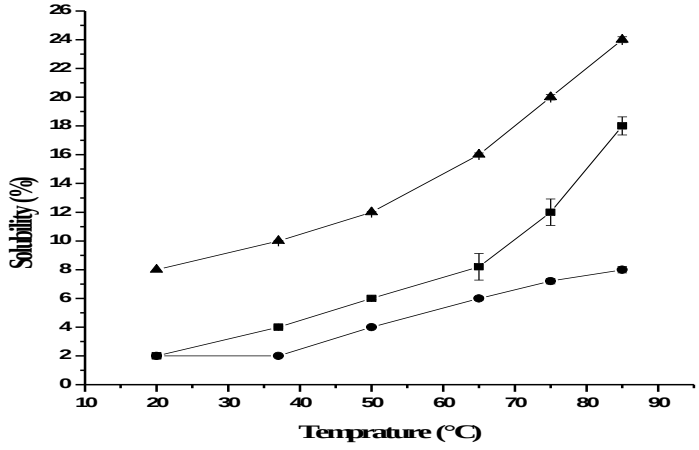

Figure 3.6: Solubility of native cassava starch (—■—), retrograded cassava starch (—●—) and Starch 1500® (—▲—) at different temperatures.

3.6. Kawakita Parameters/ Compaction Data Analysis

The Kawakita equation describes the relationship between the volume reduction of powder column and the applied pressure. Kawakita constants indicate the behavior of the powder from the bulk density state to the tapped density state (Ohwoavworhua *et al.*, 2007). The Kawakita plots for native cassava starch, retrograded cassava starch and Starch 1500® are presented in Fig 3.7. Values of "*a"* and "*ab*" were obtained from the slope and intercept, respectively. The constant "*a*", is given as a reciprocal of the slope from the linear portion of the plot and equivalent to the value of "C" at infinitely high pressures, 1*/ab* is the intercept. The constants of Kawakita equation can be used to estimate the flow and cohesiveness properties of powders. Constant "*a*", describes the compressibility and constant "1*/b*" describes cohesive properties of powders or the fastness of how the final packing stage is achieved (Autamashih *et al.*, 2011).

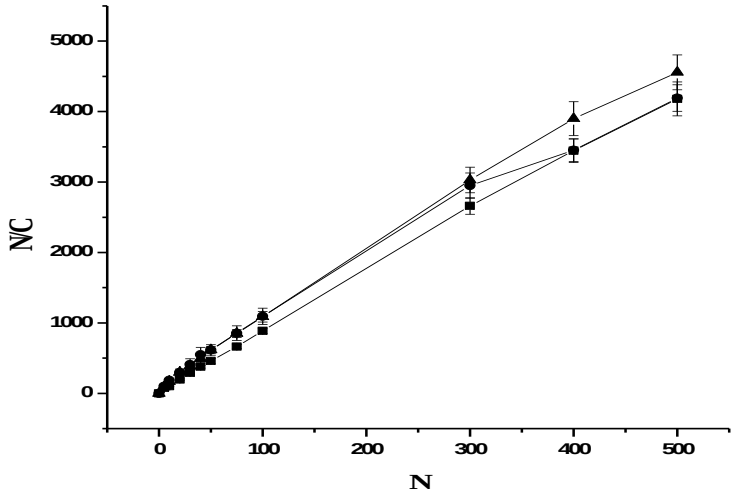

Figure 3.7: The plots of N/C versus N of native cassava starch (—■—), retrograded cassava starch (—●—) and Starch 1500® (—▲—) with equations of Y = 6.23x + 33.34, Y = 8.86x + 145.78 and Y = 9.25x + 109.42, respectively, where Y is N/C and X is N.

From Table 3.3, the rank order of constant "a" was Starch 1500® < Retrograded cassava starch < native cassava starch. This indicates that Starch 1500® densified the least (i.e., small

compressibility values) and native cassava starch densified (i.e., high compressibility values) the highest. This does not necessarily mean the native cassava starch is more compressible than the modified cassava and Starch1500®, since native starch gains its original state upon decompression (release of stress), elastic deformation takes place. On the other hand, constant "1/b" indicated that retrograded cassava starch achieved the final packing slowly (i.e., the greater cohesive values). Native cassava starch achieved the final packing state rather quickly. The Kawakita analysis supported the fact that the modification of starch improves the powder flowability. The smaller 'a' values of retrograded cassava starch indicates good flowability and no problem regarding powder flow will be expected during tableting by direct compression.

Table 3.3: Kawakita constants of native cassava starch, retrograded cassava starch and Starch 1500®.

	Kawakita Compressibility (a)	Kawakita Cohesiveness (1/b)	Correlation Coefficient (R^2)
Native cassava starch	0.161	5.351	0.999
Retrograded cassava starch	0.112	16.453	0.992
Starch 1500®	0.108	11.829	0.996

3.7. Analysis of Heckel Plots

The phenomena and mechanisms involved during compaction of pharmaceutical materials have become an important concept in the design and development of solid dosage forms. Successful compaction of powders requires an understanding of the fundamental properties including both physicochemical and mechanical properties (Jain, 1999). The physicochemical properties including particle size, size distribution, density and angle of repose of the powders determine the flowability. The mechanical properties refer to the compaction properties including tensile strength and deformation. These parameters are generally difficult to be altered in contrast to the flowability properties (Maarschalk and Bolhuis, 1998). Powder packing with increasing compression load is normally attributed to particle rearrangement, elastic and plastic deformation and particle fragmentation as discussed earlier. The Heckel analysis is a popular method of determining the volume reduction mechanism under the compression force and is based on the assumption that powder compression follows first order kinetics with the interparticulate pores as the reactants and the densification of the powder as the product (Ohwoavworhua and Osinowo,

2010). Heckel proposed equation to express density in term of packing fraction as a function of applied pressure to determine the deformation behavior of powder under stress (Heckel, 1961). The Heckel plots for native cassava starch, retrograded cassava starch and Starch 1500® are presented in Fig 3.8.

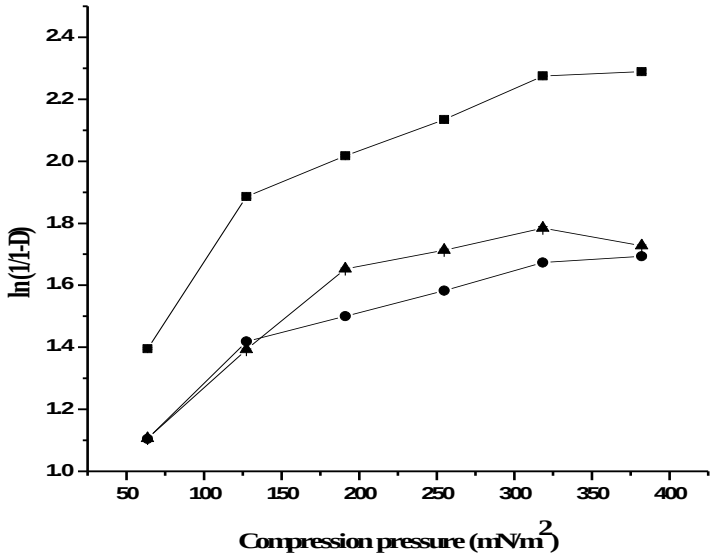

Figure 3.8: Heckle plot of tablets produced from native cassava starch (—■—), retrograded cassava starch (—●—) and Starch 1500® (—▲—) at different compression pressure

A Heckel profile is normally distinguished by three different regions, an initial non-linear part followed by a linear part where the data obey the expression, and finally a non-linear region. The expression of these three different regions is normally explained with the underlying rate controlling compression mechanisms that dominate the respective regions. For the first part, two main explanations could be seen in the literature; firstly that the curvature is regarded to be dependent on particle rearrangement during compression and secondly that the curvature is due to particle fragmentation (Heckel, 1961). Regarding the second part, it is generally widely accepted that particle deformation, either plastic or elastic, is the controlling mechanism. And for the third part, it is argued that elastic deformation of the compact controls the process (Sun and Grant, 2001).

The mean yield pressure, P_y, was calculated from regions of the plots showing linearity. The intercept, A, the point at which an intact tablet was just formed during compression, was determined from the extrapolation of the region used for the determination of P_y. The D_A and D_B values were calculated from equations 2.14 and 2.15, respectively. The values of D_0, P_y, D_A and D_B for the three starches are presented on Table 3.4.

Table 3.4: Some Heckel parameters of native cassava starch, retrograded cassava starch and Starch 1500®.

	K	A	P_y (MNm^{-2})	D_o	D_A	D_B
Native Cassava Starch	0.002	1.618	487.804	0.415	0.801	0.386
Retrograded Cassava Starch	0.001	1.242	740.74	0.448	0.711	0.262
Starch 1500®	0.001	1.457	980.392	0.422	0.767	0.344

The slope, k relates to the mean yield pressure which is the minimum pressure required to cause deformation. Fig 3.8. shows that the slope (k) decreases in the following order: Native cassava starch > Retrograded cassava starch > Starch 1500®. K, of Heckel plot was intended to give a measure of theplasticity of compressed material. Consequently, greater slopes indicated a greater degree of material plasticity whereas a small value indicates brittle fracture (Heckel, 1961). The results indicate that retrograded cassava starch has relatively greater plasticity nature than Starch 1500®. Since the greater slope of retrograded cassava starch indicates the smaller P_y values, it can be interpreted that it undergoes plastic deformation. The relative higher P_y value observed in Starch 1500® indicates that the granules have lower ability to deform plastically as compared to retrograded cassava starch.

The D_0 value is used to describe the initial rearrangement phase of densification as a result of die filling and this is obtained from the ratio of the loose density to the particle density. Table 3.3. shows that retrograded cassava starch has larger D_0 value than Starch 1500® and native starch, implying that initial packing of the granules as a result of die filling is relatively high.

D_B value describes the phase of rearrangement of particles during the initial stages of compression and tends to indicate the extents of particles or granules fragmentation, although

fragmentation can occur concurrently with plastic or elastic deformation of constituent particle, D_B value of retrograded cassava starch is lower than both Starch 1500® and native starch, which shows that there is a lower fragmentation of retrograded starch during compression relative to the two starches.

3.8. Effects of Magnesium Stearate

3.8.1. Effect of Magnesium Stearate on Tableting Properties of the Starches

Lubrication plays a key role in successful manufacturing of pharmaceutical solid dosage forms. Lubricants are excipients that, when present in small amounts between two contacting, rubbing surfaces reduce die wall friction during tablet compression and ejection. Among the different lubricants that are utilized in the pharmaceutical industry, magnesium stearate is the most commonly used (Wang *et al*., 2010; Li and Wu, 2014). It is generally accepted that magnesium stearate forms an adsorbed lubricant film around host particles during mixing (Swaminathan *et al*., 2006; Li and Wu, 2014). This result in a decrease in solid-solid contact, including contact between tablet and die wall; hence, reduction in die wall friction. However, the above mentioned lubricant film also interferes with the bonding properties of the host particles by acting as a physical barrier. This causes a decrease in compact strength, especially with excessive lubricant amounts and/or prolonged mixing time (De Boer *et al*., 1978; Otsuka *et al*., 2004). The effect of lubricant on compact strength depends on a number of factors such asconcentration,mixing time (Bolhuis *et al*., 1981; Otsuka *et al*., 2004) and specific surface area (Almaya and Aburub, 2008). These properties provide some rationale for the changes in processing characteristics and properties of finished drug products often encountered in the scale-up of solid dosage formulation.

In the present study, each starch powder was blended with variable proportions of magnesium stearate. Each blend was tested for compactibility by compressing tablets at a weight equivalent to 400 mg. Weight and thickness of the tablets produced from native cassava starch, retrograded cassava starch and Starch 1500® at different magnesium stearateconcentration are presented in Table 3.5.

From table 3.5., tablets from native cassava starch weighed between (386.22 ± 3.10 to 399.34 ± 1.98), tablets from retrograded cassava starch weighed between (400.33 ± 2.64 to 402.10 ± 1.65) and tablets from Starch 1500® between (402.16 ± 3.35 to 403.80 ± 4.83). The theoretical weight per tablet was 400 mg, and official variation allowed is ±5% (BP, 2009).Weight variation was very low i.e. less than ±3.1% for both retrograded cassava starch and Starch 1500® formulations

Table 3.5: Weight and thickness of tablets produced from native cassava starch, retrograded cassavastarch and Starch 1500® with different lubricant concentration.

	Magnesium stearate conc. (%)	Native cassava starch (± SD)	Retrograded cassava starch (± SD)	Starch 1500® (± SD)
Weight (mg)	0	388.94 ± 2.45	401.17 ± 1.22	403.80 ± 4.83
	0.05	392.10 ± 2.67	400.47 ± 3.23	403.27 ± 2.54
	0.1	396.47 ± 2.64	401.26 ± 2.74	402.16 ± 3.35
	0.25	386.22 ± 3.10	402.10 ± 1.65	402.17 ± 3.55
	0.5	392.64 ± 2.96	402.06 ± 1.56	403.20 ± 2.88
	0.75	394.42 ± 2.75	401.42 ± 2.37	403.45 ± 2.96
	1	399.34 ± 1.98	400.33 ± 2.64	403.70 ± 3.09
Thickness (mm)	0	3.97 ± 0.04	4.11 ± 0.01	4.22 ± 0.03
	0.05	3.96 ± 0.03	4.23 ± 0.01	4.23 ± 0.03
	0.1	3.96 ± 0.04	4.32 ± 0.01	4.23 ± 0.02
	0.25	3.96 ± 0.03	4.33 ± 0.03	4.23 ± 0.01
	0.5	3.98 ± 0.03	4.43 ± 0.03	4.33 ± 0.02
	0.75	3.98 ± 0.11	4.44 ± 0.05	4.34 ± 0.05
	1	3.96 ± 0.10	4.45 ± 0.05	4.44 ± 0.10

Mean ± SD (n = 3)

at all levels of lubricant concentration. This indicates that the flow of the powders was very efficient and uniform. The highest weight variation was observed in the case of native cassava starch formulations which was ±7.04%.

3.8.2. Effect of Magnesium Stearate on Tablet Crushing Strength and Friability

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness and friability. Tablet hardness

is defined as the load required to crush or fracture a tablet placed on its edge. Sometime it is also termed as tablet crushing strength. Crushing strength can be affected by the presence of lubricant and its concentration, as well as by compression force (Jain, 1999). The extent of lubricant action was studied by measuring the hardness and friability of tablets prepared using different lubricant concentration. In this study, all formulations were found to be susceptible to the lubricant concentration used.

As shown in Fig. 3.9, the crushing strength values of the tablets decreased as the concentration of lubricant increased. This could be due to an adsorbed lubricant film around host particles during mixing of the formulation with magnesium stearate. This lubricants film interferes with the bonding properties of the host particles by acting as a physical barrier. In case of magnesium stearate, lubricant-excipient interaction (adhesion) is higher than lubricant-lubricant (cohesion) interactions. The strong adhesive interactions explain the formation of monomolecular magnesium stearate film over excipient. This will decrease the number of strong cohesive interactions between the excipient particles causing a decrease in tablet strength.The crushing strength of tablets prepared from unlubricated retrograded cassava starch was significantly higher than that of tablets prepared from unlubricated Starch 1500®. The crushing strength of retrograded cassava starch tablets was significantly lower than that of Starch 1500® tablets at all levels of magnesium stearate concentration. Only at 0.05% of magnesium stearate, the two starch tablets showed similar hardness. Tablets from lubricated retrograded cassava starch showed significant reduction of tablet hardness in comparison with their unlubricated tablet forms. Retrograded cassava starch was found to have higher lubricant sensitivity. This might be due to larger particle size (135.04μm) of retrograded cassava starch whose low surface area required lower concentration of magnesium stearate for effective surface coverage and subsequent reduction in the bonding strength. According to studies, with magnesium stearate, lubricant sensitivity shows a strong dependence on excipient particle size**,** where smaller particles are less affected by lubricant (Fichtner *et al.*, 2005; Almaya and Aburub, 2008).Tablet's performance related to mechanical strength is tablet friability, i.e., resistance to attrition and abrasion. Therefore, the ultimate test of the adequacy of mechanical strength of a tablet is its friability (Shafer *et al*., 1956). As seen in Fig 3.10, the friability of all formulations increased with increased lubricant concentration. The USP states that the friability value of tablets should be

less than 1% (USP, 2007). This study showed that the friability of tablets from retrograded cassava starch was below 1% when the magnesium stearate concentration used was up to 0.1%. Beyond 0.1% of magnesium stearate concentration, the friability of the tablets increased significantly. Interestingly, the friability of the tablets from unlubricated retrograded cassava starch showed highest friability (0.097 ± 0.015) than those tablets whose cassava starch were

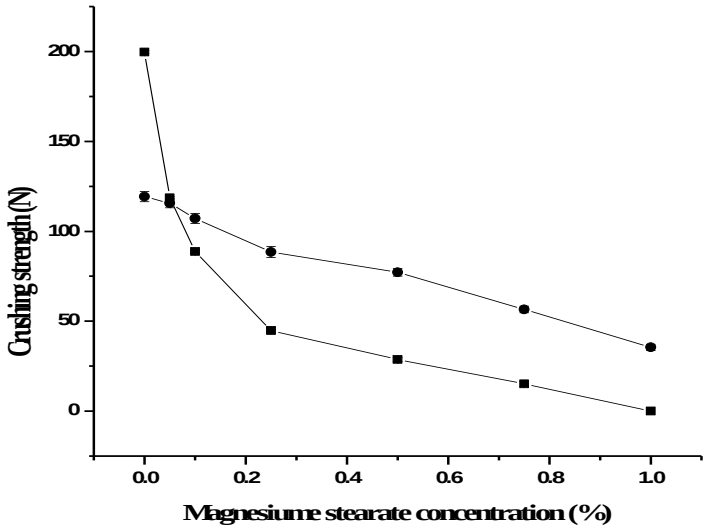

Figure 3.9: Crushing strength of tablets produced from retrograded cassava starch (—■—) and Starch 1500® (—●—) with different lubricant concentration

lubricated with 0.01% (0.007 ± 0.002) and 0.025% (0.029 ± 0.002) magnesium stearate. This indicates that inadequate lubrication causes friction and adhesion among powder particles resulting in less intact tablets during the ejection phase. In the case of Starch 1500®, all tablets except tablets containing 1% of magnesium stearate showed acceptable friability. The results indicate that tablet hardness decreases significantly with increased magnesium stearate concentration.

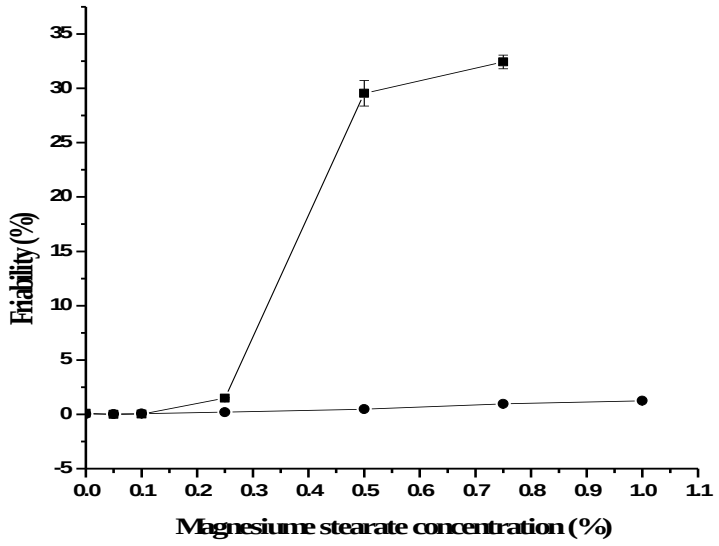

Figure 3.10: Friability of tablets produced from retrograded cassava starch (—■—) and Starch 1500® (—●—) with different lubricant conc.

3.8.3. Effect of Magnesium Stearate on Tensile Strength of Tablets

Tensile strength can be used to characterize the compactibility of pharmaceutical powders. And it is usually used to assess the mechanical strength of tablets. Tensile strength of tablets may indicate bonding strengths of the tablets. The effects of different concentration of magnesium stearate on the tensile strengths of tablets prepared from retrograded cassava starch and Starch 1500® are shown in Fig 3.11. Tensile strength decreases with increase in lubricant concentration. This is expected as hardness of tablets decreases with increase in the concentration of lubricant and tensile strength is directly proportional to tablet crushing strength (Eq. 2.12). The tensile strength of tablets produced from retrograded cassava starch ranges from 31.561 ± 0.863 Kg/cm^2 to 0 Kg/cm^2 and tablets from Starch 1500® ranges from 18.365 ± 0.921 Kg/cm^2 to 5.185 ± 0.471 Kg/cm^2. The tensile strength of tablets prepared from retrograded cassava starch was radically reduced after 0.1% and reached zero at 1% magnesium stearate concentration and for Starch 1500® tablets, the tensile strength showed significant reduction after 0.5% magnesium stearate concentration (Fig. 3.11). These results are in agreement with the tablet hardness profile

of the tablets at subsequent magnesium stearate concentration. Generally, retrograded cassava starch tablet showed higher tensile strength than Starch 1500® at very low (<0.1%) magnesium stearate concentration but beyond 0.1% magnesium stearate concentration, tablets generated from Starch 1500® showed higher tensile strength.

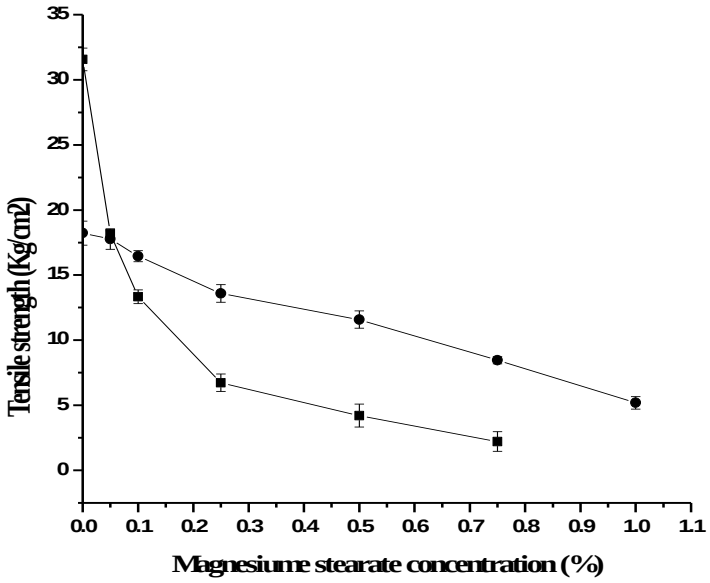

Figure 3.11: Tensile strength of tablets produced from retrograded cassava starch (—■—) and Starch 1500® (—●—) with different lubricant concentration.

3.8.4. Effect of Magnesium Stearate on Disintegration Time

It is well known that hydrophobic lubricants like magnesium stearate increase the disintegration time of tablets. Magnesium stearate can greatly increase hydrophobicity which lowers the solvent penetration rate. When a tablet does not allow solvents to penetrate, it will have a longer disintegration time (Rashid *et al*., 2010). The effects of magnesium stearate on the disintegration time of tablets produced from native cassava starch, retrograded cassava starch and Starch 1500® are presented in Fig 3.12. Only tablets made from native cassava starch and Starch 1500® passed

the test requiring disintegration times of less than 15 min. Tablets formulated with retrograded cassava starch exhibited a markedly longer disintegration period than native cassava starch and Starch 1500®. This might be due to the presence of high cohesive force in retrograded starch tablet. Tablets made of retrograded cassava starch showed decreased disintegration time as the

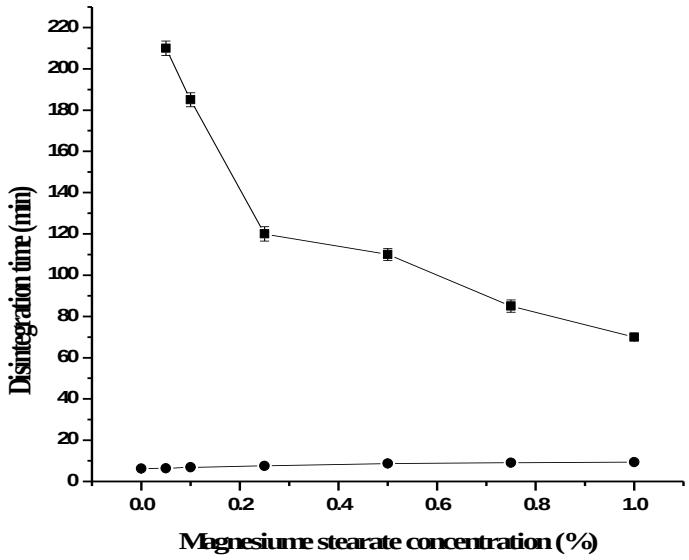

Figure 3.12: Disintegration time of tablets produced from retrograded cassava starch (—■—), and Starch 1500® (—●—) with different lubricant concentration.

concentration of magnesium stearate increased. Tablets produced using 0.25, 0.5, 0.75 and 1% of magnesium stearate showed disintegration time less than 2 h whereas, tablets containing less than 0.25% of magnesium stearate showed longer disintegration time. This is explained with regard to effect of lubricant film on the bonding property of the starch as evidenced by reduced hardness of the tablets after lubrication, since there is positive correlation between tablet disintegration time and hardness of a tablet (Özyazici and Sevg, 2003).

4. CONCLUSION

Physicochemical properties of physically modified cassava starch was investigated and compared with those of starch 1500®. The physicochemical characterization from the foregoing is evident that retrogradation changed the physicochemical properties of the native cassava starch. The retrograded cassava possessed powder properties appropriate for direct compression tableting process. Modified starch showed increased moisture sorption, and bulk density. And its swelling power at lower temperature (< 75 ^{o}C) was increased but solubility was decreased. Retrograded cassava starch exhibited excellent flow property, lower CI and good compactibility, which indicate its potential use as a directly compressible excipient. The Kawakita analysis supported the fact that the modification of starch improves the powder flowability. The smaller 'a' values of retrograded cassava starch indicates good flowability and no problem regarding powder flow will be expected during tableting by direct compression.

The lubricant sensitivity test revealed that retrograded cassava starch has higher lubricant sensitivity than that of starch 1500® by yielding tablet with less crushing strength and friability above the acceptable values. Unlubricated retrograded cassava starch gave tablets with higher crushing strength (199.73 ± 0.152) and friability value (0.097 ± 0.015). When tablets were prepared with lubricated retrograded cassava starch with even very low concentration of magnesium stearate, the crushing strength of the tablets decreased significantly.

During compression retrograded cassava starch had relatively high initial packing of the granules as a result of die filling, and it exhibited plastic deformation with a lower fragmentation compared to the native cassava starch and Starch 1500®. Heckel parameters of the starches indicated that retrograded cassava starch has relatively greater plasticity nature than Starch 1500® and there is a lower fragmentation of retrograded starch during compression relative to the two starches.

From the foregoing it can be concluded that retrograded cassava starch has the potential to be used as an alternative directly compressible excipient as it exhibits good flow and compaction property.

SUGGESTIONS FOR FURTHER WORK

The present study provided an insight into the direct compressibility of retrograded cassava starch in tablets. Based on these promising results the following further works are suggested:

- Morphological characterization of the modified starch,
- Drug loading and release properties,
- Drug release sustaining properties.

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