

ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF PHARMACY
DEPARTMENT OF PHARMACEUTICS AND SOCIAL PHARMACY



PREPARATION AND EVALUATION OF PREGELATINIZED
PLECTRANTHUS EDULIS (ETHIOPIAN POTATO) STARCH AS AN
ALTERNATIVE DIRECT COMPRESSION EXCIPIENT IN PARACETAMOL
TABLET FORMULATIONS

By
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A Thesis Submitted to College of Health Sciences of Addis Ababa University in Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmaceutics in the Department of Pharmaceutics, School of Pharmacy

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This is to certify that the thesis investigated by Yonas Demissie, Entitled:

“Preparation and evaluation of pregelatinized *Plectranthus edulis* (Ethiopian potato) starch as an alternative direct compression excipient in paracetamol tablet formulations” and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Dedicated To My Mother
With Love, Appreciation and Respect

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ACRONYMS

ANOVA:	Analysis of variance
APIs:	Active pharmaceutical ingredients
BP:	British Pharmacopoeia
CI:	Carr's index
DP:	Degree of polymerization
DT:	Disintegration time
EPHARM:	Ethiopian pharmaceutical share company
HR:	Hausner ratio
PGS:	Pregelatinized starches
RH:	Relative humidity
RPM:	Revolution per minute
SD:	Standard deviation
SP:	Swelling power
USP/NF:	United States Pharmacopoeia/National Formulary
UV/Vis:	Ultra violet/visible
W/V:	Weight by volume
W/W:	Weight by weight

ABSTRACT

Plectranthus edulis (Vatke) (Ethiopian *potato*) is an indigenous annual tuber crop which belongs to the family Lamiaceae. It is a diploid dicotyledonous plant with a height up to 150 cm. It has the potential of being used as an alternative source of starch for various applications in pharmaceutical, food, paper, and textile industry. As native starches are weak structurally and functionally, there is a need to increase their functionality through modification. Among the various starch modification techniques, physical methods have received more attention since they are chemical free and somewhat easier than the other methods. The aim of the study was to prepare and characterize pregelatinized *Plectranthus edulis* starch and evaluate its functionality as a direct compression excipient in tablet formulations.

Starch extraction was carried out from the tubers of *Plectranthus edulis* using 0.075% (w/v) of sodium metabisulphite. The native *Plectranthus edulis* starch was physically modified by pregelatinization at different conditions. The pregelatinized *Plectranthus edulis* starch, prepared at optimum conditions (starch to water ratio of 1:3, at 65 °C for 5 min), was selected for direct compression studies as it had the best powder compaction and flow properties among the fifteen tested pregelatinized *Plectranthus edulis* starch products. This pregelatinized *Plectranthus edulis* starch product was compared against Starch 1500[®] and the native *Plectranthus edulis* starch for physicochemical characterization. To investigate the effect of lubricant concentrations on post-compaction properties of the starch products, lubricant sensitivity test was conducted for native *Plectranthus edulis* starch, pregelatinized *Plectranthus edulis* starch and Starch 1500[®] by preparing tablets at different magnesium stearate concentrations (0%, 0.25%, 0.5%, 0.75%, 1%, 1.5%, and 2%). The tablets were tested for weight variation, friability, crushing strength, tensile strength and disintegration time. Dilution potentials of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] were determined by assessing friability, crushing strength, tensile strength and other parameters in tablet formulations containing various paracetamol concentrations (20%, 30%, 40% and 50% (w/w)).

The X-ray diffractogram (XRD) of the pregelatinized *Plectranthus edulis* starch indicates that the pregelatinization process decreased the crystallinity of the starch. The major peaks that were observed in the XRD of native *Plectranthus edulis* starch disappeared following pregelatinization. Nonetheless, there was no total loss of crystallinity as indicated by the presence of a peak at $17.2^{\circ} 2\theta$ in the XRD of pregelatinized *Plectranthus edulis* starch. The bulk density was found to increase from 0.6 ± 0.01 g/ml to 0.72 ± 0.01 g/ml following pregelatinization. The Hausner ratio and Carr's index of pregelatinized *Plectranthus edulis* starch (1.15 ± 0.02 and 13.25 ± 1.21 , respectively) and Starch1500[®] (1.21 ± 0.02 and 17.92 ± 0.72 , respectively) were significantly lower than the native *Plectranthus edulis* starch (1.40 ± 0.03 and 28.56 ± 1.77 , respectively) ($P < 0.05$), suggesting the former has got better flowability than the native starch. The native *Plectranthus edulis* starch did not flow through the funnel but after modification the starch product was found to be a free flowing powder with $20.08 \pm 1.01^{\circ}$ angles of repose and 6.97 ± 0.2 g/sec flow rate. Compacts of native *Plectranthus edulis* starch were too soft and friable across the different lubricant concentrations and hence it was not included in all of the post-compaction studies. Pregelatinized *Plectranthus edulis* starch was able to accommodate 0.5% magnesium stearate with tablet hardness and friability value of 75.8 ± 3.67 N and $0.74 \pm 0.01\%$, respectively. Compacts of Starch 1500[®], however, were acceptably hard (> 60 N) up to 0.25% of magnesium stearate concentration indicating pregelatinized *Plectranthus edulis* starch was found to be less lubricant sensitive. Both pregelatinized *Plectranthus edulis* starch and Starch 1500[®] were able to accommodate up to 30% of the active pharmaceutical ingredient (API) with crushing strength and friability values of (65.34 ± 3.28 N and $0.75 \pm 2.09\%$) and (61.32 ± 4.12 N and 0.98 ± 3.11), respectively. At all levels of paracetamol powder, tablets of Starch 1500[®] exhibited less crushing strength and were more friable as compared to those of pregelatinized *Plectranthus edulis* starch ($P < 0.05$). Disintegration and dissolution tests of acceptable direct compression paracetamol tablets for both starch products met the pharmacopoeial requirements (BP, 2009; USP 30-NF 25, 2007).

In general, the pregelatinization process improved the compressibility and flowability of *Plectranthus edulis* starch and the modified starch product has better flowability and

compressibility than native *Plectranthus edulis* starch and Starch 1500[®]. Hence, pregelatinized *Plectranthus edulis* starch can be used as an alternative direct compression excipient in tablet formulations.

Key words: direct compression, dilution potential, filler-binder, lubricant sensitivity
Plectranthus edulis starch, pregelatinization

1. INTRODUCTION

1.1 Starch

Starch is one of the utmost suitable, naturally occurring, non-soluble, biodegradable, abundantly available and renewable biopolymer amongst other biomolecular resources (Martin, 2015; Paramakrishnan *et al.*, 2016). It exists within the plant cells in the form of granules (Shujun *et al.*, 2007) which are mainly found in seeds, roots and tubers, as well as in stems, leaves, fruits and even pollens. The granules have microscopic sizes with diameters ranging from 0.1 to 200 μm and occur in all shapes (spheres, ellipsoids, polygon, platelets, and irregular tubules) depending on the botanical source. The size of the granules is defined by the length of the α -glucan chains, amylose-amylopectin ratio and branching degree of amylopectin (Ashogbon and Akintayo, 2014; Alcázar-Alay and Meireles, 2015).

Starch is of commercial importance because of its inertness, abundance and cheapness. A commercial starch is obtained from cereals (corn, waxy corn, high amylose corn, wheat and various rice varieties) and from tubers and roots (particularly potato and cassava). Starch has become a valuable ingredient in the food industry, where it is used as thickener, gelling, bulking and water retention agent, and the pharmaceutical industry where it is used as filler, binder and disintegrant in tablet formulations (Odeku and Picker-Freyer, 2007).

Starch is known as a semi-crystalline material (i.e., the granules contain alternating crystalline and amorphous regions) and the degree of crystallinity decreases with increasing starch amylose content (Halley and Tan, 2014). These crystalline regions are predominantly made up of amylopectin polymers of which the outer branches are hydrogen bonded to each other to form crystallites that unravel during gelatinization. The amorphous regions of granules are mainly composed of amylose and amylopectin branch points (Ratnayake and Jackson, 2006). These polymers (amylose and amylopectin) are very different structurally (Fig. 1.1). Amylose and amylopectin make up 98 to 99% of the dry weight of native granules, with the remainder comprising small

amounts of lipids, minerals, and phosphorus in the form of phosphates esterified to glucose hydroxyls (Copeland *et al.*, 2009).

Figure 1.1: Structure of amylose and amylopectin

Amylose is a relatively long, linear polymer of α -glucan containing around 99% α - (1 $\rightarrow$ 4) and 1% α - (1 $\rightarrow$ 6) linkages and makes up to 20% to 30% of normal starch. The amount of amylose present in the granule significantly affects the physicochemical and

functional properties of starch. The amylose content can vary within the same botanical variety because of differences in geographic origin and culture conditions. On the other hand, amylopectin is a much larger molecule and a heavily branched structure built from about 95% α - (1→4) and 5% α - (1→6) linkages. The structures of these polymers play a critical role in the functionality of native and modified starches (Geigenberger, 2011; Alcázar-Alay and Meireles, 2015).

Amylose has a molecular weight in the range of approximately 10^5 - 10^6 , corresponding to a degree of polymerization (DP) of 1000 to 10,000 glucose units. Amylopectin is a much larger polymer, with molecular weight of about 10^8 and a DP that may exceed one million. Most starches contain 60 to 90% amylopectin, although high amylose starches, with as little as 30% amylopectin, and waxy starches with essentially 100% amylopectin are well known (Copeland *et al.*, 2009). Studies have revealed that the branch chain-length of amylopectin affects gelatinization (Jane *et al.*, 1999). For instance, waxy starch requires high energy for gelatinization due to its high crystallinity (Alcázar-Alay and Meireles, 2015).

The amylose to amylopectin ratio is an important measure of the constituting starch polysaccharides and is predictive of some starch granular and functional properties such as crystallinity, swelling power, and viscosity (Halley and Tan, 2014). The ratio is normally variable among different varieties and can be affected by growth environments but it varies within a limited range. For example, the amylose content of sweet potato might change from 19% to 25% depending on its growth environment (Zhou *et al.*, 2015).

Much of the information about starch granule crystalline properties has been acquired from X-ray powder diffraction studies. According to several such studies, starch can be classified as A, B and C crystalline forms. In the native granular forms, the A-type crystallinity is associated mainly with cereal starches, such as maize and wheat starch (Cheetham and Tao, 1998). The X-ray patterns of these kinds of starches show stronger diffraction peaks at around 15° , 17° , 18° , and 23° 2θ . The B-type is usually

obtained from tuber starches, such as potato and canna starches. The strongest peak in the X-ray diffraction pattern of B-type starches appears at $17^{\circ} 2\theta$. There are also a few minor peaks at 2θ values of 20° , 22° , and 24° . C-type starch is a mixture of both A- and B-types. Examples of C-type starches include smooth-seeded pea starch and various bean starches (Shujun *et al.*, 2007). The crystallinity of starches from different botanical sources might be variable, for example, crystallinity of maize and potato starches could range from 30% to 40%, while wheat starch has only 13–18% crystallinity (Zhou *et al.*, 2015).

Starches from different botanical sources may not have identical properties with respect to their intended use. Indeed, the chemical composition and physical characteristics of a starch are typical of its biological origin. Hence the starch from each plant source will vary somewhat in appearance, composition and properties (Gebre-Mariam and Schmidt, 1996). More specifically, parameters such as granule size, molar mass, and chain length distribution can directly and significantly affect the physicochemical properties of starch (Zhou *et al.*, 2015).

1.2 *Plectranthus edulis* and its starch

1.2.1 *Plectranthus edulis*

Plectranthus edulis (fam., Lamiaceae), syn. *Coleus edulis* Vatke, also known as Ethiopian potato, is one of the four economically important tuber crops of the genus *Plectranthus*, together with *Plectranthus esculentus*, *Plectranthus parviflorus* and *Plectranthus rotundifolius*. *Plectranthus edulis*, a diploid dicotyledonous plant, is an indigenous crop in Ethiopia with a height up to 150 cm (Taye *et al.*, 2007; Mekbib and Weibull, 2012; Taye *et al.*, 2012) (Fig. 1.2).



(A)

(B)

Figure 1.2 *Plectranthus edulis* plant (A) and its tubers (B) (Photograph by Demissie Y)

In different growing areas of Ethiopia, different vernacular names are used for *Plectranthus edulis*. Among these are ‘*Dinicha Oromo*’ in Oromia, meaning “potato of the Oromo people”, ‘*Wolaita dono*’ (potato of the Wolaita people) around Wolaita, ‘*Gamo dinich*’ (potato of the Gamo people) around Gamo Gofa Zone, ‘*Agew Dinch*’ (potato of the Agew people) in the northwest and ‘*Gurage Dinich*’ (potato of the Gurage people) around Gurage zone – and currently as Ethiopian potato, and is highly appreciated for its taste and hunger-satisfying effect (Taye *et al.*, 2013; Soresa, 2017).

Plectranthus edulis serves as an important part of the diet of the population and is widely used as a major source of carbohydrate in many parts of Ethiopia. Moreover, it has been used as a medicinal plant and eating the cooked root avoids loss of appetite (Tsegaw and Feyissa, 2014).

1.2.2 *Plectranthus edulis* starch

Starch from the tubers of *Plectranthus edulis* was isolated using 0.075% (w/v) sodium metabisulphite and it gave a yield of about 80.4% on dry weight basis. The proximate composition of the starch on dry weight basis was found to be 0.14% ash, 0.21% lipid, 0.43% protein, and 99.22% starch. The amylose content was 30.6%. Its true density,

moisture content and pH values were 1.47 g/ml, 11.2% and 6.6, respectively (Assefa, 2015).

Scanning electron microscopy (SEM) of the starch granules showed characteristic morphology that was oblong (elliptical) with some oval in shapes. The starch showed a monomodal normal granule size distribution with a mean particle size of 36.2 μm and specific surface area of 0.302 m^2/g . The differential scanning calorimetry (DSC) thermograms of *Plectranthus edulis* starch exhibited higher onset temperature (T_0) (69.2 $^{\circ}\text{C}$), peak temperature (T_p) (74.3 $^{\circ}\text{C}$) and end set temperature (T_e) (83.3 $^{\circ}\text{C}$) values than potato starch. X-Ray diffraction pattern of the starch was typical B-type with a distinctive maximum peak at $17.5^{\circ} 2\theta$ (Assefa, 2015).

1.3 Modification of starches

Among the most important considerations for selecting a starch are its functional properties which are too restricted in tablet manufacturing. The functional properties of native starch may be improved by applying appropriate modification techniques. These modifications improve some of the inherent properties and impart new properties in native starches that make them more versatile in their applications (Alam and Hasnain, 2009; Odeniyi and Ayorinde, 2014). Although the functionality of a starch depends on the molecular size, degree of crystallinity, amylose content and, specially, viscosity properties, by and large, it could be achieved through modifications of the native starch (Martin, 2015). The various starch modification techniques have been categorized as; physical, chemical, enzymatic and genetic modifications that improve the physico-chemical properties of the starch molecules. Amongst them, physical methods have received more attention since they are chemical free and fairly easier than the other methods (Majzoobi *et al.*, 2011).

1.3.1 Physical modification

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. Classification of starches from different

botanical sources based on physical modifications depends on whether the molecular integrity of the starches are destroyed or preserved after the modification. The former encompasses all the pregelatinization processes (drum drying, spray drying, and extrusion cooking) where starch granular order is lost together with partial depolymerization of starch components and the latter are the hydrothermal processes, e.g., annealing and heat moisture treatment where the molecular integrity of the starches are preserved (Ashogbon and Akintayo, 2014).

A large number of physical methods are available today that include heat moisture treatment, annealing, retrogradation, sonication, osmotic-pressure treatment, and pre-gelatinization (Wadchararat *et al.*, 2006; Pukkahuta *et al.*, 2007; Chung *et al.*, 2009; Zuo *et al.*, 2009). Of these methods, pregelatinization is becoming a popular physical method of starch modification.

1.3.2 Chemical modification

Chemical modification involves the introduction of functional groups on the starch molecule without affecting the morphology or size distribution of the granules. It generates significant changes in starch behavior, gelatinization capacity, retrogradation and paste properties (Alcázar-Alay and Meireles, 2015). Such modification helps in the stabilization of intra and inter-molecular bonds at different positions and locations. Factors such as starch source, reaction conditions, degree of substitution, type and distribution of substituting agent along the molecule of starch affect the functional and chemical properties of the modified starches (Din *et al.*, 2017). Chemical modification generally involves esterification, etherification or oxidation of the available hydroxyl groups on the α - D-glucopyranosyl units that make up the starch polymers (Chiu and Solarek, 2009). Chemically modified starches are used for a variety of value-added products and account for one-sixth of all starch solids (Odeku and Picker-Freyer, 2009).

1.3.3 Enzymatic modification

Enzymatic modification involves the exposure of starch suspensions to appropriate 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. The industrial enzymatic processing of starch is based on (partial) hydrolysis to maltodextrins, maltose and glucose syrups. Since solubilization of starch is desired for such enzymatic treatment, the applied enzymes need to be stable and active at temperatures above 65 – 70 °C. A natural source for extreme thermostable and thermoactive enzymes are (hyper) thermophiles that have their optimal temperature for growth above 60 °C. Well-known starch-acting enzymes are α -amylases and pullulanases, which degrade it to maltooligosaccharides and glucose. Recently, a thermostable cyclodextrin glycosyl transferase (EC 2.4.1.19) that produces circular cyclodextrins was introduced on the market (Kaper *et al.*, 2003).

The use of amylomaltases (EC 2.4.1.25) to modify starches is expected to find applications in the food stuff, cosmetics, pharmaceuticals, detergents, adhesives and drilling fluids as a plant and chemical free alternative to gelatin. The enzymes amylomaltases (α -1, 4- α -1, 4 glucosyl transferases) found in Eukarya, bacteria and archaea representatives, break an α -1,4 bond between two glucose units to subsequently make a novel α -1,4 bond producing a modified starch which can be used in forming a thermo-reversible gel. The enzymes used have to be free of enzymatic components that can cause undesirable damage to the starch molecule. The starches that can be used for modification should contain amylose (Kaur *et al.*, 2012).

Enzymatic modification of starch could be used to decrease viscosity and improve gel stability, appearance, texture, and resistance to heat. Moreover, it could also be used to produce amylose-free starch, which is of great interest in many industries (Auh *et al.*, 2006).

1.3.4 Genetic/biotechnology modification

The advancement of genetic engineering technologies has made the genetic modification of starch in plants possible by targeting the enzymes of the starch biosynthetic pathway. This transgenic technology has a potential to produce novel starches which can reduce or eliminate the use of environmentally hazardous post-

harvest chemical and enzymatic modification. Genetic modification can be carried out by traditional plant-breeding techniques or through biotechnology (Kaur *et al.*, 2012).

1.4 Pregelatinized starch

1.4.1 Pregelatinization of starch

During processing of starch, many changes occur in the physicochemical properties. The most important one can be considered as gelatinization. Starch granules are insoluble in cold water, but they absorb water in aqueous medium reversibly. When starch granules are heated in excess water, at a certain temperature, the swelling becomes irreversible and the structure of the granule is altered significantly. This process is called gelatinization (Arik Kibar *et al.*, 2010) and the temperature at which gelatinization occurs is called the "gelatinization temperature". For a population of granules, the range for gelatinization temperature is usually between 5 to 10°C, indicating that fractions of granules exhibit different gelatinization temperatures (Lund and Lorenz, 1984). Gelatinization occurs initially in the amorphous region, favored by the weak hydrogen bonds present in this area. The process then extends to the crystalline region. Amylose presence reduces the fusion point in the crystalline region and the amount of energy necessary to initiate gelatinization (Alcázar-Alay and Meireles, 2015).

The progression and the extent of gelatinization are primarily determined by raw material properties as well as the applied product parameters. From the side of the raw material properties the gelatinization process is influenced by characteristics of the starch granules: composition, morphology, molecular architecture, and molecular weight. Besides these, for the production of the final product, additional ingredients are added incorporating different components majorly influencing the gelatinization process. Furthermore, the addition of water is of particular interest, because the starch-to-water ratio determines the extent of gelatinization (Schirmer *et al.*, 2015). At the gelatinization temperature, the molecular order of the starch granules is irreversibly destroyed by structural changes which involve changes of shape and size of granules, absorption of

water and swelling, crystallite melting, and leaching of amylose (amylopectin) from the granules (Spigno and De Faveri, 2004).

Pregelatinized starches (PGS), also referred to as instant starch slurries, are those that have been simply precooked and drum dried to give products that readily disperse in cold water to form moderately stable suspensions (Anastasiades *et al.*, 2002). Starch can be pregelatinized fully or partially. Both fully and partially pregelatinized grades are commercially available. Partially PGS is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant. Partial pregelatinization renders the starch flowable and directly compressible. Full pregelatinization produces a cold-water soluble starch that can be used as a wet granulation binder. Typically, PGS contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. Normally the fully PGS contains 20–30% amylose and the rest amylopectin, which is about the same ratio (1 : 3) as for the partially pregelatinized form (Rowe *et al.*, 2009).

Pregelatinization of natural starches often leads to increase in their swellability, solubility percentage and water holding capacity. The higher values of these parameters for PGS relative to native ones might be due to disruption of weak associative bonds in the amorphous region of the granule and amylose leaching out (Wootton and Bamunuarachch, 1978; Alebiowu and Itiola, 2002; Adedokun and Itiola, 2010).

Traditional PGS are prepared by drum drying, spray drying and extrusion cooking. Drum-drying results in specific physicochemical modifications of starch granules performed in two consecutive stages: gelatinization and drying. In a double drum dryer, gelatinization takes place inside the “pool” of material formed between the upper halves of two horizontal drums. The actual drying starts only after the gelatinized material leaves the pool through the narrow gap between the drums and forms a thin film upon the surface of the drums. Drum-drying is capable of imparting a variety of textures and porous structures to the product – dictated strongly by the intensity of the treatment – which are expected to influence its functional properties (Anastasiades *et al.*, 2002).

Spray drying is a very common technique used for preparing starch-based materials because of its low cost and available equipment. It is very rapid drying process which converts liquid solution droplets mostly into amorphous or semi-amorphous particulates. Due to these reasons, pregelatinized starch without losing granular integrity has been prepared by spray drying since a long time ago (Fu et al., 2012). Native starch is slurried in water at room temperature. The slurry is injected through an atomization aperture in a nozzle assembly to form a fine spray. Steam is injected through another aperture in the nozzle assembly into the atomized starch spray to gelatinize the starch, the entire operation taking place in an enclosed chamber. The time for passage of the material through the chamber, i.e. from the atomization aperture through the vent aperture, defines the cooking or gelatinization time. The gelatinized starch is recovered essentially as granules. The technology is broadly applied to both native and chemically-modified starches (Chiu and Solarek, 2009). Pregelatinized starch prepared by spray drying has significantly better properties than a drum-dried sample which set quickly to a grainy, chunky consistency (Fu et al., 2012).

Starch pregelatinization can also be carried out by extrusion technology. Conventional extrusion cooking physically modifies starch and makes it swell through the unique combination of high temperature, pressure and shear forces in the presence of moisture. It is a very efficient technology having advantage of low cost, high-temperature, short-time process and versatile nature. Although there is increased use of extrusion processing, there is no fully developed theory to predict the effects of process variables on various raw materials and their mixtures (Gat and Ananthanarayan, 2015; Liu et al., 2017).

Starch gelatinization and associated properties are determined by various methods, including measuring the viscosity changes, X-ray diffraction, amylose-iodine binding (blue value), enzymatic digestibility, NMR, light extinction and solubility or sedimentation of swollen granules (Lund and Lorenz, 1984).

1.4.2 Description of pregelatinized starch

PGS occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste. Examination of fully PGS as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e. no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin shows characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially PGS (e.g. Starch 1500[®] and Sepistab ST200) show retention of birefringence patterns typical of unmodified starch granules (Rowe *et al.*, 2009).

The process of gelatinization causes substantial changes in both chemical and physical nature of granular starch due to the rearrangement of intra- and intermolecular hydrogen bonding between water and starch molecules resulting in the collapse or disruption of molecular orders within the starch granules (Majzoobi *et al.*, 2011). It has played important role in affecting micromeritic properties, such as particle size and shape, surface area, density, and flow properties of starch materials.

Starch 1500[®] (formerly STA-Rx 1500[®]), partially hydrolyzed corn starch, is the most widely used pregelatinized starch in the market. It is used mainly for direct compression and capsule filling. Although it was claimed to have many advantages over starch USP with respect to fluidity and compressibility, the flow properties were poor as compared with other filler-binders for direct compression. A major drawback is, however, it suffers from high sensitivity to hydrophobic lubricants such as magnesium stearate and its compacts form a viscous layer in contact with water delaying water penetration and prolonging disintegration (Bos *et al.*, 1992; Mitrevej *et al.*, 1996). Starch 1500[®] is prepared by spray drying technique. Spray drying is a well known technique for producing spherical and semispherical particles of small sizes (Rojas *et al.*, 2012).

1.5 Tablet excipients

The International Pharmaceutical Excipients Council (IPEC) defines excipients as "Substances, other than the API in finished dosage form, which have been appropriately

evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use” (The International Pharmaceutical Excipients Council, 1995). Excipients are used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients. They are also necessary in ensuring the manufacturing process is thriving and the quality of the formulation can be guaranteed. The appropriate selection of excipients in the formulation is critical in development of a successful product (Getachew *et al.*, 2016). Filler-binders or diluents, disintegrating agents and lubricants are the major types of excipients that are used for production of tablets, which are present in almost all tablet formulations (Bastos *et al.*, 2008).

1.5.1 Direct compression excipients (filler-binders or diluents)

Ideally, a diluent should be chemically inert, nonhygroscopic, and hydrophilic. Having an acceptable taste is important for oral formulations, and cost is always a significant factor in excipient selection. A diluent for direct compression formulations is often subject to prior processing to improve flowability and compression (Conway, 2008). It has a dual role in a direct compaction formulation. Not only does it increase the bulk of the dosage unit, but it also promotes the binding of the constituent particles of the formulation. Thus the term filler-binder is preferred and is used here (Bolhuis and Armstrong, 2006).

1.5.2 Binders

Binders are adhesives that are added to solid dosage formulations. The primary role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet. In a wet-granulation process, binders promote size enlargement to produce granules and thus improve flowability of the blend during the manufacturing process. Binders may also improve the hardness of the tablets by enhancing intragranular as well as intergranular forces. In a direct compression process, binders often act as fillers and impart compressibility to the powder blend. The cohesive properties of binders may reduce friability of the tablets and thus aid in their durability and elegance (Hamed *et al.*, 2005). A binder should impart adequate

cohesion without retarding disintegration or dissolution. Binders can be added either as a solution or as a dry powder. Binders added as dry powders are mixed with other powders prior to agglomeration, dissolving in water or solvent added during granulation, or added prior to compaction (Conway, 2008).

1.5.3 Disintegrants

Disintegrants are added to a formulation to overcome the cohesive strength imparted during compression, thus facilitating breakup of the formulation in the body and increasing the surface area for dissolution (Conway, 2008). The compaction force used in tablet manufacture can affect disintegration: in general, the higher the force the slower the disintegration time. Even small changes in formulation may result in significant effects on dissolution and bioavailability (Ashford, 2001). Several mechanisms of action of disintegrants have been suggested, such as facilitating water uptake, swelling of particles, exothermic wetting reaction, particle repulsion and particle deformation recovery. There are also groups of disintegrants that function by producing gases (Alderborn, 2001).

Starch is the commonest disintegrant in tablet formulation and is believed to act by swelling and by capillary action due to the pore structure of the tablet. However, current research has shown that most starches exert their disintegrant actions by deformation. Starch grains are generally elastic and at certain compression pressure, starch may undergo permanent deformation. These permanently deformed grains are rich in energy and when exposed to water, the energy is released causing disintegration of tablets (Onyishi et al., 2013).

1.5.4 Other Excipients

Lubricants are commonly added to help in the tableting of many formulations. Following compression, a tablet must be ejected out of the tablet press die. Lubricants reduce the friction between the tablet and the die metal surface, which reduces the ejection force and helps to ensure that the tablet is cleanly ejected and without cracking or breakage.

Furthermore, the presence of lubricants in formulated powder mixtures reduces interparticulate friction leading to improved flow properties. Such effects are mainly attributed to the ability of lubricants to be distributed as a surface film on the base/carrier material. In a general way, hydrophobic lubricants are more efficient than hydrophilic lubricants. On the other hand, hydrophobic lubricants can also alter other physicochemical properties of tablets, such as tensile strength (hardness), disintegration time, and drug release. Magnesium stearate, a metallic salt boundary lubricant, is probably the most commonly used hydrophobic lubricant for pharmaceutical tableting; Metallic salt lubricants are typically added to formulations in the range of 0.25 to 5.0%. Stearic acid is the most commonly used fatty acid boundary lubricant. It is typically added in a concentration ranged between 0.25 - 3% (Bastos *et al.*, 2008 ; Rashid *et al.*, 2010; Morin and Briens, 2013). Like lubricants, glidants are fine powders and may be required for tablet compression at high production speeds to improve the flow properties of the material into the die or during initial compression stages. They are added in the dry state immediately prior to compression and, by virtue of their low adhesive potential, reduce the friction between particles. Colloidal silica is popular, as are starches and talc. Antiadherents can also be added to a formulation that is especially prone to sticking to the die surface (or picking). Water insoluble lubricants such as magnesium stearate can be used as antiadherents, as can talc and starch (Conway, 2008).

1.6 Tablet manufacturing methods

Tablets are prepared by three general methods: wet granulation, dry granulation (roller compaction or slugging), and direct compression. The purpose of both wet and dry granulation is to improve flow of the mixture and/or to enhance its compressibility. Wet granulation is laborious, involving considerable material handling, as well as several processing steps. It is expensive because of equipment, energy and space requirements. Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to a granulation of the desired particle size. The advantage of dry

granulation is the elimination of both heat and moisture in the processing. Dry granulations can be produced also by extruding powders between hydraulically operated rollers to produce thin cakes which are subsequently screened or milled to give the desired granules size (USP 30 - NF 25, 2007; Bushra *et al.*, 2008).

Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment. The formulation of direct compression is simple including an API, a diluent, a disintegrant and a lubricant (Bushra *et al.*, 2008). The most striking feature of direct compression is its apparent simplicity. Less equipment is required; and the number of stages in the overall tableting process, each of which will require validation, is reduced. There are also lower labor costs, reduced processing time, and lower energy consumption (Bolhuis and Armstrong, 2006). In terms of tablet quality it has the further advantage over wet granulation method that no heat or moisture is used; consequently, thermolabile and moisture-sensitive compounds may be tableted without degradation (Parrott, 1989). However, direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the material during mixing may induce static charge and lead to segregation. This may lead to the problems like weight variation and content uniformity. Direct compression excipients are the specialty products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively costly than the respective raw materials. Most of the direct compression materials can accommodate only 30-40% of the poorly compressible active ingredients like paracetamol that means the weight of the final tablet to deliver the 500 mg of paracetamol would be more than 1300 mg. The large tablets may create difficulty in swallowing (Gohel and Jogani, 2005).

An excipient for direct compression should have the ability to incorporate a certain amount of drug and form a tablet of sufficient strength. Paracetamol is known to be a drug with a brittle and elastic behavior upon consolidation, making it poorly compressible. Thus, its combination with highly plastic-deforming material is needed to counteract this effect (Rojas *et al.*, 2013). To increase the use of direct compression in

pharmaceutical tableting, novel excipients with enhanced flow and compressibility, which can accommodate API variability, are needed (Mîinea *et al.*, 2011).

1.7 The present study

Ethiopia heavily relied on imported starch for pharmaceutical applications and spends a huge sum of money annually. So it is desirable to exploit starch from cheaper indigenous sources. The country has many native plant species which can be used as a source of starch for pharmaceutical purposes and some these species have been investigated in tablet formulations. One potential source could be *Plectranthus edulis*. Though native *Plectranthus edulis* starch was isolated, characterized, and evaluated for tablet disintegrating properties by wet granulation, its pregelatinized form has not yet been investigated as an alternative direct compression excipient in tablet formulations. Modified starches of *Plectranthus edulis* may offer a wide range of functional properties suitable for pharmaceutical applications in the pharmaceutical industry.

The research questions for this study were:

- Does pregelatinization of *Plectranthus edulis* starch provide a direct compression excipient?
- Does the pregelatinized *Plectranthus edulis* starch compare favorably with Starch 1500®?
- How does lubricant sensitivity of pregelatinized *Plectranthus edulis* starch look like in comparison with Starch 1500®?
- How does pregelatinized *Plectranthus edulis* starch perform as a directly compressible excipient in paracetamol tablet formulation in comparison with Starch 1500®?

Accordingly in this study, starch obtained from *Plectranthus edulis* tubers (Ethiopian potato) was physically modified by pregelatinization and was evaluated for its potential application as a directly compressible excipient using paracetamol as a model drug.

1.8 Objectives of the study

1.8.1 General Objective

To evaluate pregelatinized *Plectranthus edulis* starch as an alternative direct compression excipient in tablet formulations.

1.8.2 Specific Objectives

- To prepare different pregelatinized *Plectranthus edulis* starches for application as direct compression excipient; and evaluate their physicochemical properties against Starch 1500[®];
- To evaluate direct compression properties of pregelatinized *Plectranthus edulis* starch in comparison with Starch 1500[®];
- To evaluate lubricant sensitivity of pregelatinized *Plectranthus edulis* starch in comparison with Starch 1500[®];
- To formulate paracetamol tablets of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] and compare their tableting properties.

2. EXPERIMENTAL

2.1 Materials

Plectranthus edulis tubers were collected from local cultivating farmer in Gamo Gofa Zone, Chench-Woreda, Southern Ethiopia. Iodine Resublimed (Reagent Chemical Services Ltd., UK), sodium hydroxide and potassium iodide (Loba Chemie Pvt. Ltd., India), acetic acid glacial (Labmerk Chemicals Pvt. Ltd, India), sodium chloride and potassium phosphate monobasic (Analyticals® CARLO ERBA: Milano, Italy), paracetamol powder (Anqia Lu'an Pharm, China), croscarmellose sodium NF (Ac-Di-Sol®) (FMC Corporation, USA), sodium metabisulphite, potassium chloride, sodium metabisulphite and magnesium stearate (BDH Chemicals Ltd Poole, England), hydrochloric acid 37% (Riedel-deHaen®, Germany) were used as received.

2.2 Methods

2.2.1 Isolation of starch

Plectranthus edulis starch was isolated and purified following the procedure described by Gebre-Mariam and Schmidt, (1998). *Plectranthus edulis* tubers were washed, trimmed to remove defective parts and peeled. Immediately after peeling, the tuber flesh was chopped, wet milled, and suspended in large quantities of distilled water containing 0.075% (w/v) of sodium metabisulphite. The suspension was then allowed to settle overnight, and the supernatant was decanted. The sediment was repeatedly treated with sodium metabisulphite solution until the supernatant was clear. The suspension was then passed through fine muslin to remove cell debris and the translucent suspension was collected and allowed to settle. The sediment was washed several times with distilled water by filtering and re-suspending until the wash water was clear and free of suspended impurities. The resulting starch was air-dried at room temperature, and stored in airtight container, after milling and sieving (224 µm), for further use.

2.2.2 Preparation of pregelatinized starch

The pre-gelatinized form of *Plectranthus edulis* starches were prepared using established methods with slight modifications (Waliszewski *et al.*, 2003; Odeku *et al.*, 2008). Aqueous starch slurries (starch to water ratio of 1:3) were heated on thermostated water bath (GFL[®], D3006, Germany) at 60, 65, 69, 74 and 80 °C with stirring for 5, 10 and 15 min. The resultant pre-gelatinized starches were placed into stainless steel tray in the form of thin film and dried in a convection oven at 40 °C for 48 hr, then powdered using laboratory mill to pass through a fine sieve (224µm) and stored at room temperature in air tight glass jars.

2.2.3 Compaction properties of pregelatinized *Plectranthus edulis* starch

Compaction properties of the starch products were evaluated following the method described by Zuluaga *et al.*, (2007). Compacts of the starches were produced by compressing the powder at a fixed compaction force (adjusted to achieve hardness values between 60 to 80 N for the standard Starch 1500[®]) using an eccentric single punch tablet machine (ERWEKA[®] EKO Korsch, 7891, Germany). The compacts were evaluated for tensile strength and friability.

2.2.4 Amylose content determination

Estimation of the amylose content (%) of the starch samples was determined by a colorimetric assay method reported elsewhere (Juliano, 1971). A quantity of each sample (100 mg) was weighed into a 100 mL volumetric flask and heated for 10 min with 1 ml of 95% ethanol and 9 ml of 1 N sodium hydroxide in a boiling water bath to gelatinize the starch. The material was then cooled and made up to 100 mL with distilled water. A portion of the starch solution (5 mL) was pipetted into a 100 mL volumetric flask. 1 mL of 1 N acetic acid and 2 mL of iodine solution (0.2 g and 2 g potassium iodide in 100 ml of DW) were added and made up to volume (100 mL) with distilled water. After 20 min, the material was shaken and the absorbance reading was determined at 610 nm using a spectrophotometer (CM 2203, Solar, Belarus, Russia).

$$\% \text{Amylose} = 3.06 \times \text{Absorbance} \times 20 \dots\dots\dots (2.1)$$

*3.06 is conversion factor, *20 is dilution factor

2.2.5 Crystallinity study

For determination of starch crystallinity, XRD method was used. The X-ray diffraction pattern of the starch samples were taken with X-ray diffractometer (Rigaku, MiniFlex600, Germany) equipped with Cu anode with monochromator detector. A Cu source X-ray tube target voltage and current being 40 kV and 15 mA, respectively. Divergence, scatter and receiving slits were at 1.250°, 13.0mm and 13.0mm values, respectively. The sample was scanned continuously within a 2θ range of 3-35° at 10 °/min scan speed with measuring scan step of 0.02.

2.2.5. Characterization of powder properties of the starches

2.2.5.1 Determination of true density

For true density determination, fluid displacement method was utilized using xylene as immersion fluid. 2 g starch samples were placed in a volumetric flask (25 ml) which was then filled with xylene and weighed following the determination of the weight of the empty volumetric flask and the volumetric flask filled with xylene. Xylene was added in such a way that it washes down and overlay the sample. After 10 min, the sedimented starch was stirred with a small glass-stirring rod to release entrapped air. True density (g/ml) was calculated using equation 2.2. It was measured as a mean of three measurements.

$$\text{True density}(\rho) = \frac{W_1 \times S_g}{[(W_1 + W_2) - W_3]} \dots\dots\dots (2.2)$$

Where W_1 = Weight (g) of starch sample, W_2 = Weight (g) of volumetric flask filled with xylene, W_3 = Weight (g) of volumetric flask plus sample plus xylene left after displaced by the sample, and S_g = Specific gravity of xylene (g/ml) (0.87).

2.2.5.2 Determination of bulk density, tapped density and related properties

Carr's index, Hausner ratio, angle of repose, and flow rate were used to characterize the powder properties of the *Plectranthus edulis* starches (native and modified). 60 g sample of starch powder was transferred to a 250 ml calibrated glass cylinder and the volume occupied was noted after light tapping and bulk density was calculated. The

cylinder was then subjected to 500 taps to calculate the volume change and tapped density was determined. Carr's index and Hausner ratio were calculated as per equations 2.3 and 2.4, respectively.

$$\text{Carr's index} = \frac{\rho_t - \rho_b}{\rho_t} \times 100\% \dots\dots\dots (2.3)$$

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_b} \dots\dots\dots (2.4)$$

Where ρ_t = tapped density, ρ_b = bulk density.

Flow rate and angle of repose of the starch powders were determined by using the standard funnel method. Here 60 g starch powder was placed and allowed to flow through a stemless funnel having 10 mm aperture from a 10 cm height. For the duration of flow, time in seconds was recorded and used to calculate flow rate ($\text{Flow rate} = \frac{m}{t}$; where m is mass in gram and t is time in second). The average diameter and height of the powder piles formed were recorded. Angle of repose was determined from the height and radius of powder pile according to equation 2.5 below.

$$\text{Angle of repose}(\theta) = \tan^{-1}\left[\frac{h}{r}\right] \dots\dots\dots (2.5)$$

Where h and r are the height (cm) and radius (cm) of the starch powder pile, respectively.

2.2.6 Physicochemical characterization of the starches

2.2.6.1 Swelling power and solubility

Swelling power and solubility was determined as described by Odeku and Picker-Freyer, (2007). *Plectranthus edulis* starch samples (native and pregelatinized, 0.5 g) were weighed directly into a pre-weighed centrifuge tubes, and 10 ml distilled water was added in each tubes. The tubes were then kept in a thermostatically controlled water bath (GFL[®], D3006, Germany) at 27, 37, 50, 65, 75, and 85 °C for 30 min with frequent mixing at 2 min intervals. The tubes were then cooled to room temperature and centrifuged at 3000 rpm for 15 min, and the supernatant was removed and the residue obtained was weighed (W_r). The supernatant was dried at pre-weighed Petri dishes to constant weight (W_s) in an oven at 130 °C for 2 hrs. The residue obtained after drying

the supernatant represents the amount of starch solubilized in water. The solubility was calculated as g per 100 g of sample on dry weight basis. The residue obtained was weighed to obtain the swelling of the starch. All determinations were done in triplicate. The water solubility index (WSI) and swelling power (SP) were calculated using equations 2.6 and 2.7, respectively.

$$WSI = \frac{WS}{0.5g} \times 100\% \dots\dots\dots (2.6)$$

$$SP = \frac{Wr}{0.5(100-WSI)} \times 100\% \dots\dots\dots (2.7)$$

2.2.6.2 Moisture content

Moisture content of the powders was measured by gravimetric method as per the method described by Olayemi *et al.*, (2008) with slight modification. The powder samples (2 g each) were spread onto Petri dishes (dried and weighed) uniformly and dried in an oven (Kottermann® 2711, Germany) at a temperature of 130 °C to a constant weight. The percent moisture content was determined from the loss of weight according to equation 2.8. Results were expressed as a mean of three parallel determinations.

$$\% \text{ Moisture content} = \frac{W_b - W_a}{W_b} \times 100 \dots\dots\dots (2.8)$$

Where W_b and W_a are sample weights before and after drying, respectively

2.2.6.3 Moisture sorption properties

Moisture sorption properties were determined according to the method described by Olayemi *et al.*, (2008) with slight modification. For moisture sorption studies, Pyrex desiccators containing distilled water, saturated solutions of sodium chloride or appropriate concentration of sodium hydroxide were prepared to provide different relative humidity chambers and stored at room temperature. *Plectranthus edulis* starches (native and pregelatinized) and Starch 1500® were pre-dried in an oven

(Kottermann[®] 2711, Germany) for 4 h at 120 °C. Three grams of the starches were spread evenly on each Petri dish (dried and weighed) and transferred to particular relative humidity chamber. Samples were equilibrated for one week at room temperature. The weights after a week were recorded and the moisture content of each sample was calculated as the weight difference of the starches before and after equilibration in a given relative humidity. Water sorption capacities of the starches were expressed as percent moisture sorbed.

2.2.7 UV calibration curve of paracetamol

Stock solution containing 0.2 mg/ml of paracetamol in phosphate buffer of pH 5.8 was prepared. From this stock solution, six different concentrations (0.002, 0.004, 0.006, 0.008, 0.01, and 0.012 mg/ml) were prepared. The UV absorbance readings of these solutions were measured at 243 nm using UV/Visible spectrophotometer (CM 2203, Solar, Belarus, Russia). Phosphate buffer (pH 5.8) was used as a blank. Then, the absorbances versus concentration of solutions were plotted and a calibration curve with a linear regression equation and correlation coefficient were obtained. Triplicate determination was carried out.

2.2.8 Tablet preparation

2.2.8.1 Lubricant sensitivity study

The tablets containing *Plectranthus edulis* starches (native *Plectranthus edulis* starch & pregelatinized *Plectranthus edulis* starch) or Starch 1500[®] were compressed with magnesium stearate at concentrations of 0, 0.25%, 0.5%, 1.0%, 1.5%, and 2% (w/w). Forty grams batch of each mixture was mixed for 5 min in Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland). Ten mm flat surfaced compacts (tablets) of the starches were produced with 300 mg size by compressing the powder at a fixed compression force (adjusted to achieve hardness values between 60 to 80 N for the standard Starch 1500[®]) using an eccentric single punch tablet machine (ERWEKA[®] EKO Korsch, 7891, Germany). The tablet properties were determined 24 hr after compression.

2.2.8.2 Dilution potential

As for testing dilution potential of *Plectranthus edulis* starches (native *Plectranthus edulis* starch & pregelatinized *Plectranthus edulis* starch (prepared at 65 °C for 5 min)) or Starch 1500[®], 300 mg tablets (made by direct compression) containing 20%, 30%, 40% and 50% paracetamol were prepared. As indicated in Table 2.1, respective amounts of paracetamol, Ac-Di-Sol[®] (disintegrant) and starch (filler-binder) were mixed for 10 min in the Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland) and after addition of 0.5% magnesium stearate (lubricant), mixing was continued for 5 min. Paracetamol tablets were compressed on the single punch tablet machine (ERWEKA[®] EKO Korsch, 7891, Germany) at a constant compression force (adjusted to achieve crushing strength values between 60 and 80 N for the standard Starch 1500[®] formulation). In all cases, the tablet properties were determined 24 hr after preparation.

Table 2.1: Paracetamol tablet formulations with *Plectranthus edulis* starches or Starch 1500[®] as direct compression excipients

Formulations	Ingredients					
	Paracetamol (%)	NPES (%)	PGPES (%)	Starch	AC-Di- Sol (%)	Mg
				1500 [®] (%)		Stearate (%)
1	20	75.50	-	-	4	0.50
	20	-	75.50	-	4	0.50
	20	-	-	75.50	4	0.50
2	30	65.50	-	-	4	0.50
	30	-	65.50	-	4	0.50
	30	-	-	65.50	4	0.50
3	40	55.50	-	-	4	0.50
	40	-	55.50	-	4	0.50
	40	-	-	55.50	4	0.50
4	50	45.50	-	-	4	0.50
	50	-	45.50	-	4	0.50
	50	-	-	45.50	4	0.50

NPES: native *Plectranthus edulis* starch, PGPES: pregelatinized *Plectranthus edulis* starch

2.2.9 Evaluation of tablets

2.2.9.1 Weight and thickness

From each formulation, 20 tablets were randomly selected and weighed individually on an analytical balance (ADAM, Adam equipment, Milton Keynes, UK) and then the average weight and standard deviations were calculated. Tablet thickness was measured using sliding caliper scale (Nippon Sokutei, Japan).

2.2.9.2 Crushing strength

Ten tablets were taken from each batch and the crushing strength of the tablets was determined using hardness tester CALEVA, G.B., Caleva Ltd., THT2, UK). In this, each tablet was placed between two anvils and the force that just caused the tablet to break was recorded as the crushing strength. The average crushing strength was taken.

2.2.9.3 Tensile strength

The radial tensile strength was calculated using the data obtained from crushing strength, diameter, and thickness of the tablet using equation 2.9.

$$\sigma_x = \frac{2F}{\pi DT} \dots\dots\dots (2.9)$$

where σ_x is the tensile strength, F is the force required to break the tablet, D is the diameter of the tablet, and T is the tablet thickness.

2.2.9.4 Friability

Ten tablets of known weight from each batch were placed in the plastic chamber of a friability tester (ERWEKA® GmbH, TAR 20, Germany) and were subjected to combined effects of abrasion and shock by running the apparatus at a speed of 20 rpm for 5 min. Afterwards, the tablets were dusted and weighed, and the percent loss in weight was calculated as percent friability.

2.2.9.5 Disintegration time

Disintegration time test was carried out according to USP/NF specification (USP 30-NF 25, 2007). Six tablets were placed in a disintegration tester (CALEVA, G.B. Caleva Ltd., UK) filled with distilled water at 37 ± 2 °C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

2.2.9.6 Dissolution test

The dissolution tests were performed according to the USP/NF (USP 30-NF 25, 2007) specifications using dissolution apparatus Type II (ERWEKA, DT600, Germany). The

dissolution medium was 900 ml phosphate buffer (pH 5.8) solution maintained at 37 ± 0.5 °C and the rotation speed of the apparatus was set at 50 rpm. Five ml aliquots of the dissolution media were removed at 5, 10, 15, 20, 30, 45 and 60 min and filtered using Whatman No.1 filter paper. Equal amounts of fresh medium kept at the same temperature were transferred into the dissolution vessels to keep the sink condition. One ml of the filtered samples were diluted to 25 ml and absorbance readings were taken with UV/Visible spectrophotometer (CM 2203 Solar, Belarus, Russia) at 243 nm. Phosphate buffer (pH 5.8) was used as a blank. All the necessary corrections for dilution were made when calculating the drug content. Three dissolution studies were performed on the tablets for each batch and the average percent drug dissolved plotted against time to generate a dissolution curve.

2.2.9.7 Data analysis

Statistical analysis was performed using Analysis of Variance (ANOVA) and paired t-test with statistical software Origin 6.0 (OriginLab™ Corporation, USA). Tukey multiple comparison test was used to compare the individual difference in the physicochemical properties of the starches and tablet properties. At 95% confidence interval, p-values of ≤ 0.05 were considered statistically significant. All the data measured and reported are averages of a minimum of triplicate measurements and the values are expressed as mean $\pm$ standard deviation.

3 RESULTS AND DISCUSSION

3.1 Pre-compression evaluation

3.1.1 Micromeritic studies

For good tablets to be formed, the powder blend has to flow uniformly and form firm compaction. Good flowability ensures uniformity in die fill and thus uniformity in tablet weight. It also facilitates blending of fine powders encountered in direct compression blends (Atichokudomchai and Varavinit, 2003). Table 3.1 shows density and density related properties of pregelatinized *Plectranthus edulis* starches.

Table 3.1: Bulk, Tapped and True densities of pregelatinized *Plectranthus edulis* starches prepared at different temperatures and time

Temperature (°C)	Time (min)	Density (g/ml)		
		Bulk	Tapped	True
60	5	0.62 ± 0.01	0.76 ± 0.00	1.57 ± 0.31
	10	0.64 ± 0.02	0.77 ± 0.03	1.55 ± 0.12
	15	0.66 ± 0.00	0.79 ± 0.01	1.54 ± 0.34
65	5	0.72 ± 0.01	0.83 ± 0.01	1.56 ± 0.03
	10	0.67 ± 0.01	0.79 ± 0.02	1.52 ± 0.11
	15	0.66 ± 0.02	0.77 ± 0.01	1.51 ± 0.04
69	5	0.67 ± 0.01	0.80 ± 0.00	1.53 ± 0.02
	10	0.66 ± 0.04	0.79 ± 0.01	1.50 ± 0.23
	15	0.70 ± 0.02	0.79 ± 0.02	1.50 ± 0.17
74	5	0.63 ± 0.01	0.77 ± 0.04	1.49 ± 1.10
	10	0.62 ± 0.03	0.76 ± 0.01	1.48 ± 1.03
	15	0.63 ± 0.00	0.74 ± 0.01	1.46 ± 0.13
80	5	0.70 ± 0.00	0.83 ± 0.01	1.47 ± 0.08
	10	0.74 ± 0.02	0.85 ± 0.00	1.45 ± 0.25
	15	0.71 ± 0.04	0.82 ± 0.00	1.44 ± 0.17

Mean ± SD (n = 3)

As shown in Table 3.1, the bulk densities of the pregelatinized starch products increased following pregelatinization at all conditions, i.e., at all temperature and time points in comparison with the native *Plectranthus edulis* starch. On the other hand, true densities of the pregelatinized *Plectranthus edulis* starches were found to be decreasing with increasing temperature and time of gelatinization. This might be due to the loose granular packing following hydrogen bond breakage and amylose diffusion out of the granules during pregelatinization. The bulk density of a powder is dependent on particle packing and changes as the powder consolidates (Staniforth, 2001).

Powder flow is influenced by many solid state properties, including crystal habit, bulk density, particle size, and shape (Perumal and Podaralla, 2008). Table 3.2 shows the powder flow properties of *Plectranthus edulis* starch products pregelatinized at different conditions.

Table 3.2: Powder flow properties of pregelatinized *Plectranthus edulis* starches prepared at different temperatures and time

Temperature (°C)	Time (min)	Hausner ratio	Carr's index (%)	Angle of repose (degree)	Flow rate (g/sec)
60	5	1.23 ± 0.03	18.42 ± 1.31	21.15 ± 1.25	5.78 ± 1.07
	10	1.20 ± 0.01	16.88 ± 0.76	23.42 ± 1.17	5.09 ± 1.29
	15	1.20 ± 0.05	16.46 ± 1.15	22.18 ± 1.28	5.98 ± 1.57
65	5	1.15 ± 0.02	13.25 ± 1.21	20.08 ± 1.01	6.97 ± 0.20
	10	1.18 ± 0.04	15.19 ± 1.09	24.16 ± 2.30	5.77 ± 0.53
	15	1.17 ± 0.02	14.29 ± 0.87	22.42 ± 0.32	5.68 ± 1.06
69	5	1.19 ± 0.03	16.25 ± 1.67	23.25 ± 0.80	5.57 ± 1.12
	10	1.20 ± 0.01	16.46 ± 1.33	21.37 ± 1.08	6.01 ± 0.67
	15	1.13 ± 0.04	11.39 ± 0.83	19.50 ± 1.21	6.15 ± 0.42
74	5	1.22 ± 0.04	18.18 ± 1.54	22.00 ± 0.67	4.73 ± 2.10
	10	1.23 ± 0.03	18.42 ± 1.17	22.70 ± 0.34	5.74 ± 0.87
	15	1.17 ± 0.01	14.86 ± 0.45	20.14 ± 0.23	5.57 ± 1.42
80	5	1.19 ± 0.02	15.66 ± 2.21	19.90 ± 0.81	5.15 ± 0.23
	10	1.15 ± 0.04	12.94 ± 1.81	20.82 ± 1.23	6.18 ± 0.45
	15	1.15 ± 0.01	13.41 ± 1.11	21.94 ± 0.91	5.63 ± 0.13

Mean ± SD (n = 3)

From the values of HR, CI, and angle of repose of the fifteen starch products, the pregelatinization process has improved the starch's powder flowability relative to the native *Plectranthus edulis* starch which has no flow property.

Pregelatinized *Plectranthus edulis* starch prepared at 65 °C for 5 min was considered for comparison against native *Plectranthus edulis* starch and Starch 1500[®] with respect to their powder properties. Table 3.3 shows moisture content, density and density related properties of *Plectranthus edulis* starches (native and pregelatinized) and Starch 1500[®].

Table 3.3: Powder properties of native and pregelatinized (prepared at 65 °C for 5 min) *Plectranthus edulis* starches and Starch 1500®.

Powder properties	NPES (±SD)	PGPES (±SD)	Starch 1500® (±SD)
Moisture content (%)	11.37 ± 0.15	9.03 ± 0.07	10.84 ± 0.16
True density (g/ml)	1.46 ± 0.02	1.56 ± 0.03	1.47 ± 0.01
Bulk density (g/ml)	0.60 ± 0.01	0.72 ± 0.01	0.66 ± 0.01
Tapped density (g/ml)	0.84 ± 0.01	0.83 ± 0.00	0.80 ± 0.00
Hausner ratio	1.40 ± 0.03	1.15 ± 0.02	1.21 ± 0.02
Carr's index (%)	28.56 ± 1.77	13.25 ± 1.21	17.92 ± 0.72
Angle of repose (degree)	*	20.08 ± 1.01	23.42 ± 0.97
Flow rate (g/sec.)	*	6.97 ± 0.20	5.12 ± 1.03

NPES: native *Plectranthus edulis* starch, PGPES: pregelatinized *Plectranthus edulis* starch, Mean ± SD, * no flow of the powder

The moisture content of dry starch varies from 6 - 16%, depending on the process used for drying the starch and season of collection. Higher levels of moisture can lead to microbial growth and subsequent deterioration in quality. The maximum moisture content recommended for safe storage of starch is 13% (Moorthy, 2002). As indicated in Table 3.3, 11.37 ± 0.15%, 9.03 ± 0.07% and 10.84 ± 0.16% are the results for the moisture contents of native *Plectranthus edulis* starch, pregelatinized *Plectranthus edulis* starch and Starch 1500®, respectively. Pregelatinized *Plectranthus edulis* starch showed significantly lower moisture content than the native *Plectranthus edulis* starch (P < 0.05). This agrees with the observation of Okunlola and Odeku (2009).

The rank order of true density is pregelatinized *Plectranthus edulis* starch (1.56 ± 0.03 g/ml) > Starch 1500® (1.47 ± 0.01 g/ml) > native *Plectranthus edulis* starch (1.46 ± 0.02 g/ml). Pregelatinized *Plectranthus edulis* starch showed significantly (P < 0.05) the highest true density value. The bulk and tapped densities are applied as an indirect

method for predicting the flow and compactibility properties of the powders (Builders *et al.*, 2013). As shown in Table 3.3, the rank order for bulk density was pregelatinized *Plectranthus edulis* starch > Starch 1500[®] > native *Plectranthus edulis* starch while the rank order for tapped density was native *Plectranthus edulis* starch > pregelatinized *Plectranthus edulis* starch > Starch 1500[®] and their differences was statistically significant ($p < 0.05$) in both cases. The particle size and shape of the starches may be responsible for the differences in the density values.

In order to determine the values of Hausner ratio (HR) and Carr's index (CI), the density values were used. CI is a measure of powder bridge strength and stability, and the HR provides an indication of the degree of densification which could result from vibration of the feed hopper, for example, during tableting, with higher values predicting significant densification of powders. Lower CI or lower HR of a material indicate better flow properties than higher ones (Alebiowu and Itiola, 2002; Shah *et al.*, 2008). A CI of <10 or HR of <1.11 is considered 'excellent' flow whereas CI > 38 or HR > 1.60 is considered 'very very poor' flow. There are intermediate scales for CI between 11–15 or HR between 1.12–1.18 is considered 'good' flow, CI between 16–20 or HR between 1.19–1.25 is considered 'fair' flow, CI between 21–25 or HR between 1.26–1.34 is considered passable flow, CI between 26–31 or HR between 1.35–1.45 is considered 'poor' flow, and CI between 32–37 or HR between 1.46–1.59 is considered 'very poor' flow (Shah *et al.*, 2008). HR and CI values of pregelatinized *Plectranthus edulis* starch (1.15 ± 0.02 , 13.25 ± 1.21) and Starch 1500[®] (1.21 ± 0.02 , 17.92 ± 0.72), respectively have significantly lower values than that of the native *Plectranthus edulis* starch (1.40 ± 0.03 , 28.56 ± 1.77) ($P < 0.05$), suggesting better flowability than the native starch.

Powder flowability can be obtained by assessment of interparticulate friction. The angle of repose (θ) is a parameter that is dependent on interparticulate friction and cohesion. It could be used as a qualitative measure of the tendency of powdered or granulated materials to flow, for instance, from hoppers through the feed frame into tableting machines. Such uniformity of flow will minimize weight variations in tablets produced. Its value will be high if the powder is cohesive and low if the powder is non-cohesive.

Angles of 30° or below are usually indicative of free flowing materials while an angle of 40° or above indicates a poor flow. The angle of repose is affected by the particle size distribution and it usually increases with a decrease in particle size (Birudaraj *et al.*, 2005; Okunlola and Odeku, 2009). The results of the angle of repose were in line with CI and HR. Native *Plectranthus edulis* starch did not flow through the funnel to form a cone and, therefore, the angle of repose could not be determined. The angle of repose observed in pregelatinized *Plectranthus edulis* starch (20.08 ± 1.01) was significantly higher than Starch 1500® (23.42 ± 0.97) ($p < 0.05$). Furthermore, direct measure of the flow property showed that pregelatinized *Plectranthus edulis* starch (6.97 ± 0.2 g/sec) could have a better flow rate than Starch 1500® (5.12 ± 1.03 g/sec) ($p < 0.05$). In general, these results indicate that pregelatinization remarkably improved the flow property of native *Plectranthus edulis* starch which might be due to a lower degree of interparticle interactions as in the report indicated by Zuluaga *et al.*, (2007).

3.1.2 Amylose content determination

The amylose content of starches is important because amylose largely determines the gelling ability (Adedokun and Itiola, 2010) and solubility (Zhu *et al.*, 2008) of starches. There are many different procedures available to measure amylose. The most frequently used method is colorimetry (iodine binding with amylose). Amylose, in aqueous solution, interacts with triiodide ion (I_3^-) to form a blue colored helical complex (λ_{max} , 600-610nm). The short outer linear chains of amylopectin weakly interact with iodine (I_3^-) to form a violet colored complex (λ_{max} , 530-540nm) (Gebre-Mariam and Schmidt, 1996).

In this study, this difference in the “iodine binding capacity” has been used for the estimation of amylose contents of the starch samples using Eq. 2.1. Accordingly, the amylose contents of native *Plectranthus edulis* starch and pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) were estimated to be $30.4 \pm 2.08\%$ and $30.3 \pm 2.89\%$, respectively. Pregelatinization didn't affect the amylose to amylopectin ratio. This is because physical modification do not bring about a change in the overall

amylose content of a starch product (Zobel, 1984). Native *Plectranthus edulis* starch's amylose content (30.4%) was in line with that reported by (Assefa, 2015) (30.6%) and their difference was not significant ($P > 0.05$). The accuracy of the method was confirmed by the results obtained for potato starch (29.56%) which fell within the range of amylose contents of potato starch (Zhu *et al.*, 2008) determined by various methods.

3.1.3 Crystallinity

X-ray diffraction pattern is the “fingerprint” of the crystal structure within starch grains (Zeng *et al.*, 2011). It can be used to detect changes in crystallinity brought about by physical or chemical treatment of starch granules. The method has been used as a tool to measure the extent of gelatinization (Lund and Lorenz, 1984). The X-ray powder diffraction patterns of native *Plectranthus edulis* starch (A) and pregelatinized *Plectranthus edulis* starch (prepared at 65 °C for 5 min) (B) are depicted in Fig. 3.1.

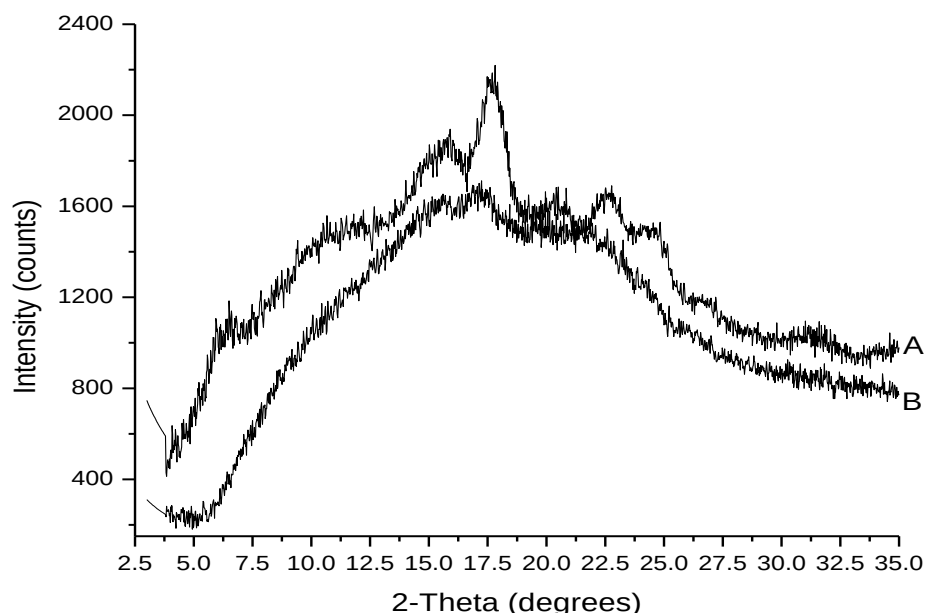


Figure 3.1: X-ray powder diffractograms of native *Plectranthus edulis* starch (A) and pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) (B)

The native *Plectranthus edulis* starch showed the highest peak intensity in the X-ray powder diffraction pattern at 17.5° 2θ. Some minor peaks are also observed at 15.8°,

20.4°, 22.6° and 24.4° 2θ, indicating a typical B-type crystallinity (Fig. 3.1). Loss of granular order following pregelatinization of the native *Plectranthus edulis* starch is evident as exhibited by the amorphous X-ray diffractogram of pregelatinized *Plectranthus edulis* starch. Furthermore, most of the peaks that were observed in the native *Plectranthus edulis* starch disappeared in the pregelatinized *Plectranthus edulis* starch. Nonetheless, the granular order was not completely lost as low peak intensity is apparent at 17.2° 2θ in the X-ray diffractogram.

3.1.4 Swelling power and water solubility

Swelling power and solubility can be used to assess the extent of interaction between starch chains, within the amorphous and crystalline domains of the starch granule. Furthermore, they are influenced by amylose and amylopectin characteristics (Kusumayanti *et al.*, 2015; Rayan *et al.*, 2015). In other words they are not only a measure of the hydration capacity of the sample but are also indicative of the associative forces in the granules (Manek *et al.*, 2012). The swelling and solubility patterns of native *Plectranthus edulis* starch, pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) and Starch 1500® are depicted in Fig. 3.2 and Fig. 3.3, respectively. The swelling power and solubility of the starches were generally low at low temperatures but increased significantly ($P < 0.05$) at higher temperatures (85°C), which is in agreement with the properties observed for other modified starches. The swelling properties and water solubility observed in pregelatinized *Plectranthus edulis* starch and Starch 1500® were significantly ($P < 0.05$) higher than native *Plectranthus edulis* starch at all temperature points. This shows that pregelatinization increased the swelling power and solubility of the starches. This might be attributed to crystalline structure disruption (breakage of hydrogen bonding) and water molecules become linked by hydrogen bonding to the exposed OH groups of amylose and amylopectin. This causes an increase in granule swelling and solubility.

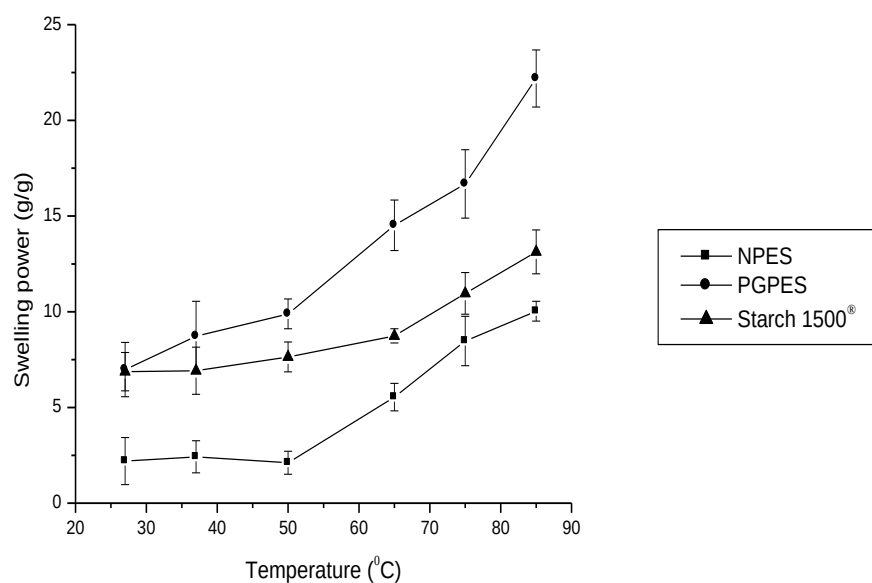


Figure 3.2: Swelling power of native *Plectranthus edulis* starch, pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) and Starch 1500[®] at different temperatures.

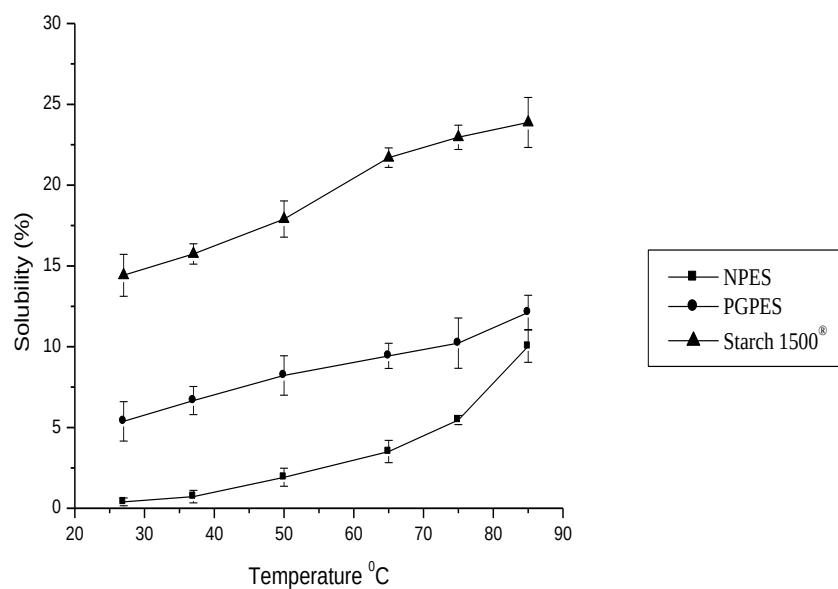


Figure 3.3: Solubility of native *Plectranthus edulis*, starch pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) and Starch 1500[®] at different temperatures.

3.1.5 Moisture sorption property

An understanding of the moisture sorption characteristics of pharmaceutical excipients is imperative since most of the physicochemical and functional properties of these materials either depend or are affected by it. For instance, knowledge of moisture sorption profiles of starches is necessary where controlled powder flow or compaction is critical. Moisture modifies the flow and mechanical properties of many powders including starches. Moisture may also induce unpredicted phase transitions in excipients which may also be imparted to the APIs when used for formulation. Generally, when starch is exposed to a moisture rich environment, the water molecules interact strongly with the polar groups of the amylose and amylopectin units (Builders *et al.*, 2013; Gebre-Mariam and Schmidt, 1996). The moisture sorption profiles of *Plectranthus edulis* starches (native and pregelatinized (prepared at 65°C for 5 min)) and Starch 1500® equilibrated at different humidity levels (20, 40, 60, 75 and 100% RH) are depicted in Fig. 3.4. Generally, the moisture sorption by the starches increased with relative humidity. As shown in the figure, the percent moisture sorbed ranged from $5.51 \pm 1.43\%$ at 20% RH to $58.6 \pm 1.37\%$ at 100% RH for Starch 1500®. Moisture sorption profile of pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) is significantly higher than native *Plectranthus edulis* starch ($p < 0.05$) at every relative humidity points except at 20%.

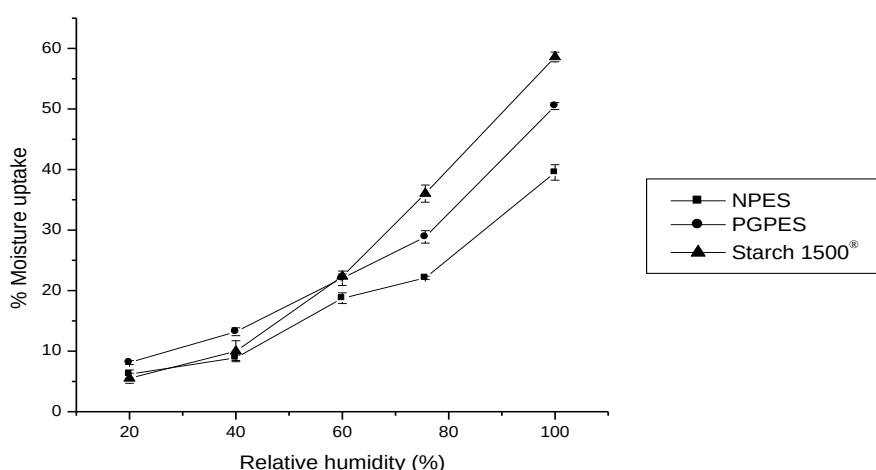


Figure 3.4: Moisture sorption profiles of native *Plectranthus edulis* starch, pregelatinized *Plectranthus edulis* starch (prepared at 65°C for 5 min) and Starch 1500®

3.2 Post-compression evaluation

3.2.1 Compaction properties of pregelatinized *Plectranthus edulis* starch

Manipulation of variables such as compactibility is required to produce a formulation with high quality and high productivity. The compaction properties of pharmaceutical powders are characterized by their compactibility. Compactibility is the capability of a material to form coherent agglomerates or mechanically strong compacts after compression (Valadez and Robles, 2014).

In this study, the starch products were subjected to a fixed compaction force and the compacts were evaluated for crushing strength and friability. Table 3.4 shows friability and crushing strength of compacts of pregelatinized *Plectranthus edulis* starches. Compacts from native *Plectranthus edulis* starch were too soft and friable and hence are not included in the post-compaction studies. This was expected because compacts from native starches are weak and suffer from lamination and capping (Rojas *et al.*, 2012). Compacts of nine of the fifteen pregelatinized *Plectranthus edulis* starch products provided acceptable crushing strength and friability values. The crushing strength of compacts of the fifteen pregelatinized starch products ranged from 30.54 ± 3.01 N to 92.59 ± 2.32 N (pregelatinized at 80 °C for 15 min and at 60 °C for 10 min, respectively) while the friability of the compacts with acceptable properties ranged from $0.52 \pm 0.02\%$ to $0.92 \pm 0.51\%$ for the starch products prepared at 65 °C for 5 min and at 60 °C for 15 min, respectively. Comparison against compacts of the standard (Starch 1500®) with respect to crushing strength and friability was made for the starch product prepared at optimum conditions (starch to water ratio of 1:3, at 65 °C for 5 min). Accordingly, 90.20 ± 3.45 N and $0.52 \pm 0.02\%$ were the observed crushing strength and friability of the optimized *Plectranthus edulis* starch product. The aforementioned crushing strength of pregelatinized *Plectranthus edulis* starch was significantly higher than that of Starch 1500® (78.1 ± 5.61 N) (indicated in Table 3.5 at zero magnesium stearate level) ($P < 0.05$). The friability of compacts of the pregelatinized *Plectranthus edulis* starch prepared at 65°C for 5 min and that of Starch 1500® were found to be comparable ($P > 0.05$).

Table 3.4: Friability and crushing strength of compacts of pregelatinized *Plectranthus edulis* starches prepared at different temperatures and time

Temperature (°C)	Time (min)	Friability (%)	Crushing strength (N)
60	5	Friable	78.16 ± 2.92
	10	Friable	92.59 ± 2.32
	15	0.92 ± 0.51	88.22 ± 3.17
65	5	0.52 ± 0.02	90.20 ± 3.45
	10	0.55 ± 0.00	68.72 ± 4.33
	15	0.68 ± 0.03	72.57 ± 2.67
69	5	0.72 ± 0.01	62.18 ± 1.80
	10	0.53 ± 0.02	72.86 ± 3.33
	15	0.58 ± 0.01	78.47 ± 2.91
74	5	0.61 ± 0.02	68.16 ± 3.77
	10	0.63 ± 0.00	61.02 ± 2.99
	15	Friable	66.71 ± 2.53
80	5	Friable	42.23 ± 4.56
	10	Friable	34.12 ± 2.55
	15	Friable	30.54 ± 3.01
Mean ± SD (n = 10)			

From the result seen in Table 3.4, the pregelatinization process has improved the starch's compaction properties. A report by Jenkins and Donald (1995) proposed that the presence of amylose in the crystalline region might have a potential to disrupt crystalline packing of amylopectin. Therefore, due to amylose erosion by pregelatinization (Jane, 2009), a reduced hindrance may result for the double helical chains to approach each other. Consequently, upon exposure to a compaction pressure, the crystalline regions of the starch granules form closely packed and more ordered arrangement within the starch granules.

3.2.2 Lubricant sensitivity of pregelatinized *Plectranthus edulis* starch

In tablet compression, lubricants are used in powder form to reduce frictional forces at the interface between powder, granule and tablet surface with the die wall. Lubricants can also help to reduce the sticking of tablets to punches in the tableting machine and the wear of tooling; they improve the flow and filling of substances into the cavities (Gbenga and Adebolu, 2009). In spite of the importance of lubricants in solid dosage forms, problems can occur when lubricants are added to excipient/API mixtures. The compaction and/or disintegration time of binders, fillers, and disintegrants has been reported to be negatively affected by the presence of lubricants (Rashid *et al.*, 2010).

Pregelatinized *Plectranthus edulis* starch and Starch 1500[®] compacts (tablets) were prepared at different magnesium stearate concentrations of 0, 0.25, 0.5, 0.75, 1, 1.5 and 2% (w/w) to investigate the effect of lubricant concentrations on post-compaction properties of the starch products. The tablets were then tested for weight variation, friability, crushing strength, tensile strength and disintegration time.

The weight and thickness of compacts of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] with magnesium stearate at different concentrations were determined. Accordingly, different levels of lubricant concentrations did not result tablets with significant weight and thickness differences ($P > 0.5$).

Tablet hardness is not an absolute indicator of tablet strength since some formulations, when compressed into very hard tablets, tend to “cap” on attrition, losing their crown portions. Conventional compressed tablets that lose less than 1% of their weight during the friability test are generally considered acceptable (Lee, 2008; Okunlola and Odeku, 2011). As indicated in Table 3.5, friability of the tablets generally increased for both starch products as the level of magnesium stearate increased from 0 to 2% (w/w) ($P < 0.05$). This is due to the fact that magnesium stearate reduces the ability of the powders to form strong compacts because of its weak binding force with other particles (Lee, 2008; Gbenga and Adebolu, 2009). The tablets prepared from pregelatinized *Plectranthus edulis* starch and pregelatinized *Plectranthus edulis* starch (prepared at 65°C

for 5 min) with magnesium stearate concentration up to 0.5% and those prepared from Starch 1500[®] with magnesium stearate concentration up to 0.25% had friability values of less than 1%. In addition; less friable tablets were obtained from pregelatinized *Plectranthus edulis* starch than Starch 1500[®] across the different magnesium stearate concentrations.

Crushing strength is a measure of the bond strength and ability of the tablets to withstand the stress of packaging, transportation and handling (Odeniyi and Ayorinde, 2014). The crushing strength of compacts of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] with magnesium stearate at different concentrations (0 – 2%) are also shown in Table 3.5. The results obtained indicate a trend of decrease in tablet crushing strength as the concentration of lubricant added to the starches increases ($P < 0.05$). This might be attributed to the formation of hydrophobic film around the starch particles giving a molecular coverage which makes the interparticle bond formation more difficult thereby decreasing the mechanical strength of the resulting tablets (Bastos *et al.*, 2008). Compacts of pregelatinized *Plectranthus edulis* starch were acceptably hard (> 60 N) up to 0.5% of magnesium stearate concentration (BP, 2009) unlike that of Starch 1500[®] which could accommodate only 0.25% magnesium stearate concentration. Furthermore at all levels of magnesium stearate concentration, the crushing strength of compacts of pregelatinized *Plectranthus edulis* starch was significantly higher than that of Starch 1500[®] ($P < 0.05$). From the overall result, it can be deduced that the pregelatinized *Plectranthus edulis* starch showed less lubricant sensitivity and better compactibility than the native *Plectranthus edulis* starch and Starch 1500[®] and therefore can be a promising alternative direct compression excipient.

Table 3.5: Friability and crushing strength of compacts of pregelatinized *Plectranthus edulis* starch (prepared at 65 °C for 5 min) and Starch 1500[®] at different levels of magnesium stearate

Starch product	Magnesium stearate (%)	Parameters	
		Friability (%)	Crushing strength(N)
pregelatinized <i>Plectranthus edulis</i> starch	0	0.52 ± 0.02	90.2 ± 3.45
	0.25	0.61± 0.01	83.4 ± 4.17
	0.5	0.74 ± 0.01	75.8 ± 3.67
	0.75	1.13 ± 0.02	56.1± 5.23
	1	2.45 ± 0.01	42.8 ± 3.17
	1.5	5.98 ± 0.02	38.2 ± 3.09
	2	7.43 ± 0.03	24.6 ± 2.71
Starch 1500 [®]	0	0.58 ± 0.01	78.1± 5.61
	0.25	0.65 ± 0.02	69.3 ± 4.91
	0.5	1.63 ± 0.01	52.8 ± 4.37
	0.75	1.84 ± 0.01	44.7 ± 3.42
	1	2.37± 0.03	32.2 ± 5.12
	1.5	5.42 ± 0.02	24.4 ± 4.43
	2	7.83 ± 0.01	13.3 ± 3.87
Mean ± SD (n = 10)			

The tensile strength of compacts of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] at different magnesium stearate concentrations is shown in Fig. 3.5. The decrease in tensile strength for compacts of both starch products with increasing magnesium stearate concentration was expected since tensile strength is directly proportional to crushing strength. For all levels of magnesium stearate concentrations, the tensile strength of compacts of pregelatinized *Plectranthus edulis* starch was generally higher than that of Starch 1500[®] ($P < 0.05$).

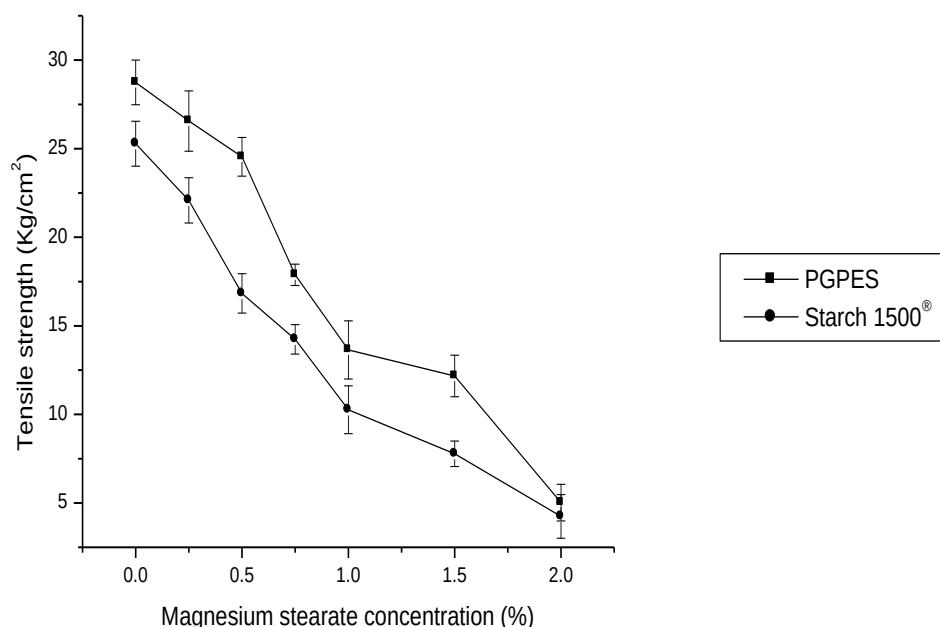


Figure 3.5: Tensile strength profile of compacts of pregelatinized *Plectranthus edulis* starch and Starch 1500[®] at different levels of magnesium stearate

Due to its hydrophobicity, magnesium stearate has a deleterious effect on the disintegration time of tablets. The hydrophobic surfaces created by magnesium stearate have been shown to reduce the rate of dissolution and bioavailability of several tablet formulations (Lee, 2008). A number of experimental findings have shown that the observed deleterious effect of magnesium stearate on disintegration time is due to its large surface area which, in combination with its hydrophobicity, hinder water penetration to affect disintegration (Wang *et al.*, 2010). The effect of lubricant (magnesium stearate) on disintegration time of compacts prepared from pregelatinized *Plectranthus edulis* starch and Starch 1500[®] is depicted in Fig. 3.6 below. The figure shows that the disintegration time of the compacts increased as the concentration of magnesium stearate increased. This was expected because of the hydrophobic hindrance of the lubricant coat towards water penetration. Comparable disintegration time was observed between pregelatinized *Plectranthus edulis* starch and Starch 1500[®]

across the different levels of magnesium stearate ($P > 0.05$). Furthermore, all of the compacts exhibited acceptable disintegration time (< 15 min).

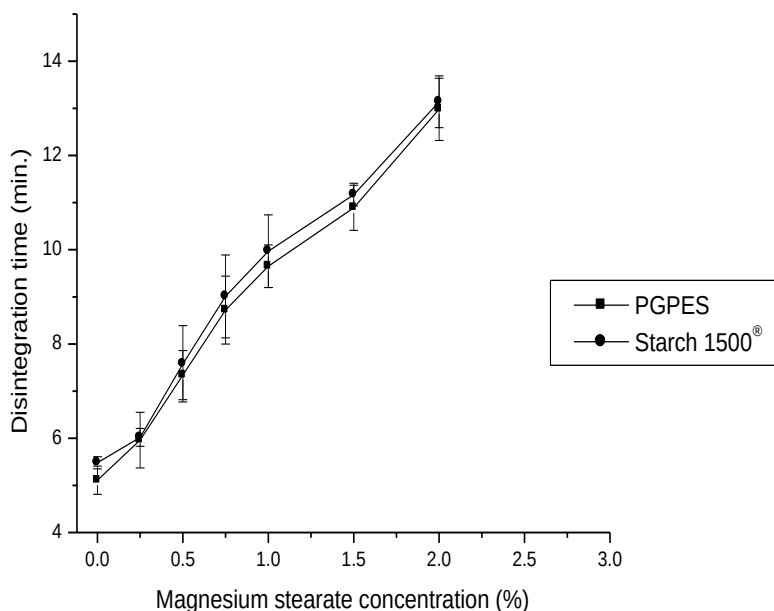


Figure 3.6 Plot of magnesium stearate concentration versus disintegration time of compacts of pregelatinized *Plectranthus edulis* starch and Starch 1500®

3.2.3 Dilution potential of pregelatinized *Plectranthus edulis* starch

An important property of direct compression excipients is their characteristic high dilution potential (also known as loading capacity or carrying capacity). The dilution potential can be defined as the amount of an API that can satisfactorily be compressed into tablets with the excipient mixture (Mîinea *et al.*, 2011; Builders *et al.*, 2013). Generally the more API that can be added to the excipients the higher its dilution potential. Paracetamol was used for assessing the dilution potential because of its poor compaction property resulting from its ability to undergo considerable elastic recovery after withdrawal of the compaction pressure (Builders *et al.*, 2010). The dilution potential of pregelatinized *Plectranthus edulis* starch in comparison with that of Starch 1500® was determined by assessing friability, crushing strength, tensile strength, and other parameters of tablets (300 mg each) prepared with different concentrations of paracetamol (20%, 30%, 40%, and 50%) as shown in Table 3.6. Crushing strength,

tensile strength and DT decreased while friability increased with increasing paracetamol concentration.

The tablets formulated both from pregelatinized *Plectranthus edulis* starch and Starch 1500[®] fulfilled the required properties up to 30% paracetamol level. However, beyond 30% paracetamol concentration, the tablets were found to be too friable with low tensile strength. The result was expected because of the elastic recovery and poor compressibility of paracetamol as reported by Builders *et al.* (2010). Therefore both of the starch products could accommodate 30% paracetamol with acceptable tablet properties.

Table 3.6: Properties of direct compression tablets formulated from pregelatinized *Plectranthus edulis* starch and Starch 1500® at different concentrations of paracetamol

Parameters	Paracetamol Content (%)	PGPES ($\pm$ SD)	Starch 1500® ($\pm$ SD)
Crushing strength (N)	20	72.65 $\pm$ 4.72	66.19 $\pm$ 2.51
	30	65.34 $\pm$ 3.28	61.32 $\pm$ 4.12
	40	58.12 $\pm$ 3.46	48.29 $\pm$ 3.13
	50	24.33 $\pm$ 3.21	19.27 $\pm$ 4.61
Tensile strength (Kg/cm ²)	20	23.41 $\pm$ 4.17	22.18 $\pm$ 3.11
	30	20.72 $\pm$ 5.24	19.46 $\pm$ 5.78
	40	18.47 $\pm$ 6.42	15.37 $\pm$ 4.28
	50	7.75 $\pm$ 3.19	6.14 $\pm$ 2.27
Friability (%)	20	0.56 $\pm$ 1.03	0.84 $\pm$ 2.15
	30	0.75 $\pm$ 2.09	0.98 $\pm$ 3.11
	40	1.08 $\pm$ 3.71	1.78 $\pm$ 2.65
	50	1.61 $\pm$ 2.06	1.97 $\pm$ 2.79
DT (min)	20	4.03 $\pm$ 0.54	6.30 $\pm$ 0.76
	30	2.10 $\pm$ 0.38	4.28 $\pm$ 0.41
	40	1.42 $\pm$ 0.76	3.29 $\pm$ 0.82
	50	1.02 $\pm$ 0.32	2.10 $\pm$ 0.67

Mean $\pm$ (SD), PGPES: pregelatinized *Plectranthus edulis* starch, DT: disintegration time

3.2.4 Paracetamol tablet properties

3.2.4.1 Weight and thickness

Paracetamol tablets prepared under the same compression force were examined for their weight and thickness uniformity. The weight and thickness of tablets formulated from pregelatinized *Plectranthus edulis* starch and Starch 1500® at different paracetamol concentrations were determined (Table 3.7). The tablet formulations satisfy the British Pharmacopoeia (BP, 2009) specifications for weight uniformity ($\pm$ 5%

deviation from the average weight) for tablets weighing 250 mg or more. The tablet formulations didn't show significant variations with respect to their thickness ($P > 0.05$).

Table 3.7: Weight and thickness of tablets formulated using pregelatinized *Plectranthus edulis* (prepared at 65 °C for 5 min) and Starch 1500® as direct compression excipients at different paracetamol concentrations

Parameters	Paracetamol content (%)	PGPES (±SD)	Starch 1500® (±SD)
Weight (mg)	20	300.41 ± 1.27	299.02 ± 1.98
	30	299.28 ± 1.67	298.13 ± 2.85
	40	297.22 ± 3.13	297.94 ± 3.13
	50	298.93 ± 2.05	297.83 ± 2.19
Thickness (mm)	20	2.01 ± 0.00	2.00 ± 0.00
	30	2.00 ± 0.00	2.00 ± 0.00
	40	2.00 ± 0.00	2.00 ± 0.00
	50	2.00 ± 0.00	2.00 ± 0.00

Mean ± SD (n=20), PGPES: pregelatinized *Plectranthus edulis* starch

3.2.4.2 Crushing strength and friability

As shown in Table 3.6, crushing strength of tablets prepared from pregelatinized *Plectranthus edulis* starch reduced with increasing paracetamol concentration. The tablets containing up to 30% (w/w) of paracetamol using both pregelatinized *Plectranthus edulis* starch and Starch 1500® as filler-binder were found to be acceptable in hardness ($> 60\text{N}$). However, at all levels of paracetamol the crushing strength of tablets prepared from pregelatinized *Plectranthus edulis* starch was significantly higher than Starch 1500® ($P < 0.05$).

Percent friability of the tablets increased for the two starch products as the concentration of paracetamol increased. This might be due to the poor compressibility and elastic recovery of paracetamol.

3.2.4.3 Tensile strength

Tablet strength is an important property for safe transportation and handling by patients as well as for finishing the compacts in a coating machine. Insufficiently hard tablets, in addition to exhibiting the effects of excessive friability, are prone to breakage and chipping particularly during transportation (Gohel and Jogani, 2002). Tensile strength could give information about the bonding strength and brittleness of the materials (Zenon and Teixeira, 2007). Unlike crushing strength, it allows the dimensions of the compact to be taken into account. As indicated in Table 3.6, tensile strength ranged from 7.75 ± 3.19 to 23.41 ± 4.17 (kg/cm²) and from 6.14 ± 2.27 to 22.18 ± 3.11 (kg/cm²) for pregelatinized *Plectranthus edulis* starch and Starch 1500[®], respectively. The decrease in tensile strength with increasing paracetamol concentration might be due to the poor compressibility and elastic recovery of paracetamol which took dominance at higher concentrations.

3.2.4.4 Disintegration time

Table 3.6 shows that all of the tablets complied with BP, (2009) specifications for the disintegration time of uncoated tablets (within 15 min). The tablets disintegration time ranged from 1.02 ± 0.32 to 4.03 ± 0.54 min and from 2.10 ± 0.67 to 6.30 ± 0.76 min for tablets formulated from pregelatinized *Plectranthus edulis* starch and Starch 1500[®], respectively. As paracetamol concentration increased, the disintegration time of the tablets significantly decreased ($P < 0.05$). This might be attributed for tablet hardness reduction up on increasing of paracetamol concentration which resulted in faster disintegration. This result is in agreement with previous findings in which disintegration time of the tablets increased with breaking strength (Ahmed *et al.*, 1998). The more compact a tablet is the less the porosity and hence the less penetration of water into the tablet and as a result longer disintegration time.

3.2.5 Calibration curve and dissolution test

3.2.5.1 UV calibration curve of paracetamol

From stock solution of 0.2 mg/ml of paracetamol in phosphate buffer (pH 5.8), standard calibration curve was plotted at six different concentrations (0.002, 0.004, 0.006, 0.008,

0.01 and 0.012 mg/ml). The absorbance (at 243 nm) versus concentration of the solutions was plotted and a calibration curve with a linear regression equation of: $Y = 0.051X + 0.040$ (where Y is the absorbance and X is the concentration in mg/ml) and correlation coefficient (R^2) of 0.999 were obtained (Fig. 3.7).

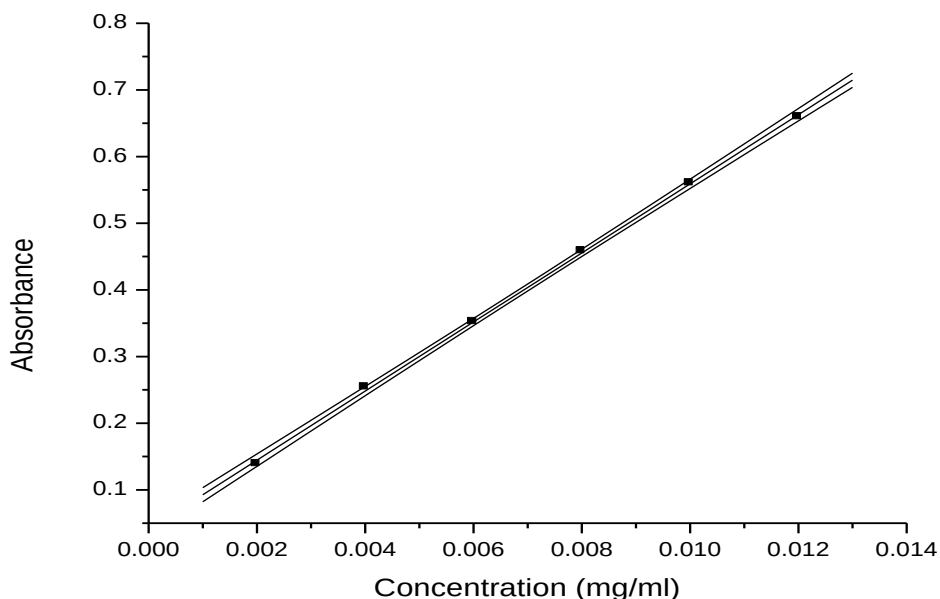


Figure 3.7: Standard calibration curve of paracetamol in phosphate buffer (pH 5.8) at 243 nm with 95% confidence bands for the mean; ($R^2 = 0.999$).

3.2.5.2 Dissolution profile

Tablets containing pregelatinized *Plectranthus edulis* starch (prepared at 65 °C for 5 min) at 20% and 30% of paracetamol levels (F1 and F2, respectively) and Starch 1500® at 20% and 30% of paracetamol levels (F3 and F4, respectively) were selected for further dissolution studies. The amount of paracetamol released was plotted against time and representative plots are presented in Fig. 3.8. From the figure it can be seen that the dissolution corresponded to the disintegration property of the tablets - faster tablet disintegration resulted in a faster drug release. The tablet formulations at 30% paracetamol showed a higher dissolution rates than the tablet formulations at 20% paracetamol for both direct compression excipients (pregelatinized *Plectranthus edulis*

starch & Starch 1500[®]; however, the variation was not significant ($P > 0.05$). Furthermore, the formulations at both levels of paracetamol with the two direct compression excipients released more than 80% within 30 min fulfilling the specifications set by USP 30-NF 25, (2007) and a complete dissolution was obtained in 60 min.

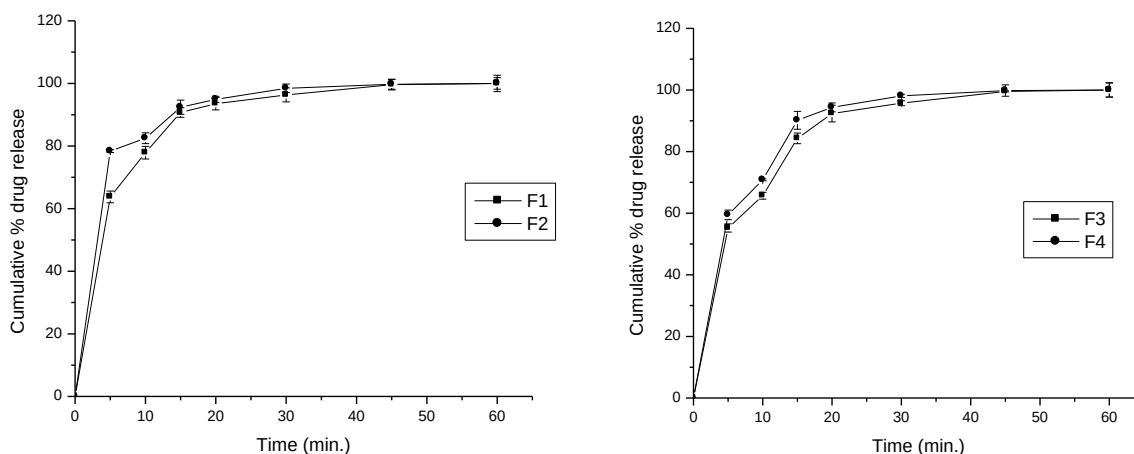


Figure 3.8: Dissolution profiles of directly compressed paracetamol tablets formulated from pregelatinized *Plectranthus edulis* starch (prepared at 65 °C for 5 min) (left) and Starch 1500[®] (right) as direct compression excipients

4 CONCLUSION

Pregelatinization of *Plectranthus edulis* starch at optimum conditions provided not only good flow but also compressibility. The native *Plectranthus edulis* starch did not flow through the funnel and exhibited poor compressibility. Furthermore, it did not form intact tablets even at higher compression pressures. After pregelatinization, however, the pregelatinized *Plectranthus edulis* starch formed intact tablets with acceptable attributes.

The XRD result of pregelatinized *Plectranthus edulis* starch confirmed the partial disruption of molecular orders within the starch granules. This further confirmed the pregelatinized *Plectranthus edulis* starch to have better compressibility. Dilution potential study in paracetamol tablet formulations showed that pregelatinized *Plectranthus edulis* starch and Starch 1500[®] had comparable tolerance to the inclusion of poorly compressible active pharmaceutical ingredients.

Hence, since pregelatinized *Plectranthus edulis* starch showed acceptable properties for application as direct compression excipient for some of the parameters evaluated, it may serve as a suitable alternative direct compression excipient.

5 SUGGESTIONS FOR FURTHER WORK

Further study on the following directions is suggested:

- Investigate the deformation characteristics of pregelatinized *Plectranthus edulis* starch;
- Characterize the particle size, size distribution and morphology of pregelatinized *Plectranthus edulis* starch.
- Evaluate tablet disintegrant properties of pregelatinized *Plectranthus edulis* starch.
- Study long-term stability of pregelatinized *Plectranthus edulis* starch as a pharmaceutical excipient in formulations.

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