PREPARATION AND CHARACTERIZATION OF PREGELATINIZED ENSET STARCH AND EVALUATION OF ITS USE AS BINDER AND DISINTEGRANT IN TABLET FORMULATIONS

A Thesis Submitted to the School of Graduate Studies 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

By

Abrham Wondimu (B.Pharm)

Under the supervision of Prof. Tsige Gebre-Mariam, Department of Pharmaceutics, School of Pharmacy, Addis Ababa University

May, 2010

ADDIS ABABA UNIVERSITY SCHOOL OF GRADUATE STUDIES

PREPARATION AND CHARACTERIZATION OF PREGELATINIZED ENSET STARCH AND EVALUATION OF ITS USE AS BINDER AND DISINTEGRANT IN TABLET FORMULATIONS

By

Abrham Wondimu (B.Pharm)

Department of Pharmaceutics

School of Pharmacy

Approved by:

Name	Signature	Date
Prof. Tsige Gebre-Mariam (Advisor)	_____	May 7, 2010
Dr. Anteneh Belete (Examiner)	_____	May 7, 2010

Dedicated to Motherland Ethiopia

ACKNOWLEDGEMENTS

All praise belongs to the Almighty God with whose blessings I have accomplished what I had started to do.

My sincere gratitude and appreciation go to my advisor Professor Tsige Gebre-Mariam; for his valuable guidance, keen interest and constant encouragement.

I also want to thank all the staff members of the Department of Pharmaceutics, School of Pharmacy, for their co-operation during this work. My appreciation also goes to Dr. Mesfin Redi, Department of Chemistry, for providing me with quartz cuvette.

I am highly indebted to Ethiopian Pharmaceutical Manufacturing Sh.Co. (EPHARM) and Cadila Pharmaceuticals PLC, who provided me with different pharmaceutical materials used in this study.

Many thanks to Fekade Tefera, Elias Aklog, Bezayit Solomon, Tesfa Marew, Kedir Tahir, Naod G/Samuel, Efrem Nigusu, Tadele Atnafu and Mulugeta Fente for their support and encouragements during this work.

To all my family and friends, your help, support in times of need and words of encouragement will forever stay with me.

Finally, I would like to acknowledge Addis Ababa and Mekelle Universities for sponsoring my study.

Abrham Wondimu

May, 2010

Table of Contents **Pages**

List of Tables

List of Figures

Abstract

Ensete ventricosum (Welw.) Cheeseman which belongs to the family Musaceae is a potential source of starch in Ethiopia. Starch is usually modified either chemically or physically to augment its convenience for industrial use. In this study, enset starch was modified by a physical method called pregelatinization. Properties of pregelatinized enset starch such as, densities, flow, swelling power, percentage solubility, moisture sorption, and compactability were investigated and compared to those of native enset starch and Starch 1500®. The comparative binding and disintegrant abilities of these starches in tablet formulations were also studied using paracetamol as a model drug. The granules prepared with the starches at different binder concentrations were characterized for particle size distribution, friability, and flow properties and the tablets were tested for crushing strength, friability, disintegration time, and dissolution rate using standard methods. The results indicated that pregelatinization improved the flowability of enset starch. Generally, the swelling power and percent solubility of the starches were found to increase with temperature and the values are higher for pregelatinized starches. The moisture sorption profiles indicate that the relative humidity during tablet production and storage should be carefully controlled. The compaction study revealed that the tensile strength of the compact of pregelatinized enset starch (10.14 Kg/cm^2) and Starch 1500® (12.24 Kg/cm^2) were comparable ($p > 0.05$). Compacts from native enset starch, however, presented significantly lower tensile strength (5.60 Kg/cm^2). The results also indicate that granules and the tablets prepared with pregelatinized enset starch and Starch 1500® exhibit comparable characteristics. An increase in binder concentration provided tablets with increased crushing strength and disintegration time and decreased friability. The study also revealed that the softening of the tablets prepared with native starch as a disintegrant was reduced when prepared with pregelatinized starch. The dissolution studies of the paracetamol tablets showed that the release of the drug was within acceptable range (quantity dissolved in 30 min ≥ 80%). Thus, it can be concluded that pregelatinized enset starch can be a better binder and disintegrant than the native one in tablet formulations.

Key Words: Enset Starch; Pregelatinized Starch; Tablet; Binder; Disintegrant.

1. INTRODUCTION

1.1 Starch

Starch is the most abundant storage reserve carbohydrate in plants. It is found in many different plant organs, including seeds, fruits, tubers and roots, where it is used as a source of energy during periods of dormancy and re-growth (Roper, 2002). A range of native starches from different sources with highly different functionalities are already on the market. Each starch is named according to its plant source, e.g. potato starch, maize starch, cassava starch, rice starch. These groups are distinctly different from each other with respect to chemical composition and physical properties (Copeland *et al*., 2009).

Starch is made up of two polymers of D-glucose: amylose, an essentially unbranched α [1→ 4] linked glucan, and amylopectin, which has chains of α [1→ 4] linked glucoses arranged in a highly branched structure with α [1→ 6] branching links (Figure 1.1). Amylose and amylopectin make up 98–99% 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. Starch granules range in size from 1 to 100 μm diameter and shape of polygonal, spherical, lenticular, and can vary greatly in content, structure and organization of the amylose and amylopectin molecules, the branching architecture of amylopectin, and the degree of crystallinity (Lindeboom *et al*, 2004).

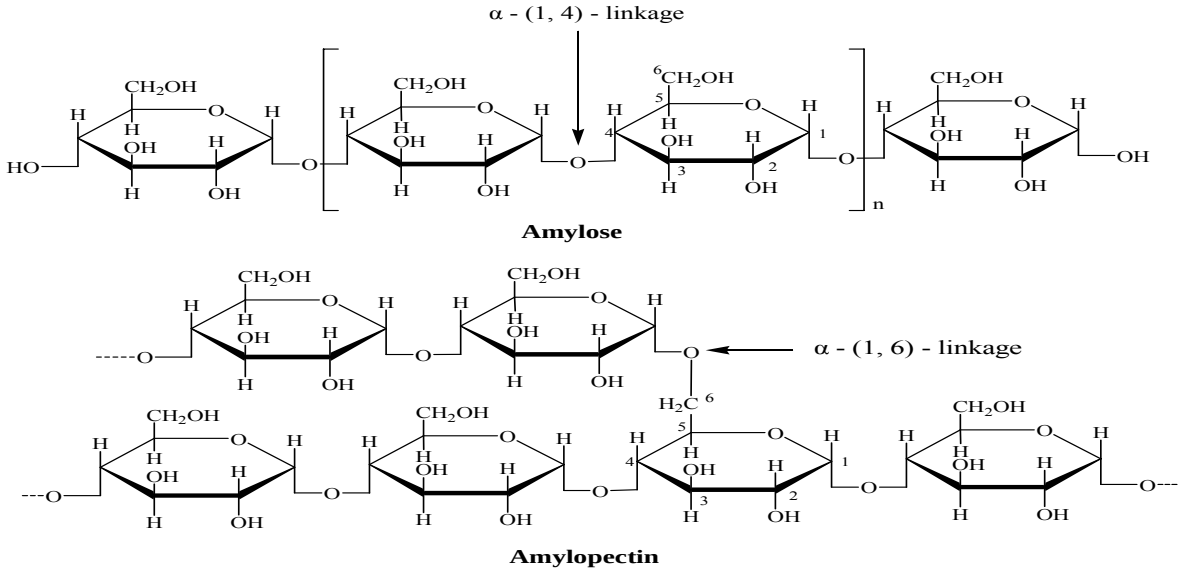

Figure 1.1: Chain structure of amylose and amylopectin

Amylose has a molecular weight ranging 10^5 – 10^6, corresponding to a degree of polymerization of 1000 – 10,000 glucose units. Less than 0.5% of the glucoses in amylose are in α [1→ 6] linkages, resulting in a low degree of branching. Amylopectin is a much larger polymer, with molecular weight about 10^8 and a degree of polymerization that may exceed one million. Most starches contain 60 – 90% amylopectin, although high-amylose starches, with as little as 30% amylopectin, and waxy starches with essentially 100% amylopectin are well known. Amylopectin has about 5% of its glucoses in α [1→ 6] linkages, giving it a highly branched, tree-like structure and a complex molecular architecture that can vary substantially between different starches with regard to placement and length of branches (Copeland *et al.*, 2009).

A great deal of attention has been devoted to starch and its derivatives mainly in the context of the food, plastics and pharmaceutical industries. This is not only because starch is readily available, inexpensive and inert material but also because of the ease with which its physicochemical properties can be altered through chemical or enzymatic modification and/or physical treatment (Newman *et al*., 1996; Steve, 2004).

1.2 Enset plant and its starch

1.2.1 Overview of enset plant (*Enset ventricosum* (Welw.) Cheeseman)

Ensete ventricosum (Welw.) Cheeseman belongs to the family Musaceae, and the genus Enset. Enset looks like a large, thick, single-stemmed banana plant. Both enset and banana have an underground corm, a bundle of leaf sheaths that form the pseudostem, and large leaves (Figure 1.2). Enset, however, is usually larger than banana, with the plant up to 10 m tall and pseudostem up to one meter in diameter (Brand *et al*., 1997). Because of its resemblance to the banana plant, enset is often referred as "False Banana" as it does not bear edible fruit. Instead, it is used for the production of starchy foods (Pijls *et al*., 1995).

The plant is the most important staple food for 7 - 10 million people in the south and southwestern parts of Ethiopia. The plant is grown at altitudes ranging from 1500 - 3100 m above sea level, but scattered plants can also be found at lower altitudes. For optimum growth, the crop requires an average rainfall of 1100 - 1500 mm per year and average monthly temperature of 16 - 20 °C (Tsegaye and Struik, 2003).

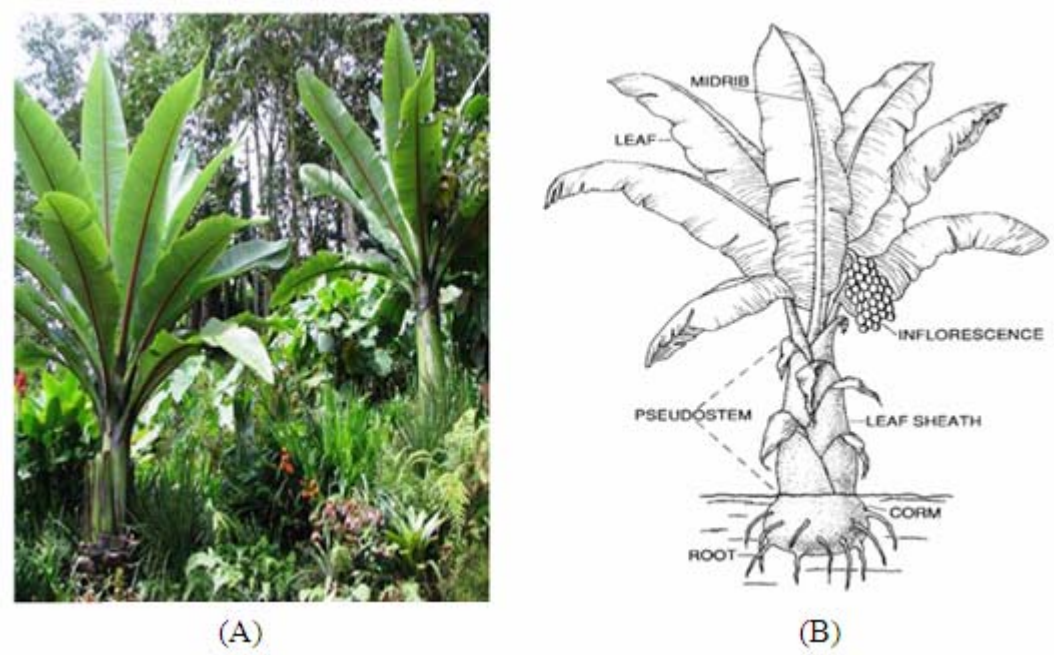

Figure 1.2: Enset plant in the garden (A) and its parts (B).

The major foodstuffs obtained from enset are locally known as *kocho, bulla* and *amicho*. In the preparation of kocho and bulla, the pseudostem and corms are cut and crushed and the exuding liquid containing starch is collected. Most of the water is allowed to drain away and bulla is collected leaving the fibrous material, kocho, behind. Amicho is the boiled enset corm, usually of a younger plant. The major constituent of bulla is starch (Gebre-Mariam and Schmidt, 1996a; Brand *et al*., 1997).

1.2.2 Enset Starch

Starch accounts for more than 90% of bulla (on dry weight basis). The starch is composed of moisture (14.0%), ash (0.16%), fat (0.25%), protein (0.35%), and amylose (29.0%). Fat and protein content of enset starch are significantly higher than potato starch but lower than that of maize (Gebre-Mariam and Schmidt, 1996a).

Scanning electron micrographic study showed that enset starch has a characteristic shape that is somewhat angular and elliptical with the average volumetric particle diameters of about 46 μm. The swelling power and solubility of enset starch were shown to be lower than that of potato starch but higher than that of maize; and the differential scanning calorimetric (DSC)

analysis at a starch to water ratio of 1:2 revealed that the onset, peak and end temperature of gelatinizations to be 61.8, 65.2 and 71.7 °C, respectively (Gebre-mariam and Schmidt, 1996a).

Native enset starch has been shown to have similar binding and disintegrating properties to that of potato starch in granulated tablet formulations (Gebre-Mariam and Schmidt, 1996b). Moreover, sodium starch glycolate prepared from enset starch demonstrated comparable disintegrant efficiency to that of Primojel® (Sodium starch glycolate produced by carboxymethylation and cross-linking of potato starch) (Gebre-Mariam *et al*., 1996a). This evidenced the potential candidacy of enset starch for modification, to replace the commercialized modified starches from overseas with local products.

1.3 Modification of starches

Native starches from various plant sources have their own unique properties. To the extent possible, these inherent characteristics are exploited by the processors to meet specific needs. Native starches, however, are inherently unsuitable for most applications and; therefore, must be modified chemically and/or physically to enhance their positive attributes and/or to minimize their defects (Chiu and Solarek, 2009).

1.3.1 Chemical modification of starches

Chemical modification of starch is based on reaction of free hydroxyl groups of the anhydrous glucose units with functional groups of chemicals, resulting in starch derivatives. The reaction(s) chosen for starch modification usually exert a major change on a desirable physical property. Low levels of modification can dramatically alter the physical properties of starch such as paste viscosity, gelling, swelling power, and water holding capacity (Taggart, 2004). Chemical modification can be accomplished by oxidation, substitution (etherification and esterification), dextrinization, acid-thinning, or cross-linking (Bemiller, 1997).

1.3.2 Physical modification of starches

Since chemical modification is costly and the regulation of chemically modified starch is quite strict and there are environmental concerns, more and more physical modifications appear. Pregelatinization, sonication, ball milling, heat-moisture treatment, and pulsed electric fields treatment are some of the physical methods used for starch modification (Jackson *et al*., 1990;

Stute, 1992; Morrison and Tester, 1994; Maache-Rezzoug *et al*., 2008; Chung *et al*., 2009; Han *et al*., 2009; Zuo *et al*., 2009). These days, pregelatinization is a popular physical method of starch modification for industrial purposes.

1.4 Pregelatinized starch

1.4.1 Pregelatinization of starch

Pregelatinized starches also referred to as instant starch slurries, are those that have been simply precooked to give products that readily disperse in cold water to form moderately stable suspensions (Nakorn *et al*., 2009). When starch granules are heated in water to progressively higher temperatures, a point is reached where the polarization cross starts to disappear and the granules begin to swell irreversibly. This phenomenon, associated with the disruption of granular structure, is called 'gelatinization'. In this context, gelatinization can be defined as the collapse (disruption) of molecular orders (breaking of H-bonds) within the granule, along with concomitant and irreversible changes in properties. During gelatinization, amylose molecules begin to leach from the granules as they are disrupted under shear (Biliaderis, 2009; Hoover, *et al*., 2009).

Pregelatinized starch can be produced by various methods such as spray cooking, drum drying and extrusion. During a spray cooking process, starch 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 (Chiu and Solarek, 2009).

Pregelatinized starch can be also prepared by the drum drying method, in which a cooked starch sheet is produced from starch slurry on a hot drum; the starch is ground after drying to a desired particle size. A double drum dryer consists of two counter rotating horizontal cylinders of equal diameters. The cylinders are hollow and are heated by steam condensing on their inside surface. One of the cylinders can be usually adjusted at right angles to its axis so that the

gap between the two drums may be varied. The starch suspension is fed into the wedge-shaped space formed between the two drums (pool) where it heats up and gelatinizes. The gelatinized starch is calendared into a thin layer as it passes through the gap forced by the rotary action of the closely spaced drums. Right after the gap this layer splits into two films of gelatinized material, one for each drum. These films progressively dry as they rotate being adhered to the drums and are finally scraped off by 'doctor' blades extending the whole length of the drums. Thus, drum dryers are essentially conduction dryers, the drying effect being obtained by the transfer of heat from the condensing steam through the metallic body of the cylinders to the film of the material covering the external surface of the drums (Kalogianni *et al*., 2002). By changing process parameters of a double drum dryer such as feed concentration, drums speed, temperature and pressure, and the gap between the drums it is possible to obtain pregelatinized starches with different functional characteristics (Anastasiades *et al*., 2002; Kalogianni *et al*., 2002).

Extrusion technology is also used for pregelatinization of starch. Screw speed, die temperature and diameter, feed rate and feed moisture content are among the variables that could affect the properties of the extruded starch (Valle *et al*., 1995; Pérez-Sira and González-Parada, 1997; Alves *et al*., 1999; Sebio and Chang, 2004). Gelatinizing starch with subsequent drying in an oven has been also used for pregelatinization of starch at laboratory scale (Waliszewski *et al.,* 2003; Odeku *et al*., 2008), and this method was used in this study.

1.4.2 Properties of pregelatinized starch

Several physico-chemical properties of pregelatinized starches have been characterized so far. For instance, pregelatinization has played important role in affecting micromeritic properties, such as particle size and shape, surface area, density, and flow properties of starch materials. According to Odeku *et al*. (2008), the scanning electron micrographs of the pregelatinized dioscorea starches showed no evidence of the presence of starch granules reported for the native forms of the various species of dioscorea starches. This phenomenon was attributed to the process of gelatinization that causes substantial changes in both the chemical and physical nature of granular starch due to the rearrangement of intra- and inter-molecular hydrogen bonding between water and starch molecules leading to collapse, deformation and loss of granule structure. Studies also revealed that pregelatinized starches exhibited lower values of

the Hausner's ratio, suggesting better flowability than the native starches. The values of mean particle diameter and particle density for the pregelatinized starch were, however, higher than those for the native starches (Alebiowu and Itiola, 2002; Odeku *et al*., 2008; Adedokun and Itiola, 2009).

The swelling power, solubility percentage, and water holding capacities of pregelatinized starches were also studied. According to the studies, pregelatinized starches showed higher water absorption capacity, swelling ability, and percentage solubility than the native starches due to the disruption of associative bonds and amylose leaching out during gelatinization (Wootton and Bamunuarachchi, 1978; Alebiowu and Itiola, 2002; Adedokun and Itiola, 2009; Nakorna *et al*., 2009). Pérez-Sira and González-Parada (1997) reported that the apparent viscosity of pregelatinized starch suspensions showed a marked reduction with an increase in shear force; this denoted their pseudoplastic character. Compaction study revealed that pregelatinized starch underwent plastic deformation (Maarschalk *et al*., 1997).

1.5 Pharmaceutical applications of native and modified starches

Native starch is one of the most widely used excipients in the manufacture of solid dosage forms, probably due to its abundance, relative cheapness, and inertness (Dare *et al*., 2006). Starches obtained from different food crops have shown enough potential as filler, binder, disintegrant and glidant in tablet formulations (Alebiowu and Itiola, 2002). The function of starch can depend on how it is incorporated into the formulation. Starch function as a disintegrant when added in the dry state before adding a lubricant. It may exhibit both binding and disintegrant properties when it is incorporated as a paste or dry before granulation with other agents (Newman *et al*., 1996). It has been also reported that starch can be used for capsule manufacturing, alternative to hard gelatin capsule (Vilivalam *et al*., 2000, Bae *et al*., 2008).

A number of specially modified starches have been also used in pharmaceutical field. Modification of starches has been required to provide starch products suitable for specific purposes. Chemically modified starches have shown promise in the pharmaceutical industry as sustained release matrices. For example, starches substituted with groups like carboxymethyl (Nabais *et al*., 2007) or hydroxypropyl (Onofre and Wang, 2010) or aminoethyl (Mulhbacher

et al., 2001) or acetate (Pohja *et al*., 2004; Tarvainen *et al*., 2004), and starches cross-linked by various agents such as epichlorohydrin and sodium trimetaphosphate have all retarded drug release from solid dosage forms at various levels (Lenaerts *et al*., 1998; O'Brien *et al*., 2009).

The contribution of physical modification has been also reported. Spray dried starch has been utilized for direct compression (Mitrevej *et al*., 1996). Partially pregelatinized starch performs the multiple functions of a binder, disintegrant, flow-aid and self-lubricant and its versatility being effective in a variety of processing methods for solid oral dosage forms describing the multipurpose usage of starch polymers in pharmaceutical applications (Colorcon, 2005). Using hot starch pastes is not recommended in high shear granulation because the introduction of heat can cause process variations. Cold pastes can be processed, but time is lost while waiting for the pastes to cool thus negating the benefits of the high shear functionality. Native starch paste requires higher energy for efficient granulation and require longer time for drying due to its higher viscosity which incurs additional time and cost in the overall production. However, pregelatinized starch slurries prepared in cold water with reasonable viscosity can be utilized for better granulation; therefore, using pregelatinized starch is an excellent way to reduce process time and cost while preserving optimal properties in a well constructed formulation (2005).

1.6 Tablet excipients

A pharmaceutical excipient is defined as an inactive ingredient or any component other than the active ingredient added intentionally to the medicinal formulation (Lee, 2008). Excipients are used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients (Chan and Chew, 2007). They are also essential in ensuring that the manufacturing process is successful and that the quality of the resultant formulation can be guaranteed. The appropriate selection of excipients in the formulation is critical in development of a successful product (Conway, 2008).

The following general criteria are essential for excipients: physiological inertness; physical and chemical stability; conformance to regulatory agency requirements; absence of interference with drug bioavailability; absence of pathogenic microbial organisms; and commercial availability at low cost (Chan and Chew, 2007).

For tablets, excipients ensure that the tableting operation can run satisfactorily and to ensure that tablets of specified quality are prepared (Alderborn, 2002). Depending on the intended function, excipients to be used in tablets are subcategorized into different groups. The functions of the most common types of excipients used in tablets are described below.

1.6.1 Binders

Agents used to impart cohesive qualities to the powder material are referred to as binder or granulating agent. They impart cohesiveness to the tablet formulation, as well as improving the free flowing qualities of granules by imparting desired hardness and size (Lee, 2008; Rudnic and Schwartz, 2000). Binders can be added to the powder either as a dry powder or as a solution. Both solution binders and dry binders are included in the formulation at relatively low concentrations, typically 2 - 10% by weight. Common traditional solution binders are starch, sucrose and gelatin. More commonly used binders today, with improved adhesive properties, are polymers such as polyvinyl pyrolidone and hydroxypropyl methylcellulose. Important example of dry binder is microcrystalline cellulose. Solution binders are generally considered the most effective, and this is therefore the most common way of incorporating a binder into granules (Alderborn, 2002).

Binders have significant effect on the granule properties. Bhutanis and Bhatia (1975) reported that the amount of moisture retained by granules after drying increase with the increasing concentration of binding agents. Alebiowu and Itiola (2001) showed that increasing the binder concentration increased the mean granule size. The effect of binders on tablet property was also studied. It was shown that with an increase in binder concentration, the strength and disintegration time of tablet increased with a corresponding decrease in percent friability (Esezobo and Pilpel, 1976; Agrawal and Prakasam, 1988; Zubair *et al*., 1988; Gebre-Mariam and Schmidt, 1996b; Adane *et al*., 2006; Adetunji *et al*., 2006;). The nature and concentration of binders have been also reported as having an effect on drug release property of the tablet (Jacob and Plein, 1968; Karr *et al*., 1990; Symecko and Rhodes, 1997).

1.6.2 Disintegrants

Tablets must have sufficient strength to withstand the stresses of subsequent manufacturing operations such as coating, packaging, and distribution processes. However, once the tablet is taken by the patient, it must break up rapidly to ensure rapid dissolution of the active ingredient in immediate - release preparations. To overcome the cohesive strength produced by the compression process and to break down the tablet into the primary particles as rapidly as possible, the disintegrants are combined with other excipients during the tableting process (Lee, 2008). Several mechanism 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, 2002).

Of all the commonly used disintegrants, starch is by far the most widely used material. It has been generally accepted that starch acts as a disintegrating agent through swelling action when exposed to water and by capillary action (Patel and Hopponen 1966; Gadalla *et al*., 1989). Though the native starch has been widely used as a tablet disintegrant, the softening effects that it has on tablet at effective concentration along with the increasing demand for faster disintegration and dissolution and improved bioavailability of drugs administered by conventional oral tablets has resulted to some extent in its replacement by more active disintegrants, like "super-disintegrants". These super-disintegrants include sodium starch glycolates, cross-linked polyvinyl pyrolidone and cross-linked carboxymethyl cellulose (Gebre-Mariam *et al*., 1996a). But due to the higher cost of super-disintegrants, pharmaceutical formulators are looking for alternative cheaper disintegrants. The disintegrant characteristics of pregelatinized starches from various botanical sources were also examined in tablet formulation (Alebiowu and Itiola, 2003; Odeku *et al*., 2008).

The nature and concentration of disintegrants has been shown to affect the strength, disintegration time and dissolution rate of tablets (Gebre-Mariam and Schmidt, 1996b; Marais *et al.*, 2003; Adane *et al.*, 2006; Adebayo *et al*., 2008).

1.6.3 Other excipients

Diluents are fillers designed to makeup the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. Lactose is the most common filler in tablet. Lubricants are used to reduce friction; for example, between tablet and the die of tablet machine; therefore, ejection of tablets can occur easily. Stearic acid and stearic acid salts, primarily magnesium stearate are the most effective lubricants. Talc is a widely used glidant-an ingredient added to the formulation in order to improve the flow properties of the material to be fed into the die. Colorants are used to facilitate identification and to enhance the esthetic appearance of the product (Kotteke and Rudnic, 2002).

1.7 The present study

In Ethiopia, before half a decade, the estimated demand for starch in local industries was about three tons per day and almost all supplied from abroad (Gebeyehu, 2004). Hence, in countries which import starch such as Ethiopia, it is desirable to exploit starch from cheaper indigenous sources. Studies indicated that Ethiopia has variety of starch sources (Gebre-Mariam and Schmidt, 1996a; Gebre-Mariam and Schmidt, 1998; Adane *et al*., 2006; Mohammed *et al*., 2007; Paulos *et al*., 2007). Further studies indicated that native starches from *Ensete ventricosum* (Gebre-Mariam and Schmidt, 1996b,), *Dioscorea abyssinica* (Gebre-Mariam and Schmidt, 1996c,), and *Colocasia esculenta* (Adane *et al*., 2006) have shown promising usefulness in pharmaceutical area, and also chemically modified starches (sodium starch glycolate) from local sources have been shown to be as good as commercialized ones (Gebre-Mariam *et al*., 1996a; Gebre-Mariam *et al*., 1996b). To date, most studies on pregelatinized starches have been limited to widely available starches such as maize, potato, rice and cassava (Valle *et al*., 1995; Pérez-Sira and Gonzalez-Parada, 1997; Anastasiades *et al.*, 2002; Nakorn *et al*., 2009). Modified starches from other botanical sources may yield starches with special properties and offer a wide range of functional properties permitting numerous applications. So far, no work has been done on pregelatinization of enset starch. Thus, the aim of the present work is to prepare and investigate the physicochemical properties of pregelatinized enset starch as a potential binder and disintegrant in paracetamol tablets. Furthermore, a preliminary compaction study was carried out in order to evaluate the potential use of this starch as a direct compaction excipient. The high starch content of enset lends itself as a possible alternative

source of starch. Starch 1500® (partially pregelatinized corn starch) is the most widely commercially available pregelatinized starches and was included in the study for comparative purposes. Paracetamol, which is both poorly compressible and sparingly soluble drug, normally requires a binder and disintegrant to form satisfactory tablets. Thus, it was selected as a model drug for this study.

1.8 Objectives of the study

1.8.1 General objective

To prepare and study the properties of pregelatinized enset starch and to evaluate its potential as a binder and disintegrant in tablet formulation.

1.8.2 Specific objectives

- To modify enset starch by pregelatinization,
- To study some physico-chemical properties of the pregelatinized starch that may possibly influence its role as tablet binder and disintegrant,
- To evaluate compaction properties of the pregelatinized enset starch,
- To prepare granules by wet granulation and determine their properties,
- To evaluate properties of compressed model drug tablet prepared using pregelatinized enset starch as a binder and disintegrant, and
- To compare the properties of tablets prepared using pregelatinized enset starch with that of native enset starch and Starch 1500®.

2. EXPERIMENTAL

2.1 Materials

Bulla was purchased from local supermarkets. Paracetamol powder (China associate Co Ltd, China), sodium metabisulphite (Guangzhou Jinhaunda Chemical Reagent Co. Ltd, China), sodium hydroxide and sodium chloride (LABMERK CHEMICALS, India), povidone (China associate Co. Ltd, China), potassium phosphate monobasic (FARMITALIA CAROERBA, Italia), croscarmellose sodium, NF (Ac-Di-Sol®) (FMC Corporation, USA), and magnesium stearate (Bulvinos Chemicals Ltd, England) were used as received.

2.2 Methods

2.2.1 Isolation of starch

In the preparation of enset starch, *bulla* was suspended in large quantities of distilled water containing 0.075% w/v of sodium metabisulphite. The material was allowed to settle and the supernatant was decanted. The sedimented starch was repeatedly treated with sodium metabisulphite solution until the suspension became translucent. The material was then passed through fine muslin to remove cell debris and the translucent suspension was collected, filtered through a fine sieve (224 μm) and allowed to settle. The sedimented starch was washed several times with distilled water followed by sieving after each washing until the wash water was clear and free of suspended impurities. The resulting starch was sieved and dried in air at room temperature (Gebre-Mariam and Schmidt, 1996a).

2.2.2 Preparation of pregelatinized starch

The pregelatinized form of the enset starch was prepared using established methods with slight modification (Waliszewski *et al*., 2003; Odeku *et al.,* 2008). Aqueous starch slurry (starch to water ratio of 1:2) was heated on thermostated water bath (GFL®, D3006, Germany) at 62^{o}C with stirring for 15 min. The resultant pregelatinized starch was placed into stainless steel tray in the form of thin film (1–2 mm) and dried in a convection oven at 60^{o}C for 24 h, then powdered using laboratory mill (Retsch, Type sk1, West-Germany) and then by coffee blender to pass through a fine sieve (100 μm) and stored at room temperature in air tight glass jars.

2.2.3 Characterization of starch

2.2.3.1 Determination of true density

The true density was determined by 50 ml liquid pycnometer at room temperature, using toluene as displacement liquid.

2.2.3.2 Determination of bulk density, tapped density and related properties

Thirty gram of starch was transferred into 250 ml measuring cylinder. The volume occupied by the starch powders was read and the bulk density was calculated as g/ml. The bulk in the cylinder was then tapped for 1 min using tapped densitometer (ERWEKA, Type svm, Germany). This provided a fixed drop of one-half inch at rate of 250 taps/min. The volume occupied by the starch was recorded and tapped density was calculated as g/ml. The Carr's index was calculated using Equation 2.1 and Hausner ratio using Equation 2.2 (Schüssele and Bauer-Brandl, 2003).

$$Carr's\ index = \frac{tapped\ \ density - bulk\ \ density}{tapped\ \ density} \times 100 \quad \text{.....(2.1)}$$

$$Hausner\ \ ratio = \frac{tapped\ \ density}{bulk\ \ density} \quad \text{.....(2.2)}$$

2.2.3.3 Flow rate and angle of repose

Flow rate and angle of repose of the starch powders were determined by using the funnel method. Starch powder (30 g) was allowed to flow through a stemless funnel having a 15 mm aperture from a 10 cm height. Time in second for the duration of flow was recorded. The average diameter and height of the powder piles formed were recorded. Flow rate was determined using the relationship; Flow rate = m/t; where m is mass in gram and t is time in second. Angle of repose was calculated according to Equation 2.3.

$$Angle\ of\ \ repose\ (\theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{.....(2.3)}$$

where h and r are the height and radius of the starch powder pile, respectively.

2.2.3.4 Swelling power and solubility

Swelling power and water solubility index of the starches were determined according to the method of Torruco-Uco and Betancur-Ancona (2007). Starch (0.5 g) was 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 at 15, 40, 50, 60, 70, 80, and 90 ^{o}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 sediment weighed (Ws). The supernatant was dried to constant weight (W1) in an oven (Kottermann® 2711, Germany) at 105 ^{o}C for 12 hrs. The water solubility index (WSI) and swelling power (SP) were calculated as follows:

$$WSI = \frac{W1}{0.5} \times 100\% \quad \text{.....(2.4)}$$

$$SP = \frac{Ws \times 100}{0.5 \times (100 - WSI)} \quad \text{.....(2.5)}$$

2.2.3.5 Moisture sorption property

Moisture sorption properties were determined according to the method described by Odeku and Picker-Freyer (2007) 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. Native and pregelatinized starches were pre-dried in an oven (Kottermann® 2711, Germany) for 4 h at 120 ^{o}C. Five g 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.

2.2.3.6 Viscosity of starch mucilages

The viscosities of the starch mucilages at different concentrations were determined by rotational viscometer (KINEMATICA, AG, Type Viscostar + L, Switzerland) using spindle number 4 at shear rate of 20 rpm at room temperature. Native starch mucilage was prepared by suspending an appropriate quantity of native enset starch in an equal weight of distilled cold

water to form slurry. Then the required amount of boiled water was added to the slurry and the resulting mixture was heated to about 70 ^{o}C on a thermostated water bath till translucent mucilage was formed. Slurries of pregelatinized enset starch and Starch 1500® were prepared by reconstituting the appropriate amount of starches in cold water.

2.2.4 Compaction property of starches

The compaction properties of starches 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 using eccentric tablet machine (EKO Korsch, 8410-68, Berlin, Germany). The compacts were evaluated for crushing strength, tensile strength, and percent friability.

2.2.5 Preparation of binder mucilage/solution

Mucilage of native enset starch was prepared according to the method described by Gebre-Mariam and Schmidt (1996b). An appropriate quantity of native enset starch was initially suspended in an equal weight of cold distilled water to form slurry. Mucilages were produced by addition of the required amount of boiled water to the appropriate slurry and by heating the resulting mixture to about 70 ^{o}C on a thermostated water bath. The mucilages were used as granulating fluid after cooling to about 50 ^{o}C. Starch 1500® and pregelatinized enset starch mucilages were prepared by reconstituting the starches in cold water as described by Karr *et al.*, 1990. Povidone solution was prepared by dissolving the appropriate quantity in an appropriate amount of water.

2.2.6 Tablet formulations and preparation of granules

The compositions of tablet formulations are given below in Table 2.1 and 2.2. To each batch of granulation (100 g), paracetamol and an appropriate quantity of the starch mucilage or povidone solution was added as a granulating agent and mixed for 20 min in mortar. The wet mass was then passed through wet granulator with 1.6 mm sieve and dried in an oven (Kottermann® 2711, Germany). Then, the dried granules were dry screened by passing them through a 1 mm sieve. The sieved granules were mixed with specified amount of disintegrant in a turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland) for 10 min at 49

rpm. Finally magnesium stearate (0.5%) was added and the mixture was mixed for further 5 min.

Table 2.1: Paracetamol formulations containing native enset starch, pregelatinized enset starch or Starch 1500® as binder at four levels of concentrations.

Formulation ingredients	Amount of ingredients (% w/w or ml)
Paracetamol	93.0-85.5
Starch	
▪ Absolute amount	2.5, 5, 7.5 and 10
▪ % mucilage	10, 20, 30 and 40
▪ Amount of mucilage used (ml)	25
Ac-Di-Sol®	4
Magnesium stearate	0.5

Table 2.2: Paracetamol formulation containing native enset starch, pregelatinized enset starch or Starch 1500® as disintegrant at three levels of concentrations.

Formulation ingredients	Amount of ingredients (% w/w or ml)
Paracetamol	91.0-81.0
povidone	
▪ Absolute amount	3.5
▪ % mucilage	17.5
▪ Amount of mucilage used (ml)	20
Starch	5, 10 and 15
Magnesium stearate	0.5

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, 0.012 mg/ml) were prepared. The UV absorbance readings of these solutions were measured at 243 nm using UV/Visible spectrophotometer (JENWAY, 6505, England).

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 of: Y= 59.39X + 0.0247 (where Y is the absorbance and X is the concentration in mg/ml) and correlation coefficient of 0.9969 was obtained (Figure 2.1).

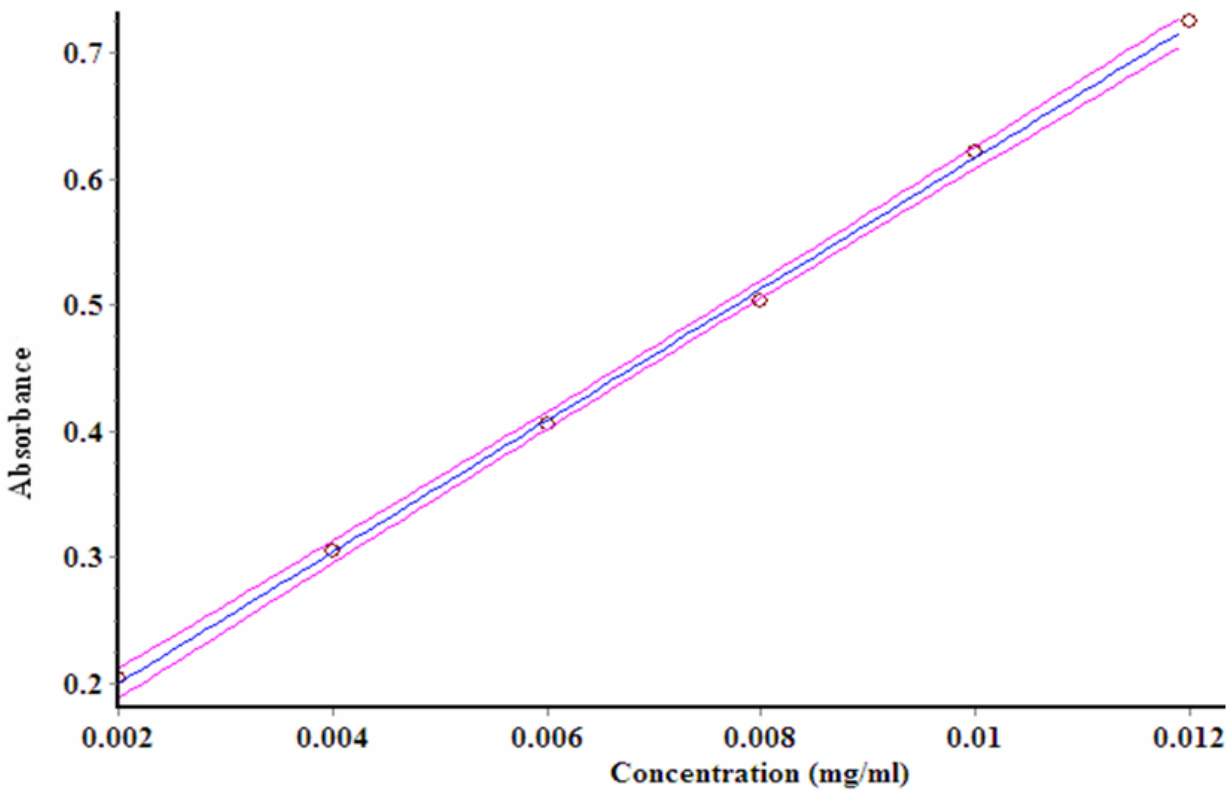

Figure 2.1: The UV absorption calibration curve of paracetamol in phosphate buffer (pH 5.8) at 243 nm with 95% confidence bands for mean, ($r^2 = 0.9969$).

2.2.8 Characterization of granules

2.2.8.1 Size distribution of granules

Thirty grams of granules from each batch were put in a set of sieves (iso 3310-1) fixed on the universal drive unit (ERWEKA, Type AR 401, Germany) arranged in mesh size from top to bottom with the coarsest sieve on the top. Then the sieves were shaken for 2 min. The granules remaining on each sieve were weighed and percent granules retained on each sieve recorded and mean granule size was calculated for each batch.

The average granule size on any sieve was determined in microns by averaging the size of the openings of the sieve through which the granules passed and the size of the openings of the sieve upon which the granules were retained. The weight retained on each sieve was converted to percentage retention and multiplied by the average of two successive sieves. The sum of these products divided by 100 yielded an average granule size.

2.2.8.2 Determination of density and density related properties

Thirty grams of each batch of granules, ranging from 224 – 1000 μm in size, were put in 250 ml measuring cylinder. The bulk density, tapped density, Carr's index and Hausner ratio of the granules were calculated in the same way as described for starch powders above (Section 2.2.3.2).

2.2.8.3 Determination of granule flow rate and angle of repose

Flow rate and angle of repose of granules were determined by using the funnel method, which is described above for starch powders in Section 2.2.3.3. The inner diameter of the orifice of the funnel used here is 10 mm.

2.2.8.4 Determination of granule friability

Ten grams of each batch of the granules larger than 315 μm was put in a friability tester (ERWEKA, Type TAR-20, Germany) and allowed to revolve for 5 min at 20 rpm dropping the granules a distance of 6 inches. The granules were then sieved using 315 μm sieve and percent loss was calculated as friability.

2.2.9 Compression of tablets

For evaluation of the starches (native and pregelatinized) as binder and disintegrant, paracetamol granules were compressed at a certain fixed compression force (adjusted to give tablets with a crushing strength greater than 70 N) on eccentric tablet machine (EKO Korsch, 8410-68, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. Target tablet weight was 500 mg. The tablets were kept for 24 h at room temperature in glass containers before their properties were evaluated.

2.2.10 Evaluation of tablets

2.2.10.1 Weight and thickness

From each formulation, 20 tablets were randomly selected and weighed individually on an analytical balance (Mettler Toledo, PR 203, Switzerland) and then the average weight and standard deviation were calculated. Tablet thickness was measured using sliding caliper scale (Nippon Sokutei, Japan).

2.2.10.2 Crushing strength

Ten tablets were taken from each batch and the crushing strengths of the tablets were determined using hardness tester (Schleuniger, 2E/205, Switzerland). Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded.

2.2.10.3 Tensile strength

The radial tensile strength was calculated using the data obtained from crushing strength, diameter, and thickness of the tablet using Equation 2.6.

$$\sigma_x = \frac{2F}{\pi DT} \quad \text{.....(2.6)}$$

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.

2.2.10.4 Friability

Ten tablets of known weight from each batch were placed in a friability tester (ERWEKA, TAR 20, Germany) and were subjected to combined effects of abrasion and shock by placing them in the plastic chamber that revolves at 20 rpm for 5 min. The tablets were then sieved and weighed, and the percent loss in weight was calculated as friability.

2.2.10.5 Disintegration time

Disintegration time test was carried out according to USP/NF specification (USP XXII/NF XVII, 1990). Six tablets were placed in a disintegration tester (CALEVA, G.B. Caleva Ltd., UK) filled with distilled water at 37±2 ^{o}C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

2.2.10.6 Dissolution test

The dissolution test was done according to the USP/NF specification using dissolution apparatus Type II (ERWEKA, DT600, Germany), with 900 ml phosphate buffer (pH 5.8) as the dissolution medium at 37 ± 0.5 ^{o}C which was stirred at a rate of 50 rpm. Five ml of aliquots of the dissolution medium were removed at 5, 10, 15, 20, 30, and 45 min and filtered using Whatman No.1 filter paper. Equal amount of fresh medium kept at the same temperature was transferred into the dissolution vessel to keep the sink condition. One ml of the filtered samples was diluted to 100 ml and absorbance readings were taken with UV/Visible spectrophotometer (JENWAY, 6505, England) 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.

2.2.11 Statistical analysis

Statistical analysis was carried out using Analysis of Variance (ANOVA) on computer software SigmaStat® 3.5 for Windows (Systat Software, Inc. Point Richmond, USA). Tukey multiple comparison test was used to compare the individual difference in the material and tablet properties of the starches. At 95% confidence interval, p values less than or equal to 0.05 were considered statistically significant. The results are reported as mean and standard deviation (SD).

3. RESULTS AND DISCUSSION

3.1 Powder properties of starches

The powder properties of the three starches obtained during the study are presented in Table 3.1. The rank order of the true density is pregelatinized enset starch (1.52 ± 0.01 g/ml) > Starch 1500® (1.48 ± 0.02 g/ml) > native enset starch (1.46 ± 0.04 g/ml). However, these differences are not statistically significant ($p > 0.05$). The ranking for bulk and tapped densities is pregelatinized enset starch > native enset starch > Starch 1500® ($p < 0.05$). The particle size and shape of the starches may be responsible for the differences in the density values. The density values were used to calculate the Hausner ratios and Carr's indices which are measures of the flowability of a powder. Hausner ratio less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow and Carr's index values 5 to 10, 12 to 16, 18 to 21, and 23 to 35 represent excellent, good, fair and poor flow properties, respectively (Wells, 2002). The Hausner ratio and Carr's index are significantly lower for the pregelatinized enset starch and Starch 1500® than those of the native enset starch ($p < 0.05$). Comparable angle of reposes were recorded for pregelatinized enset starch (17.57 ± 1.08) and Starch 1500® (20.03 ± 1.12); characteristics of material with good flow property (Wells, 2002). Moreover, direct measure of the flow property showed that pregelatinized enset starch and Starch 1500® have comparable flow rate of 15.21 ± 1.69 and 12.86 ± 0.88 g/sec, respectively ($p > 0.05$). Native enset starch, on the other hand, did not flow through the funnel and therefore no angles of repose could be determined. This had been expected because native starches have poor flow properties (Odeku and Picker-Freyer, 2007). The loose packing and poor flow property of native enset starch may cause problems during die filling. On the other hand, the high bulk and tap densities of pregelatinized enset starch coupled with its good flowability offer a unique advantage of being used as filler in tablet and capsule formulations. The better flow property of pregelatinized enset starch powder could be probably due to a lower degree of interparticle interactions as stated by Zuluaga *et al*., (2007). The table also show that the native enset starch had greater value of water content (12.37 ± 1.11%) than the pregelatinized enset starch (9.67 ± 0.32%), while Starch 1500® had 10.95 ± 0.19%. Alebiowu and Itiola (2002) and Adedokun and Itiola (2009) also reported lower values of moisture content for pregelatinized starches from various sources.

Table 3.1: Powder properties of native and pregelatinized enset starches and Starch 1500®.

Powder properties	Native ES (± SD)	Pregelatinized ES (± SD)	Starch 1500® (± SD)
Moisture content (%)	12.37 ± 1.11	9.67 ± 0.32	10.95 ± 0.19
True density (g/ml)	1.46 ± 0.04	1.52 ± 0.01	1.48 ± 0.02
Bulk density (g/ml)	0.63 ± 0.01	0.70 ± 0.02	0.60 ± 0.01
Tapped density (g/ml)	0.82 ± 0.03	0.83 ± 0.01	0.71 ± 0.01
Hausner ratio	1.30 ± 0.05	1.19 ± 0.02	1.19 ± 0.03
Carr's index (%)	23.17 ± 2.63	15.93 ± 1.62	15.90 ± 0.18
Angle of repose (degree)	*	17.57 ± 1.08	20.03 ± 1.12
Flow rate (g/sec.)	*	15.21 ± 1.69	12.86 ± 0.88

Mean ± SD (n = 3), ES: enset starch, * There was no flow of the starch in the specified condition.

3.2 Solubility and swelling power

The solubility and swelling power of the starches are depicted in Figure 3.1 and 3.2, respectively. The solubility and swelling power of the starches were generally low at low temperature (15 °C) but increased significantly at higher temperature (80 °C) ($p < 0.05$). Waliszewski *et al.* (2003) reported that the solubility and swelling power of both native and pregelatinized banana starches increased with temperature. Comparable results were also reported by Odeku *et al*. (2008). These could be due to the degree of macromolecular disorganization and also to variations in the degradation of starch during thermal treatment.

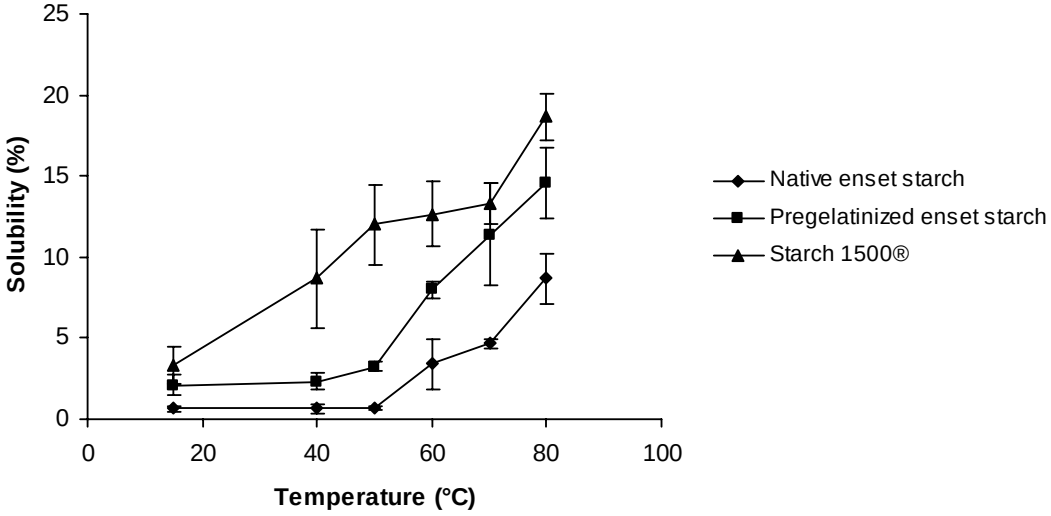

Figure 3.1: Solubility of enset starches (native and pregelatinized) and Starch 1500® at different temperatures.

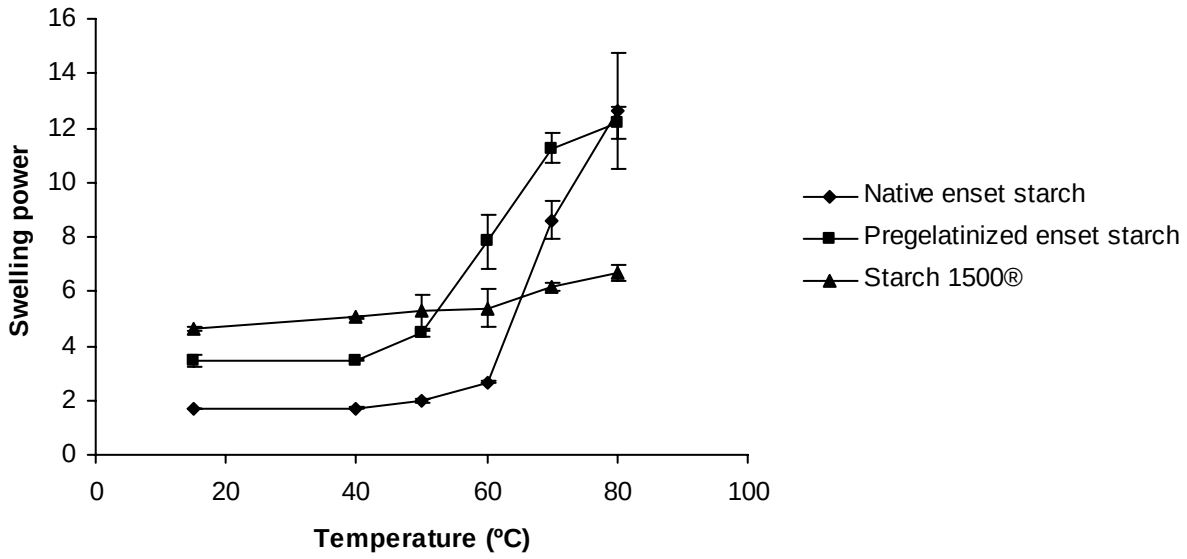

Figure 3.2: Swelling power of enset starches (native and pregelatinized) and Starch 1500® at different temperatures.

As it is clearly indicated in Figure 3.1 and 3.2, pregelatinized starches showed higher solubility and swelling power than the native starch almost at all temperature points. These increments as a result of gelatinization is to be expected, because gelatinization causes disruption of the weak associative bonds in the amorphous region of the granule enabling increased hydration of the starch molecules and leaching out of amylose and the result in this study is line with various research reports (Wootton and Bamunuarachchi, 1978; Alebiowu and Itiola, 2002; Adedokun and Itiola, 2009).

3.3 Moisture sorption property

Moisture sorption profiles of starches are shown in Figure 3.3. Moisture sorption increased generally with relative humidity. Percent moisture sorbed ranged between 5 % at low (20 %) relative humidity to over 60 % at high (100 %) relative humidity. Starch 1500® had the highest moisture sorption at 100 % relative humidity (60.2 ± 0.45 %), while pregelatinized enset starch had the highest at 20, 40, 60 and 75.6% relative humidity (8.40 ± 0.67, 13.12 ± 1.89, 21.97 ± 0.75, and 29.92 ± 1.18 %, respectively). At 40 % and 100 % relative humidity, native enset starch had the lowest moisture sorption (8.77 ± 0.49 % and 37.77 ± 0.23 %, respectively); while at 20 % relative humidity, Starch 1500® had the lowest (5.2 ± 1.11 %). The hydrophilic

nature of the starch molecule is probably responsible for the observed high moisture sorption by the starches and reinforces the necessity for moisture preclusion during storage (Riley *et al.*, 2006). Higher levels of water can lead to microbial spoilage and subsequent deterioration in starch quality. Furthermore, water has been also known to affect the flow properties of starches (Gebre-Mariam and Schmidt, 1998). Since no range can be defined in which the water content remains almost constant, during tablet production and storage, the relative humidity should be carefully controlled to obtain powders with optimum flow and compaction properties and also to prevent the deterioration of the tablets (Odeku and Picker-Freyer, 2007).

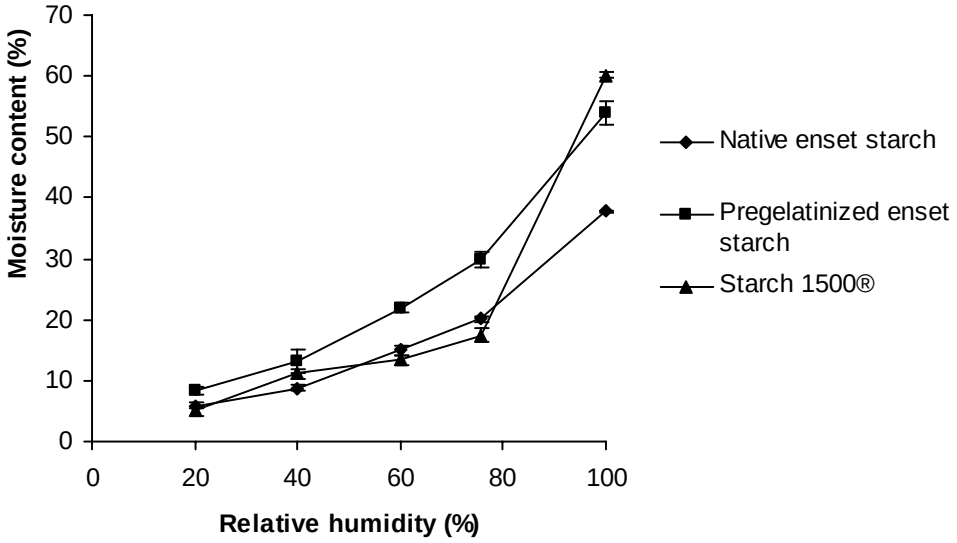

Figure 3.3: Moisture sorption patterns of enset starches (native and pregelatinized) and Starch 1500®

3.4 Viscosity of starch mucilages

The viscosities of native enset starch mucilage which is prepared at 70 °C and those of cold water reconstituted pregelatinized enset starch and Starch 1500® are depicted in Figure 3.4. As it is clearly indicated in the figure, the viscosity of native starch paste is significantly higher than the pregelatinized starches ($p<0.05$). Thus, low viscosity of pregelatinized starch in cold water can allow uniform distribution of higher binder content solutions throughout the granulation vessel and faster spray times when used for wet granulation; ensuing reduced process times, cost and complexity. In addition, this can enhance the adaptability of starch for newly emerging granulating technologies.

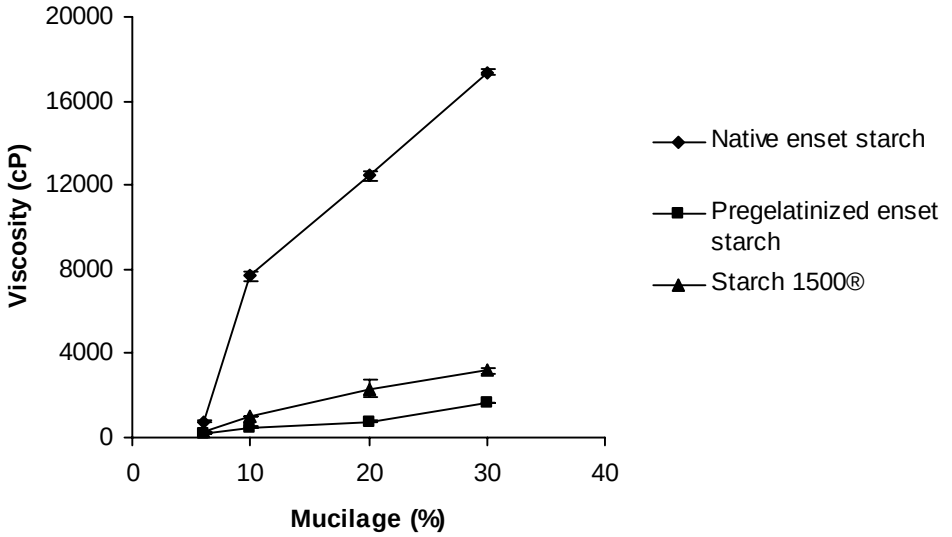

Figure 3.4: Viscosity of native enset starch mucilage at 70 °C compared to those of pregelatinized enset starch and Starch 1500® prepared by hydration in cold water.

3.5 Compaction property

Compactibility is the ability of a powder bed to form a mechanically strong tablet. The compaction properties of the starch tablets are presented in Table 3.2. The results show that the crushing strength for pregelatinized enset starch (60.50 ± 2.32 N) and Starch 1500® (67.30 ± 7.66 N) are significantly higher than that of native enset starch (26.40 ± 12.46 N) ($p < 0.05$). No significant difference was observed between the crushing strength of pregelatinized enset starch and Starch 1500® ($p > 0.05$).

Table 3.2: Compaction properties of enset starches (native and pregelatinized) and Starch 1500®

Compaction parameters	Native ES	Pregelatinized ES	Starch 1500®
Crushing strength (N)	26.40 ± 12.46	60.50 ± 2.32	67.30 ± 7.66
Tensile strength (Kg/cm^2)	5.60	10.14	12.24
Friability (%)	*	1.08 ± 0.85	0.82 ± 1.51

Mean ± SD (n = 10), ES: enset starch, * Some of the tablets were broken down during the test

Tensile strength is indicative of the bonding strength and may provide information about the laminating and capping tendencies of the material (Jain, 1999). The tensile strength of the compacts in the present study rank in the order of Starch 1500® (12.24 Kg/cm^2) > pregelatinized enset starch (10.14 Kg/cm^2) > native enset starch (5.60 Kg/cm^2). The low tensile strength of the compacts obtained with the native starch would therefore imply that it mainly underwent elastic deformation as reported by Zuluaga *et al.* (2007). In the contrary, pregelatinized starches deform plastically (Maarschalk *et al.*, 1997). Plastic deformation is the permanent deformation of a particle which is facilitated by the formation of permanent particle–particle contact regions during compaction (Jain, 1999). Therefore, pregelatinized starches can possess a higher ability to reduce the lamination tendency in tablets than the native starches (Adedokun and Itiola, 2009).

Compaction property of starch has been also known to be affected by amylose content. Embedded in the amorphous regions, amylose has been proposed to disrupt the crystalline packing of amylopectin (Jenkins and Donald, 1995). The erosion of the amylose by pregelatinization may result in a reduced hindrance for the double helical chains to approach each other. Thus, when applying the compaction force to the starch granules, the crystalline regions could be forced to become closely packed with increased intermolecular force, leading to a more order rearrangement within the starch granules. The stronger packing structure resulted in an increase in the strengths of the tablet as observed. Study by Odeku and Picker-Freyer (2007) showed that native starch with high amylose content exhibited poorer compressibility and did not form compacts, and Atichokudomchai *et al*. (2001) reported that the crushing strength of starch compact/tablet was increased due to the leaching out of amylose. Shape of particles is also known to play a significant role in the overall compaction property of particles. Irregular shape of particles facilitates more interparticular contact and higher bond formation (Odeku and Picker-Freyer, 2007).

Regarding the percent friability, the compact of the native enset starch were broken during the test, indicating the tablets were too soft to withstand the abrasion. Although it was not statistically significant ($p > 0.05$), the friability of pregelatinizied enset starch tablets was

higher than that of Starch 1500®. The relatively low value of friability of Starch 1500® compacts could be attributed to the higher strength of its compacts.

3.6 Granule properties

3.6.1 Particle size distributions

Despite the technical progress in tableting technology, the pharmaceutical properties of tablets are still controlled by the granules used in the formulation ((Miyamoto et al., 1998). Table 3.3 shows the particle size distributions of paracetamol granules prepared with various binders at different concentrations.

Table 3.3: Mean granule size and granule size distribution of paracetamol granules prepared with various binders at different binder concentrations.

Binder	BC (%w/w)	MGS (μm)	% granule retained			
			Sieve size, μm (passed/retained)			
			1000/710	710/315	315/224	224/pan
Native ES	2.5	661.53	51.22 ± 1.49	39.30 ± 2.26	7.48 ± 0.53	1.81 ± 0.47
	5	645.37	46.03 ± 3.75	44.57 ± 3.03	8.14 ± 0.56	1.30 ± 0.35
	7.5	674.20	54.23 ± 1.37	36.53 ± 2.30	8.24 ± 1.31	0.98 ± 0.12
	10	670.70	54.25 ± 1.02	35.64 ± 1.96	8.56 ± 0.70	1.02 ± 0.17
Pregelatinized ES	2.5	669.35	56.18 ± 4.87	31.96 ± 2.64	7.66 ± 1.41	4.08 ± 0.67
	5	663.23	54.04 ± 2.57	34.56 ± 2.35	7.19 ± 2.44	4.19 ± 1.75
	7.5	686.31	56.74 ± 2.05	35.42 ± 1.92	6.92 ± 0.97	0.91 ± 0.54
	10	684.25	57.04 ± 3.41	34.37 ± 2.09	7.21 ± 1.02	0.88 ± 0.32
Starch 1500®	2.5	668.59	53.56 ± 4.25	36.40 ± 0.66	8.28 ± 2.96	1.60 ± 0.57
	5	665.91	52.46 ± 3.65	37.39 ± 1.31	9.06 ± 2.53	1.19 ± 0.14
	7.5	671.84	54.80 ± 3.15	34.37 ± 0.83	9.57 ± 1.43	1.22 ± 0.08
	10	678.14	55.47 ± 3.51	35.01 ± 0.94	8.75 ± 2.03	0.77 ± 0.31

Mean ± SD (n = 3), ES: enset starch, BC: binder concentration, MGS: Mean granule size

The mean granule size and proportion of larger granules prepared by all the binders at higher concentrations (7.5 and 10 %w/w) were higher than those granules prepared at lower

concentrations (2.5 and 5 %w/w). This growth in granule size may be attributed to better binding efficiency of both native and pregelatinized starches at higher proportion of binder. These results are in concordant with the results of Alebiowu and Itiola (2001).

3.6.2 Densities and related properties

Since densities of granules are known to influence flowability and compressibility of the granules, they can affect the quality of tablet. Density and related properties of the paracetamol granules are presented in Table 3.4. As it can be seen from the table, both bulk and tap densities of paracetamol granules generally decrease with an increase in binder concentration for all types of starches. This could be attributed to an increase in particle size, which may increase the volume of granules. An increase in bulk volume in turn reduces the bulk density. Also as indicated in Table 3.4, bulk density of the paracetamol granule made from different type of starches doesn't show consistent trend of variation. At 2.5% and 5% binder concentrations, there was significant variation among the bulk densities of granules prepared with native and pregelatinized enset starches and Starch 1500® ($p < 0.05$). However, significant variation was not observed at binder concentrations of 7.5 % and 10 % ($p > 0.05$). At 2.5 % binder concentration pair wise multiple comparison procedures (Tukey test) revealed that the bulk density of granules of Starch 1500® is significantly higher than those of both native and pregelatinized enset starches ($p < 0.05$). Significant difference was not observed, however, between bulk densities of granules of native and pregelatinized enset starches at this binder concentration ($p > 0.05$). While the Tukey test at 5% binder concentration showed that bulk density of paracetamol granules with native enset starch was significantly higher than those of granules with Starch 1500® ($p < 0.05$) but no significant disparity was observed between the bulk densities of granules with native and pregelatinized enset starches and also between pregelatinized enset starch and Starch 1500® at this binder concentration ($p > 0.05$). Table 3.4 also shows that all the formulations have Carr's index below 15 % implying the granules have excellent flow property. The Hausner ratios were also observed to be less than 1.25, which also confirmed good flow property of the granules (Wells, 2002).

Table 3.4: Densities and related properties of paracetamol granules prepared with various binders at different binder concentrations.

Granule Properties	BC (% w/w)	Native ES	Pregelatinized ES	Starch 1500®
Bulk density (g/ml)	2.5	0.489 ± 0.009	0.487 ± 0.005	0.517 ± 0.000
	5	0.500 ± 0.000	0.492 ± 0.008	0.481 ± 0.004
	7.5	0.454 ± 0.020	0.467 ± 0.030	0.449 ± 0.110
	10	0.451 ± 0.110	0.462 ± 0.090	0.449 ± 0.081
Tapped density (g/ml)	2.5	0.520 ± 0.005	0.520 ± 0.005	0.556 ± 0.000
	5	0.536 ± 0.000	0.516 ± 0.007	0.517 ± 0.009
	7.5	0.481 ± 0.010	0.488 ± 0.000	0.477 ± 0.000
	10	0.471 ± 0.007	0.495 ± 0.043	0.475 ± 0.002
Hausner ratio	2.5	1.063	1.068	1.075
	5	1.072	1.049	1.075
	7.5	1.060	1.045	1.062
	10	1.044	1.071	1.058
Carr's index (%)	2.5	5.962	6.346	7.014
	5	6.716	4.651	6.963
	7.5	5.613	4.303	5.870
	10	4.246	6.667	5.474

Mean ± SD (n = 3), ES: enset starch

3.6.3 Flow rate and angle of repose

Flow rate is a direct method of determining granule flow property. Flow rates of parcetamol granules in this study are ranging from 3.05 - 3.71 g/sec (Table 3.5) and angle of reposes are below 30° for all the formulations, indicating the free flowing property of granules. Good flow property of the granulation to be compressed is necessary to ensure efficient mixing and acceptable weight uniformity for the compressed tablets (Yüksel *et al*., 2003). As shown in Table 3.5, the effect of concentration and type of the binder on the flow property was not

consistent. This indicates that factors affecting flow property of granules are complex. Kachrimanis *et al*. (2005) stated that flow properties of granules can be affected by a combination of material properties (particle size, size distribution, shape, packing density and surface properties) and operating conditions (moisture, temperature, and static charge).

Table 3.5: Flow properties of paracetamol granules prepared with various binders at different binder concentrations.

Granule properties	Binder concentration (%)	Native ES	Pregelatinized ES	Starch 1500®
Flow rate (g/sec)	2.5	3.12 ± 0.01	3.15 ± 0.03	3.50 ± 0.05
	5	3.22 ± 0.07	3.05 ± 0.02	3.16 ± 0.04
	7.5	3.52 ± 0.04	3.16 ± 0.04	3.48 ± 0.01
	10	3.71 ± 0.10	3.11 ± 0.06	3.12 ± 0.00
Angle of repose (degree)	2.5	27.93 ± 0.76	27.35 ± 0.57	27.38 ± 1.25
	5	27.98 ± 0.68	27.17 ± 0.79	26.92 ± 1.40
	7.5	27.91 ± 1.73	27.25 ± 0.06	26.75 ± 1.13
	10	28.32 ± 0.97	27.35 ± 0.32	27.11 ± 0.04

Mean ± SD (n = 3), ES: enset starch

3.6.4 Friability

Friability of the granules can be used as index of granule hardness, on the basis that hard granules would not crumble easily to dust when subjected to impact stress. The results of the friability test of granules are shown in Table 3.6. As expected, the friability of the granules generally decreased as the concentration of binders increased. As revealed by Tukey test, the percent friabilities of parcetamol granules of all the three starches at higher (10% w/w) binder concentration are significantly lower than those of granules at lower (2.5% w/w) binder concentration ($p < 0.05$). This is due to the fact that as concentration of binder increased more bonding is attained so that the strength of the granules increased and became resistant to abrasion during the test.

Table 3.6: Friability data of the granules prepared with various binders at different binder concentrations.

Binder concentrations (% w/w)	Friability (%)		
	Native ES	Pregelatinized ES	Starch 1500®
2.5	3.36 ± 0.63	4.56 ± 0.37	3.67 ± 0.64
5	3.31 ± 0.13	3.10 ± 1.01	2.83 ± 0.21
7.5	1.41 ± 0.11	2.06 ± 0.82	2.03 ± 0.31
10	0.56 ± 0.43	0.93 ± 0.64	1.60 ± 0.35

Mean ± SD (n = 3), ES: enset starch

3.7 Tablet properties

3.7.1 Weight and thickness

The paracetamol tablets prepared under the same compression force were examined for their weight and thickness uniformity. The results are summarized in Table 3.7 and 3.8. The tablets are within acceptable range of weight variation (± 5%) which is the limit of the percentage deviation allowed by British Pharmacopoeia (BP) (2000) for tablets weighing 325 mg or more. Since the weight of a tablet being compressed is determined by the amount of granulation in the die prior to compression, the weight uniformity could be attributed to the good flow property of the granules indicated in Section 3.6.3. In this study, since the drug substance forms the greater part of the tablet mass, the weight uniformity can reflect the uniformity in the content of active ingredient.

Table 3.7: Paracetamol tablet weight and thickness at different binder concentrations.

BC (%w/w)	Native ES		Pregelatinized ES		Starch 1500®	
	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)
2.5	0.52 ± 0.007	5.61 ± 0.03	0.53 ± 0.004	5.59 ± 0.10	0.53 ± 0.003	5.59 ± 0.00
5	0.51 ± 0.003	5.60 ± 0.01	0.51 ± 0.005	5.61 ± 0.05	0.51 ± 0.003	5.60 ± 0.02
7.5	0.51 ± 0.006	5.60 ± 0.04	0.52 ± 0.005	5.61 ± 0.00	0.53 ± 0.007	5.58 ± 0.03
10	0.51 ± 0.006	5.60 ± 0.00	0.52 ± 0.004	5.58 ± 0.09	0.53 ± 0.004	5.57 ± 0.05

Mean ± SD (n = 20), ES: enset starch, BC: binder concentration

Table 3.8: Paracetamol tablet weight and thickness at different disintegrant concentrations.

DC (%w/w)	Native ES		Pregelatinized ES		Starch 1500®	
	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)
5	0.52 ± 0.001	5.60 ± 0.04	0.52 ± 0.006	5.58 ± 0.00	0.51 ± 0.002	5.58 ± 0.08
10	0.52 ± 0.006	5.61 ± 0.06	0.52 ± 0.004	5.60 ± 0.10	0.51 ± 0.003	5.63 ± 0.01
15	0.51 ± 0.004	5.60 ± 0.00	0.53 ± 0.003	5.57 ± 0.09	0.51 ± 0.004	5.57 ± 0.02

Mean ± SD (n = 20), ES: enset starch, DC: Disintegrant concentration

The values of thickness (mm) for the tablets of different formulations are also given in Table 3.7 and 3.8. From the results, it may be deduced that the various formulations didn't show significant variation in the thickness of the tablets ($p > 0.05$). It has been stated that tablet thickness may vary with no change in weight due to difference in the granulation and pressure applied to the tablets, wear and tear on length of punches as well as on the speed of tablet compression (Ahmed *et al*., 2001). Therefore, the uniformity of tablet thickness among different formulations in the present study can be attributed to the constant compression force used for compression and to the uniform granulation method adopted. Tablet thickness is generally controlled to minimize appearance problems, to assure that tablets will fit into the packaging and they can be accurately counted by the filling equipment; since some filling equipments depend on the uniform thickness of the tablets as a counting mechanism.

3.7.2 Crushing strength and friability

The mechanical properties of the tablet formulations were assessed by the crushing strength and friability of the tablets. While crushing strength indicates the strength of the tablet, friability values provide a measure of tablet weakness. The relationship between binder concentration and crushing strength as well as friability for all formulations at a constant disintegrant concentration (4 % Ac-Di-Sol®) and compression force are shown in Figure 3.5 and 3.6. There was an increase in crushing strength with corresponding decrease in friability values with increased binder concentration for all formulations. This is in agreement with previous works reported at various times (Esezobo and Pilpel, 1976; Agrawal and Prakasam, 1988; Zubair *et al*., 1988; Gebre-Mariam and Schmidt, 1996b; Adane *et al*., 2006; Adetunji *et al*., 2006). It has been established that the presence of high concentration of plasto-elastic

binding agent leads to an increase in plastic deformation of the formulation and consequently to the formation of more solid bonds with increase in tablet strength and resistance to fracture and abrasion (Banker and Anderson, 1986; Gebre-Mariam and Schmidt, 1996b). For the paracetamol tablets; therefore, the increased binder concentration resulted in the reduction of elastic recovery of the tablets. Tablets prepared with the three binders show more or less similar relationships between crushing strength, friability and binder concentration.

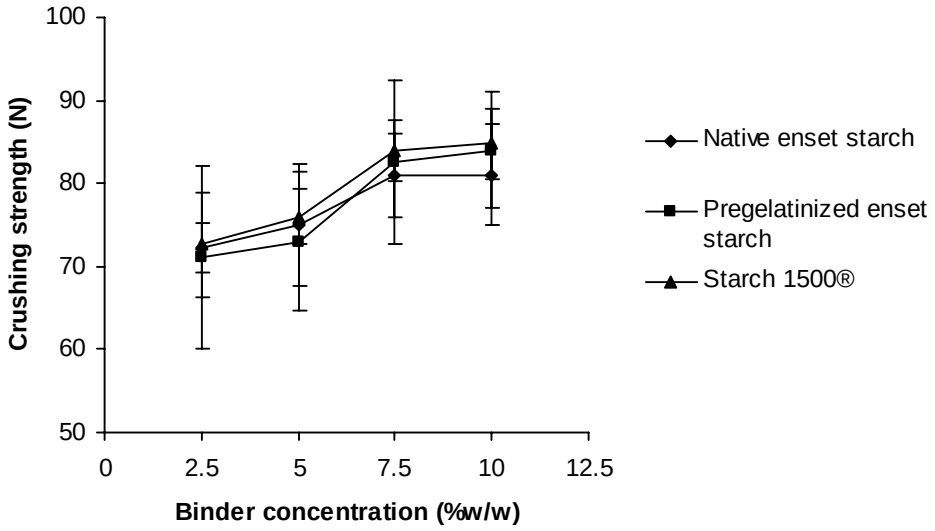

Figure 3.5: Effect of concentration of starches employed as a binder on the crushing strength of tablets.

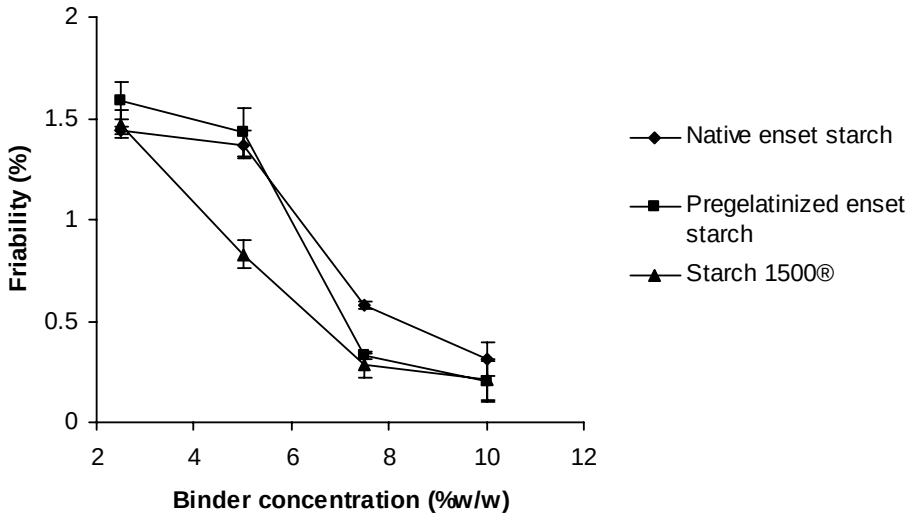

Figure 3.6: Effect of concentration of starches employed as a binder on the friability of tablets.

The effect of the starches as disintegrating agent on the crushing strength and percent friability of paracetamol tablets at constant binder concentrations (3.5 % povidone) are shown in Figure 3.7 and 3.8, respectively. The effect of starches as disintegrant on the crushing strength and percent friability differ significantly. When the concentration of the binder was constant, an increase in the concentration of native enset starch as disintegrant resulted in reduction of crushing strength and increment of percent friability. This may be attributed to the poor compressibility and softening effect of native starch at higher concentrations. On the contrary, the crushing strength increased and percent friability of the tablets decreased gradually as the concentration of Starch 1500® increased, indicating better compressibility and *in situ* binding activity of this starch. In the case of the use of pregelatinized enset starch as disintegrant, there is cutback in the crushing strength and rise in the percent friability of tablets at higher concentration, although the effect is minimal as compared to the native form of the starch. This could be credited to its better compactability than the native one.

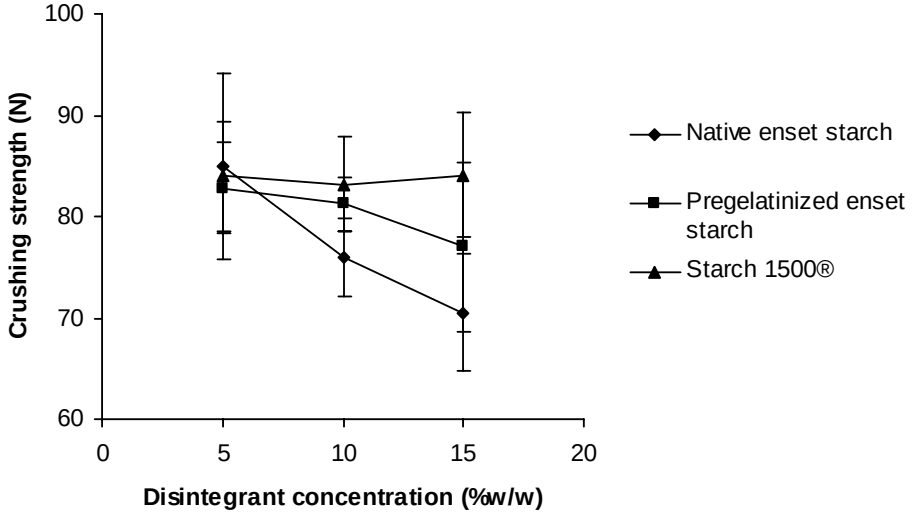

Figure 3.7: Effect of concentration of starches employed as a disintegrant on the crushing strength of tablets.

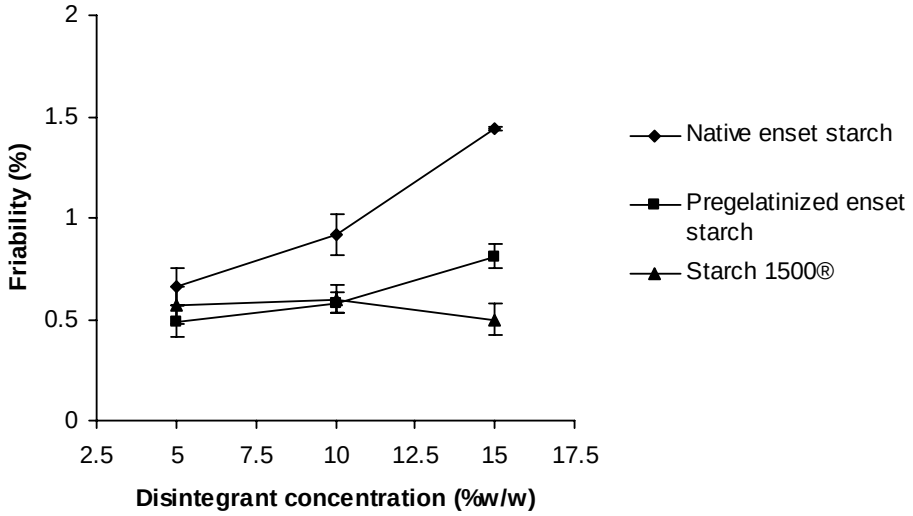

Figure 3.8 : Effect of concentration of starches employed as a disintegrant on the friability of tablets.

3.7.3 Tensile strength

The effects of different type of starch binder concentrations on the tensile strengths of the paracetamol tablets are shown in Table 3.9. The tensile strength increases with binder concentrations. This is expected since tensile strength is directly proportional to tablet crushing strength (Equation 2.6).

Table 3.10 shows that native enset starch used as disintegrant cause the highest reduction in tensile strength of the tablets. This is because of the softening effect of native enset starch.

Table 3.9: Effect of different type of starch binder concentrations on the tensile strength of paracetamol tablets.

Binder concentrations (% w/w)	Tensile strength (kg/cm^2)		
	Native ES	Pregelatinized ES	Starch 1500®
2.5	8.21	8.09	8.28
5	8.53	8.29	8.64
7.5	9.21	9.38	9.59
10	9.21	9.59	9.69

ES: enset starch

Table 3.10: Effect of different types of starch disintegrant concentrations on the tensile strength of paracetamol tablets.

Disintegrant concentrations (% w/w)	Tensile strength (kg/cm^2)		
	Native ES	Pregelatinized ES	Starch 1500®
5	9.67	9.45	9.59
10	8.63	9.24	9.41
15	8.02	8.81	9.62

ES: enset starch

3.7.4 Disintegration time

The effect of concentration of starches as a binder on the disintegration time of tablets is depicted in Figure 3.9. The disintegration time of the tablets increased as the binder concentration increased. This could be attributable to the reduced liquid penetration into the tablets due to an increase in tablet hardness at higher binder concentration. Moreover, it has been stated by Gebre-Mariam and Schmidt (1996b) that a thin film of mucilage around granules is formed with a thickness depending on the quantity of mucilage used. In the presence of water this thin film is converted into a mucilaginous viscous barrier between the granules and the water. This may act by slowing the rate at which invading water reaches the surface of the powder particles retarding the disintegration of the granules and delaying the ability of the disintegrant to promote disintegration. The longer disintegration time for tablets prepared with Starch 1500® at binder concentrations of 7.5 and 10 % w/w could be attributed to the highest crushing strength (Figure 3.5) of the tablets at these binder concentrations.

The relationship between disintegrant concentration and disintegration time at fixed binder concentration is shown in Figure 3.10. One can clearly notice from the figure that the impact of concentration on the disintegration time is disintegrant dependent. The disintegration time of tablets prepared with native enset starch decreases substantially. The disintegration time is less sensitive for the concentration of pregelatinized enset starch and Starch 1500®. This variation might be related to the impact of disintegrant concentration on the crushing strength of tablets (Section 3.7.2 and Figure 3.7). One study also showed that disintegration time was longer for harder tablets (Ahmed *et al.,* 1998).

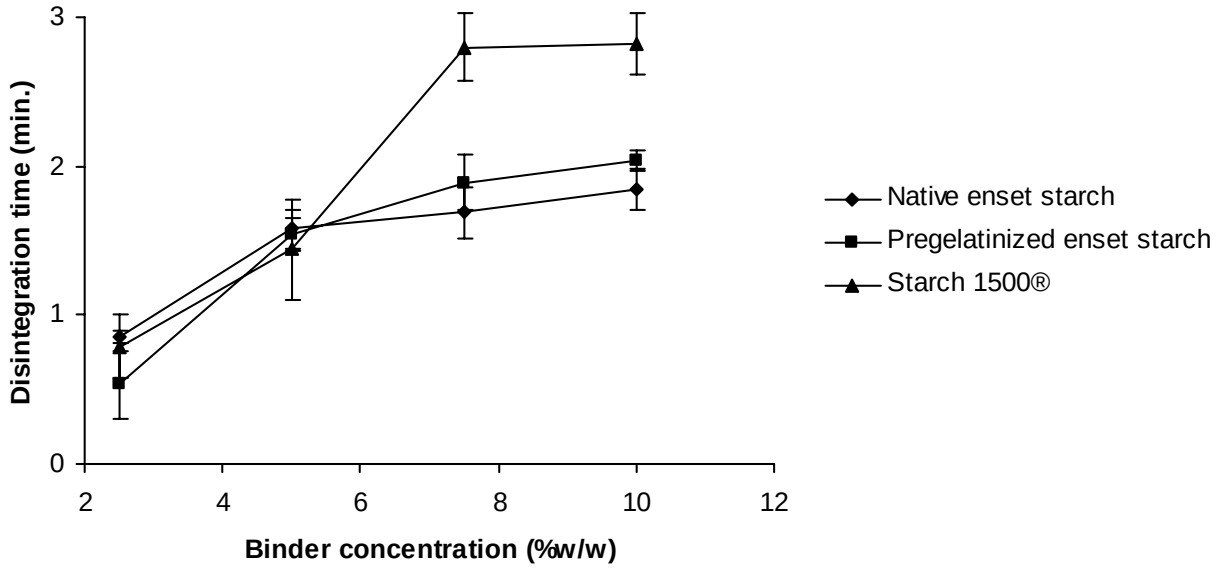

Figure 3.9: Effect of concentration of starches employed as a binder on the disintegration time of tablets.

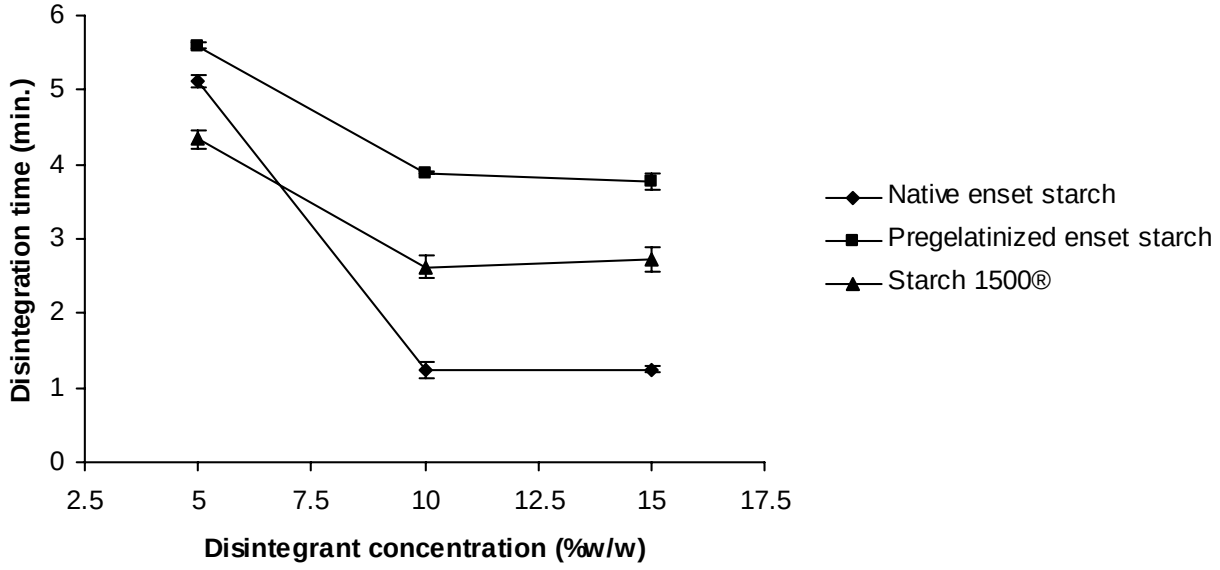

Figure 3.10: Effect of concentration of starches employed as a disintegrant on the disintegration time of tablets.

Contrary to faster disintegration suggested by their higher swelling and moisture sorption behaviors, pregelatinized starch formulations showed longer disintegration time than the native ones. This can be due to the formation of viscous mucilage by pregelatinized starch in cold water which may appear to retard the rate of entry of disintegration fluid into the tablet. Gebre-Mariam and Schmidt (1996b) stated that the rate of uptake of fluid has a pronounced effect on the disintegration times of tablets (containing starch as a disintegrant) than the extent of water uptake.

3.7.5 Drug dissolution

The dissolution test is used for measuring the time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions in an *in-vitro* test. It is intended to provide information on physiological availability of the drug substance. The dissolution profiles of paracetamol tablets at low (2.5% w/w) and high (10% w/w) starch binder concentrations are shown in Figure 3.11.

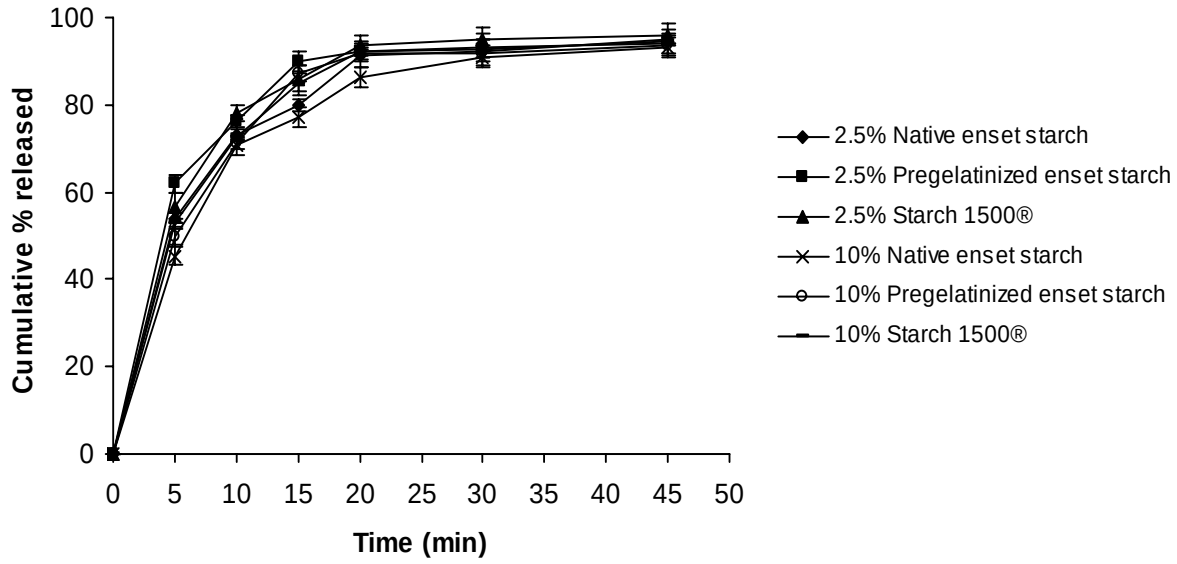

Figure 3.11: Dissolution profiles of paracetamol tablets at low (2.5% w/w) and high (10% w/w) binder concentrations.

It was observed that the tablets formulated with higher binder concentration (10% w/w) gave lower percent drug release at all time points. The higher bond strength of tablets prepared with

binder concentration of 10% w/w that prolonged the disintegration time of the tablets (Figure 3.5 and 3.9) could be responsible for the retardation of dissolution. Disintegration usually plays a vital role in the dissolution process since it determines to a large extent the area of contact between the solid and liquid (Odeku and Itiola, 2006). Slightly higher dissolution rates were obtained for formulation containing pregelatinized starches than when native starch was employed as a binder. This was in concordant with the result obtained by Karr *et al*. (1990). The amount of drug dissolved from the tablet in 30 min was comparable between pregelatinized and native enset starches and Starch 1500® formulations both at low (2.5% w/w) and high (10% w/w) binder concentrations ($p > 0.05$).

The dissolution profiles of paracetamol tablets at low (5% w/w) and high (15% w/w) disintegrant concentrations are shown in Figure 3.12. The dissolution rate of paracetamol tablet containing native and pregelatinized enset starches increased by increasing the disintegrant concentration, while that of Starch 1500® decreased as disintegrant concentration increased. The amounts dissolved from formulations at lower amount of disintegrant (5% w/w) in 30 min were in the order of native enset starch (85.2%) > pregelatinized enset starch (84.1%) > Starch 1500® (82.1%); however, the variation was not significant ($p > 0.05$). The amount of paracetamol released from tablets when Starch 1500® was used as a disintegrant was significantly lower than those of native and pregelatinized enset starches at their higher concentration ($p < 0.05$). The gel like layer formed by pregelatinized starch in cold water when it is exposed to water could be responsible for the delay of drug release from the tablet containing Starch 1500® as a disintegrant at its higher concentration (Odeku *et al*., 2008).

Figure 3.11 and 3.12 also show that paracetamol tablets prepared using native and pregelatinized enset starches and Starch 1500® as binder or disintegrant have good drug release profile. All formulations were released more than 80% in 30 min, acting in accordance with USP/NF specification.

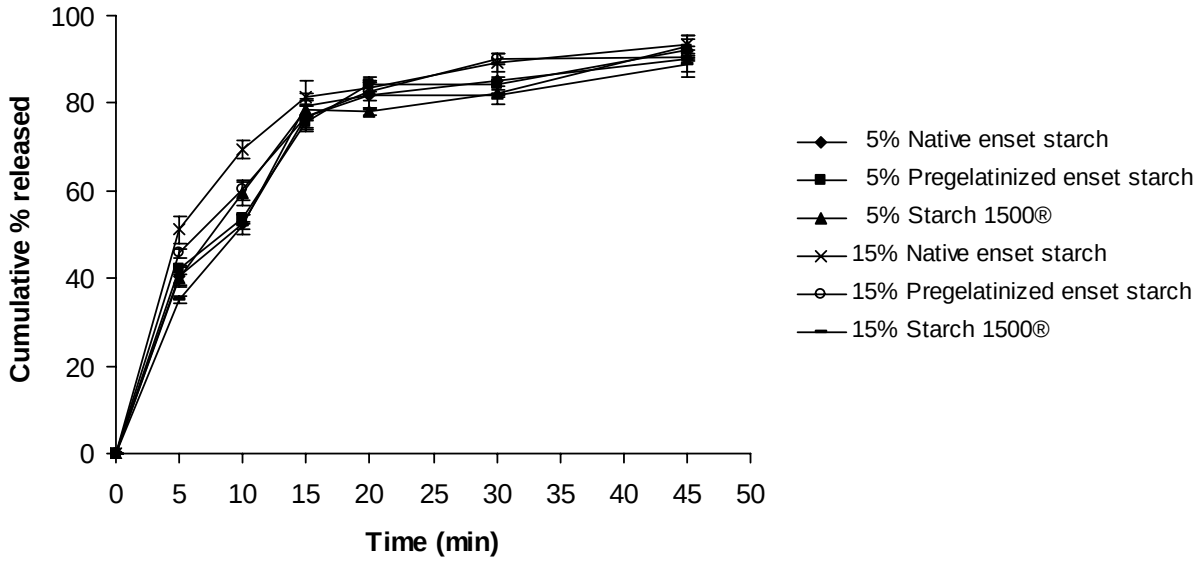

Figure 3.12: Dissolution profiles of paracetamol tablets at low (5% w/w) and high (15% w/w) disintegrant concentrations.

4. CONCLUSIONS

Pregelatinized enset starch was prepared and some of its properties were investigated. The results obtained indicate that pregelatinization improved the flowability of the enset starch. The high bulk and tapped densities of pregelatinized enset starch coupled with its good flowability offer a unique possibility of the starch being used as filler in tablet formulations. Pregelatinization increased the percentage solubility, swelling power and water holding capacity of enset starch.

From the results, the compaction property of enset starch is improved by pregelatinization and the compaction property of pregelatinized enset starch is comparable to Starch 1500®.

Formulation studies have been conducted on paracetamol tablets containing native and pregelatinized enset starches and Starch 1500® as a binder and disintegrant. All the paracetamol granules prepared exhibited good flow property as indicated by their flow rate, Carr's index, Hausner ratio and angle of repose.

The paracetamol tablets containing Starch 1500® and native and pregelatinized enset starch as binders evaluated for their crushing strength, friability and disintegration time showed comparable binding ability. All the paracetamol tablets, prepared with the three starches as binder and disintegrant, demonstrated acceptable drug release property.

The results obtained also indicate that the efficiency of the three starches as disintegrant and binder is affected by their concentration in the formulations. Increase in binders' concentration resulted in increased crushing strength and disintegration time and decreased percentage friability of tablets. Increasing the concentration of native starch when used as disintegrant reduced the crushing strength and disintegration time of the tablets and increased the percent friability of the tablets. On the other hand, crushing strength and percent friability of tablets are less sensitive to the increment of the concentration of pregelatinized enset starch when it is used as a disintegrant, implying that pregelatinized enset starch has lower softening effect than the native one.

From the foregoing, it can be concluded that pregelatinized enset starch can be considered as better tablet binder and disintegrant than the native one.

5. SUGGESTIONS FOR FURTHER WORK

The results of this study suggest further investigation on the following directions:

- Properties of the pregelatinized enset starch such as particle size distribution, pasting property, morphological characterization,
- Degree of pregelatinization,
- The application of pregelatinized enset starch as tablet and capsule filler, and
- The application of pregelatinized enset starch in food industries.

REFERENCES

Adane, M., Abdel-Mohasen, M. G., Gebre-Mariam, T. (2006). Evaluation and optimization of Godare starch as a binder and disintegrant in tablet formulations, *Ethiop. Pharm. J*. **24**: 106 - 115.

Adebayo, S. A., Brown-Myrie, E., Itiola, O. A. (2008). Comparative disintegrant activities of breadfruit starch and official corn starch, *Powder Technology* **181**: 98 - 103.

Adedokun, M. O., Itiola, O. A. (2009). Material properties and compaction characteristics of natural and pregelatinized forms of four starches. *Carbohydr. Polym.* Accepted Manuscript.

Adetunji, O. A., Odeniyi, M. A., Itiola, O. A. (2006). Compression, mechanical and release properties of chloroquine phosphate tablets containing corn and trifoliate Yam starches as binders, *Trop. J. Pharm. Res*. **5**: 589 - 596.

Agrawal, Y. K., Prakasam, K. (1988). Effect of binders on Sulfamethoxazole tablet, *J. Pharm. Sci.* **77**: 885 - 891.

Ahmed, A., Ali, S. A., Hassan, F., Ali, S. S., Haque, N. (2001). Evaluation of acetaminophen tablets by control test, *Pak. J. Pharm. Sci.* **14**: 47 - 55.

Ahmed, A., Ali, S. A., Hassan, F., Ayub, S., Haque, N. (1998) Effect of disintegrants and hardness on the disintegration time of acetaminophen tablets, *Pak. J. Pharm. Sci.* **11**: 41 - 46.

Alderborn, G. (2002). Tablets and compaction. In: Aulton, M. E., *Pharmaceutics: the science of dosage form design*. 2nd edn., Harcourt, Churchill living stone, London, Pp. 398 - 439.

Alebiowu, G., Itiola, O. A. (2002). Compressional characteristics of native and pregelatinized forms of sorghum, plantain, and corn starches and the mechanical properties of their tablets, *Drug Dev. Ind. Pharm.* **28**: 663 - 672.

Alebiowu, G., Itiola, O. A. (2003). The influence of pregelatinized starch disintegrants on interacting variables that act on disintegrant properties. URL: http://www.pharmtech.com/ (accessed on June14, 2009)

Alebiowu, G., Itiola, O. A. (2001). Effects of natural and pregelatinized sorghum, plantain, and corn starch binders on the compressional characteristics of a paracetamol tablet formulation, *Pharm. Technol.* 26-30.

Alves, R. M. L., Grossmann, M. V. E., Silva, R. S. S. F. (1999). Gelling properties of extruded yam (*Dioscorea alata*) starch, *Food Chemistry* **67**: 123 - 127.

Anastasiades, A., Thanou, S., Loulis, D., Stapatoris, A., Karapantsios, T. D. (2002). Rheological and physical characterization of pregelatinized maize starches. *J. Food Eng.* **52**: 57 - 66.

Atichokudomchai, N., Shobsngob, S., Chinachoti, P., Varavinit, S. (2001). Study of some physicochemical properties of high-crystalline tapioca starch, *Starch/Stärke* **53**: 577 - 581.

Bae, H. J., Cha, D. S., Whiteside, W. S., Park, H. J. (2008). Film and pharmaceutical hard capsule formation properties of mungbean, waterchestnut, and sweet potato starches, *Food Chemistry* **106**: 96 - 105.

Banker, G. S., Anderson, N. R (1986). Tablets. In: Lachman, L., Lieberman, H. A., Kanig, J. L., (eds.). *The Theory and Practice of Industrial Pharmacy*, Lea and Febiger Publisher, Philadelphia, pp. 293 - 345.

Bemiller, J. N. (1997). Starch modification: challenges and prospects, *Starch/stärke* **49**: 127 - 131.

Bhutanis, B. R., Bhatia, V. R. (1975). Drying rates of tablet granulations I: Effect of certain granulating adjuvants on drying rates, *J. Pharm. Sci.* **64**: 135 - 139.

Biliaderis, C.G. (2009). Structural transitions and related physical properties of starch. In: BeMiller, J., Whistler, R. (eds), *Starch: Chemistry and Technology*. 3rd edn. Academic Press, New York, pp. 293 - 372.

BP (2000). British pharmacopeia: The pharmaceutical press, Her Majesty's Stationery Office, London, vol. I and II.

Brand, S.A., Spring, A., Hiebsch, C., Yntiso, G., Tabogie, E., Diro, M., Woldemichael, G., Tesfaye, S., McCabe, J.T., Shigeta, M. (1997). *The tree against hunger: Enset based agricultural system in Ethiopia.* American Association for the Advancement of Science with Awassa Agricultural Research Center, Koyto University Center of African Area Studies and University of Florida, Directorate for International Programs, Washington, D.C.

Chan, H. K., Chew, N. Y.-K. (2007). Excipients: powders and solid dosage forms. In: Swarbrick, J. (ed.) *Encyclopedia of pharmaceutical technology,* 3rd ed., Informa Healthcare USA, Inc, New York, Vol. 3, pp. 1646-1655.

Chiu, C., Solarek, D. (2009). Modification of starches. In: BeMiller J., Whistler R. (eds) *Starch: Chemistry and Technology* 3rd edn., Academic Press, New York, pp. 629-655.

Chung, H. J., Liu, Q., Hoover, R. (2009). Impact of annealing and heat-moisture treatment on rapidly digestible, slowly digestible and resistant starch levels in native and gelatinized corn, pea and lentil starches, *Carbohydr. Polym.* **75**: 436 - 447.

Colorcon® (2005). Starch 1500® used as a binder and disintegrant in high shear wet granulation comparison to povidone and croscarmellose sodium. URL: http://www.colorcon.com.cn (accessed on March 20, 2009).

Conway, B. R. (2008). Solid dosage forms. In: Gad, S. C. (ed.) *Pharmaceutical Manufacturing Handbook: Production and Processes,* John Wiley & Sons, Inc. pp. 235 - 265

Copeland, L., Blazek, J., Salman, H., Tang, M.C. (2009). Form and functionality of starch, *Food Hydrocolloids* **23**: 1527 - 1534.

Dare, K., Akin-Ajani, D. O., Odeku, O. A., Itiola, O. A., Odusote, O. M. (2006). Effects of pigeon pea and plantain starches on the compressional, mechanical, and disintegration properties of paracetamol tablets, *Drug Dev. Ind. Pharm.* **32**: 357 - 365.

Esezobo, S., Pilpel, N. (1976). Some formulation factors affecting the tensile strength, disintegration and dissolution of uncoated oxytetracycline tablets, *J. Pharm. Pharmac.* **28**: 8 - 16.

Gadalla, M. A. F., Abd El-Hameed, M. H., Ismail, A. A. (1989). A comparative evaluation of some starches as disintegrants for double compressed tablets, *Drug Dev. Ind. Pharm.* **15:** 427 - 446.

Gebeyehu, G. (2004). The application of innovation to local Problems: Examples of good practice from Ethiopia. URL: http://info.worldbank.org/ (accessed on October 10, 2009).

Gebre-Mariam, T., Schmidt, P. C. (1996a). Isolation and physico-chemical properties of enset starch. *Starch/Stärke* **48**: 208 - 214.

Gebre-Mariam, T., Schmidt, P. C. (1996b). Characterization of enset starch and its use as a binder and disintegrant for tablets, *Pharmazie* **51**: 303 - 311.

Gebre-Mariam, T., Schmidt, P. C. (1996c). The use of a starch obtained from dioscorea abyssinica in tablet formulations, *Pharm. Ind.* **58**: 167.

Gebre-Mariam, T., Schmidt, P. C. (1998). Some physico-chemical properties of dioscorea starch from Ethiopia, *Starch/Stärke* **50**: 242 - 246.

Gebre-Mariam, T., Winnemöller, M., Schmidt, P. C. (1996a). An evaluation of the disintegration efficacy of a sodium starch glycolate prepared from enset starch in compressed tablets, *Eur. J. Pharm. Biopharm.* **43**: 124 - 132.

Gebre-Mariam, T., Winnemöller, M., Schmidt, P. C. (1996b). The use of a starch obtained from dioscorea abyssinica in tablet formulations. 2nd communications: the sodium starch glycolate from *Dioscorea abyssinica* as a disintegrant, *Pharm. Ind.* **58**: 255 - 259.

Han, Z., Zeng, X. A., Zhang, B. S., Yu, S. J. (2009). Effects of pulsed electric fields (PEF) treatment on the properties of corn starch. *J. Food Eng.* **93**: 318 - 323.

Hoover, R., Hughes, T., Chung, H.J., Liu, Q. (2009). Composition, molecular structure, properties, and modification of pulse starches: A review, *Food Res. Int.,* in press.

Jackson, D. S., Gomez, M. H., Waniska, R. D., Rooney, L. W. (1990). Effects of single screw extrusion cooking on starch as measured by aqueous high-performance size exclusion chromatography, *Cereal Chemistry* **67**: 529 - 532.

Jacob, J. T., Plein, E. M. (1968). Factors affecting dissolution rate of medicaments from tablets II: Effect of binder concentration, tablet hardness, and storage conditions on the dissolution rate of phenobarbital from tablets, *J. Pharm. Sci.* **57**: 802 - 805.

Jain, S. (1999). Mechanical properties of powders for compaction and tableting: an overview, *PSTT* **2**: 20 - 31.

Jenkins, P. J., Donald, A. M. (1995). The influence of amylose on starch granule structure, *Int. J. Biol. Macromol.* **17**: 315 - 321.

Kachrimanis, K., Petrides, M., Malamataris, S. (2005). Flow rate of some pharmaceutical diluents through die-orifices relevant to mini-tableting, *Int. J. Pharm.* **303**: 72 - 80.

Kalogianni, E. P., Xynogalos, V. A., Karapantsios, T. D., Kostoglou, M. (2002). Effect of feed concentration on the production of pregelatinized starch in a double drum dryer, *Lebensm.-Wiss. u.-Technol.* **35**: 703 - 714.

Karr, J. I., Shiromani, P. K., Bavitz, J. F. (1990). Binding efficiencies of strach N. F. and modified starches in formulations of poorly water soluble drugs, *Drug Dev. Ind. Pharm.* **16**: 821 - 835.

Kotteke, M. J., Rudnic, E. M. (2002). Tablet dosage form. In: Banker, G. S., Rhodes, C. T. (eds) *Modern pharmaceutics*, 4th ed., revised and expanded, Marcel Dekker, Inc. New York. pp. 280 - 326.

Lee, B.-J. (2008). Pharmaceutical preformulation: physicochemical properties of excipients and powders and tablet characterization. In: Gad, S.C. (ed) *Pharmaceutical Manufacturing Handbook: Production and Processes,* John Wiley & Sons, Inc. pp. 879 - 931.

Lenaerts, V., Moussa, I., Dumoulin, Y., Mebsout, F., Chouinard, F., Szabo, P., Mateescu, M. A., Cartilier, L., Marchessault, R. (1998). Cross-linked high amylose starch for controlled release of drugs: recent advances, *J. Control. Release* **53**: 225 - 234.

Lindeboom, N., Chang, P.R., Tyler, R.T. (2004). Analytical, biochemical and physicochemical aspects of starch granule size with emphasis on small granule starches: a review, *Starch/Stärke* **56**: 89 - 99.

Maache-Rezzoug, Z., Zarguili, I., Loisel, C., Queveau, D., Buléon, A. (2008). Structural modifications and thermal transitions of standard maize starch after D.I.C hydrothermal treatment, *Carbohydr. Polym.* **74**: 802 - 812.

Maarschalk, K. V. V., Vromans, H., Groenendijk, W., Bolhuis, G. K., Lerk, C. F. (1997). Effect of water on deformation and bonding of pregelatinized starch compacts. *Eur. J. Pharm. Biopharm.* **44**: 253 - 260.

Marais, A. F., Song, M., Villiers, M. (2003). Effect of compression force, humidity and disintegrants concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant, *Trop. J. Pharm. Reas.* **2**: 125 - 135.

Mitrevej, A., Faroongsarng, D., Sinchaipanid, N. (1996). Compression behavior of spray dried rice starch. *Int. J. Pharm.* **140**: 61 - 68.

Miyamoto, Y., Ryu, A., Sugawara, S., Miyajima, M., Matsui, M., Takayama, K., Nagai, T. (1998). Optimization of the granulation process for designing tablets, *Chem. Pharm. Bull.* **46**:1432 - 1437.

Mohammed, K., Endale, A., Gebre-Mariam, T. (2007). Isolation, acetylation and physicochemical characterization of Kotte Harre (*Dioscorea bulbifera*) starch obtained from Ethiopia. MSc Thesis, School of Graduate Study, Addis Ababa University.

Morrison, W. R., Tester, R. F. (1994). Properties of damaged starch granules IV: Composition of ball-milled wheat starches and of fractions obtained on hydration. *J. Cereal Sci.* **20**: 69 - 77.

Mulhbacher, J., Ispas-Szabo, P., Lenaerts, V., Mateescu, M. A. (2001). Cross-linked high amylose starch derivatives as matrices for controlled release of high drug loadings, *J. Control. Release* **76**: 51 - 58.

Nabais, T., Brouillet, F., Kyriacos, S., Mroueh, M., Amores S. P., Bataille, B., Chebli, C., Cartilier, L. (2007). High-amylose carboxymethyl starch matrices for oral sustained drug-release: In vitro and in vivo evaluation, *Eur. J. Pharm. Biopharm.* **65**: 371 - 378.

Nakorn, K. N., Tongdang, T., Sirivongpaisal, P. (2009). Crystallinity and rheological properties of pregelatinized rice starches differing in amylose content, *Starch/Stärke* **61**: 101 - 108.

Newman, A.W., Vitez, I.M., Kiesnowski, C., Mueller, R.L. (1996). Starches and starch derivatives. In: Swarbrick, J., Boylan, J.C. (eds), *Encyclopedia of pharmaceutical technology*, Marcel Dekker, New York, Vol. 14, pp. 223 - 248.

O'Brien, S., Wang, Y. J., Vervaet, C., Remon, J. P. (2009). Starch phosphates prepared by reactive extrusion as a sustained release agent, *Carbohydr. Polym.* **76**: 557 - 566.

Odeku, O. A., Itiola, O .A. (2006). Tablet Evaluation Tests. URL: http://www.Pharminfo.net. (Acceced on February 5, 2009)

Odeku, O. A., Picker-Freyer, K. M. (2007). Analysis of the material and tablet formation properties of four dioscorea starches, *Starch/Stärke* **59**: 430 - 444.

Odeku, O. A., Schmid, W., Picker-Freyer, K. M. (2008). Material and tablet properties of pregelatinized (thermally modified) dioscorea starches, *Eur. J. Pharm. Biopharm.* **70**: 357 - 371.

Onofre, F. O., Wang, Y. J. (2010). Hydroxypropylated starches of varying amylose contents as sustained release matrices in tablets. *Int. J. Pharm.* **385**: 104 - 112.

Patel, N. R., Hopponen, R. E. (1966). Mechanism of action of starch as a disintegrating agent in aspirin tablets, *J. Pharm. Sci.* **55**: 1065-1068.

Paulos, G., Endale, A., Gebre-Mariam, T. (2007). Isolation, acetylation and physicochemical characterization of cassava starch obtained from Ethiopia. MSc. Thesis, School of Graduate Study, Addis Ababa University.

Pérez-Sira, E., González-Parada, Z. (1997). Functional Properties of Cassava (*Manihot esculenta Crantz*) starch modified by physical methods, *Starch/Stärke* **49**: 49 - 53.

Pijls, L. T. J, Tirnmer, A. A. M., Wolde-Gebriel, Z., West, C. E. (1995). Cultivation, preparation and consumption of enset (*Ensete ventricosum*) in Ethiopia, *J. Sci. Food Agric.* **67**: 1 - 11.

Pohja, S., Suihko, E., Vidgren, M., Paronen, P., Ketolainen, J. (2004). Starch acetate as a tablet matrix for sustained drug release, *J. Cont. Release* **94**: 293 - 302.

Riley, C. K., Adebayo, S. A., Wheatley, A. O., Asemota, H. N. (2006). Fundamental and derived properties of Yam (Dioscorea Spp.) starch powders and implications in tablet and capsule formulation. *Starch/Stärke* **58**: 418 - 424.

Roper, H. (2002). Renewable raw materials in Europe — industrial utilization of starch and sugar, *Starch/Stärke* **54:** 89 - 99.

Rudnic, E. M., Schwartz, J. D. (2000). Oral solid dosage forms. In: Gennaro A. Z. (ed.), *Remington: the science and practice of pharmacy*. Vol. 1, 20th edn., Lippincott Williams and Wilkins, Philadelphia, pp. 858 - 893.

Schüssele, A., Bauer-Brandl, A. (2003). Note on the measurement of flowability according to the European Pharmacopoeia, *Int. J. Pharm.* **257**: 301 - 304.

Sebio, L., Chang, Y.K. (2004). Effect of processing conditions on the extrusion of white yam flour (*Diascorea rotundata*), *Trop. Sci.* **44**: 190 - 195.

Steve, J. (2004). Improving starch for food and industrial applications, *Curr. Opin. Plant Biol.* **7**: 210 - 218.

Stute, H. (1992). Hydrothermal modification of starches: the difference between annealing and heat-moisture treatment, *Starch/Stärke* **44**: 205 - 214.

Symecko, C.W., Rhodes, C. T. (1997). The Effect of compaction force and type of pregelatinized starch on the dissolution of acetaminophen, *Drug Dev. Ind. Pharm*. **23**: 229 - 238.

Taggart, P. (2004). Starch as an ingredient: manufacture and application. In: Eliassion, A. C. (ed.) *Starch in food: structure, function and applications.* Woodhead Publishing Limited and CRC Press LLC, New York, pp. 363 - 392.

Tarvainen, M., Peltonen, S., Mikkonen, H., Elovaara, M., Tuunainen, M., Paronen, P., Ketolainen, J., Sutinen, R. (2004). Aqueous starch acetate dispersion as a novel coating material for controlled release products, *J. Control. Release* **96**: 179 - 191.

Torruco-Uco, J., Betancur-Ancona, D. (2007) Physicochemical and functional properties of makal (Xanthosoma yucatanensis) starch, *Food Chemistry* **101**: 1319–1326.

Tsegaye, A., Struik, P.C. (2003). Growth, radiation use efficiency and yield potential of enset (*Ensete ventricosum*) at different sites in southern Ethiopia. *Ann. appl. Biol.* **142**: 71 - 81.

USP XXII/NF XVII (1990). United states Pharmacopeial Convention, Inc., Rockville, Maryland.

Valle, G., Boch, D.Y., Colonna, P., Vergned, B. (1995). The extrusion behavior of potato starch, *Carbohydr. Polym.* **28**: 255 - 264.

Vilivalam, V. D. Illum, L., Iqbal, K. (2000). Starch capsules: an alternative system for oral drug delivery, *Pharm. Sci. Tech. Today* **3**: 64 - 69.

Waliszewski, K. N. Aparicio, M. A., Bello, L. A., Monroy, J. A. (2003). Changes of banana starch by chemical and physical modification, *Carbohydr. Polym.* **52**: 237 - 242.

Wells, J. (2002). Pharmaceutical preformulation: the physicochemical properties of drug substances. In: Aulton, M. E. (ed.), *Pharmaceutics: The science of dosage form design*, 2nd ed., Harcourt, Churchill living stone, London, pp. 113 - 151.

Wootton, M., Bamunuarachchi, A. (1978). Water binding capacity of commercial produced native and modified starches, *Starch/Starke* **30**: 306 - 309.

Yüksel, N., Karata, A., Baykara, T. (2003). Comparative evaluation of granules made with different binders by a fluidized bed method. *Drug Dev. Ind. Pharm.* **29**: 387 - 395.

Zubair, S., Esezobo, S., Pilpel, N. (1988). The effect of interacting variables on the tensile strength disintegration, and dissolution of paracetamol tablets, *J. Pharm. Pharmacol.* **40**: 278 - 281.

Zuluaga, M.-F., Baena, Y., Mora, C.-E., D'León, L,-F. (2007). Physicochemical characterization and application of Yam (*Dioscorea cayenensis-rotundata*) starch as a pharmaceutical excipient, *Starch/Stärke* **59**: 307 - 317.

Zuo, J. Y., Knoerzer, K., Mawson, R., Kentish, S., Ashokkumar, M. (2009). The pasting properties of sonicated waxy rice starch suspensions, *Ultrason. Sonochem.* **16**: 462 - 468.

Declaration

I, the undersigned, declare that this is my original work and has not been presented for a degree in any university.

Name: Abrham Wondimu

Signature: _____

This thesis has been submitted for examination with my approval as a university advisor.

Name: Prof. Tsige Gebre-Mariam

Signature: _____

Place and date of submission: Addis Ababa, Ethiopia, April, 2010.