ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

PHYSICOCHEMICAL CHARACTERIZATION OF ACID MODIFIED DIOSCOREA STARCH AND ITS EVALUATION AS DIRECTLY COMPRESSIBLE EXCIPIENT AND DISINTEGRANT IN TABLET FORMULATIONS

By
Bilal Tessema (B. Pharm)

May, 2014

Addis Ababa, Ethiopia

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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

By
Bilal Tessema (B. Pharm)

Under the supervision of Prof. Tsige Gebre-Mariam and Dr. Anteneh Belete,
Department of Pharmaceutics and Social Pharmacy, School of Pharmacy,
College of Health Sciences, Addis Ababa University

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Bilal Tessema (B. Pharm)

Department of Pharmaceutics and Social Pharmacy
School of Pharmacy

Approved by:

Name	Signature	Date
Prof. Tsige Gebre-Mariam (Advisor)	_____	May 02, 2014
Dr. Anteneh Belete (Advisor)	_____	May 02, 2014
Dr. Fitsum F. Sahle (Examiner)	_____	May 02, 2014
Dr. Nisha Mary-Joseph (Examiner)	_____	May 02, 2014

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ACRONYMS

ANOVA:	Analysis of Variance
AMDS:	Acid Modified Dioscorea Starch
API:	Active Pharmaceutical Ingredient
BP:	British Pharmacopoeia
CL:	Chain Length
DP:	Degree of Polymerization
FTIR:	Fourier Transform Infrared
NC:	Number of Chains
NDS:	Native Dioscorea Starch
PVP:	Polyvinylpyrrolidone
SD:	Standard Deviation
SNNPR:	South Nation Nationalities and People Regional state
RH:	Relative Humidity
RPM:	Revolution Per Minute
USP/NF:	United State Pharmacopoeia/National Formulary
UV:	Ultra Violet

ABSTRACT

Starch is one of the most important and flexible food ingredients possessing value added attributes for innumerable industrial applications. *Dioscorea abyssinica* (Fam. Dioscoreaceae) is a potential source of starch for large scale production in Ethiopia. Starch is usually modified either chemically or physically to augment its convenience for industrial use. The choice of excipients remains a critical factor in pharmaceutical formulations. Acid modified dioscorea starch (AMDS) has been prepared by hydrolyzing with 6% (w/w) HCl solution at ambient conditions and evaluated as a multifunctional excipient i.e, its direct compressibility and disintegrant effect in tablet formulations. Some of the physicochemical properties of AMDS such as; densities, flow, swelling power, percentage solubility, moisture sorption, and compactability were determined and compared to those of native dioscorea starch (NDS) and Starch 1500®. The comparative direct compressibility and disintegrant effects of these starches in tablet formulations were also studied using paracetamol as a model drug and the resulting tablets were evaluated for their physico-mechanical properties. The results indicated that both swelling power and percent solubility of the starches were found to increase with increase in temperature; AMDS showed higher percent solubility 68.53%. Spray dried AMDS exhibited free flowing property with 21.37 ± 1.39° angle of repose and 13.24 ± 0.76 g/sec flow rate. The compaction study revealed that the tensile strength and disintegration time of the compact increases and percent friability decreases as compression force increases. The lubricant sensitivity test showed that spray dried AMDS and Starch 1500® tablets could be used with acceptable tablet characteristics up to 1% and 0.5% of magnesium stearate concentration, respectively. With regard to dilution potential, the spray dried AMDS could accommodate up to 40% paracetamol with acceptable criteria. The results also indicated that tablets prepared with AMDS and Starch 1500® exhibited comparable characteristics. An increase in concentration of AMDS and Starch 1500® as disintegrant provided tablets with increased crushing strength and decreased disintegration time and friability. 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 AMDS can be used as an alternative directly compressible excipient and disintegrant in tablet formulations.

Keywords: Dioscorea starch; acid modified starch; spray drying; tablet; directly compressible excipient; disintegrant; lubricant sensitivity, dilution potential, *D. abyssinica*.

1. INTRODUCTION

1.1. Starch

Starch is a semi-crystalline biopolymer that serves as a carbohydrate reserve in many plants, including cereals, roots, tubers, seeds, and fruits. Starch granules can vary in shape, size, structure, and chemical composition, depending on the origin of the starch (Elessandra & Alvaro, 2011). Chemically, starch is a polymer composed of glucose molecules that are linked together in two different forms. Amylose, which makes up 20-30% of normal starch, is an essentially linear molecule in which the glucose units are joined end-to-end by α [1→ 4] glucosidic linkage (Fig 1.1 A). Amylopectin is the major component of starch (comprising 70–80%) and is a much larger branched molecule consisting of much shorter chains of α [1→ 4] D-glucose residues connected by α [1→ 6] D-glucosidic linkages (Fig 1.1 B) (Hongsheng *et al*., 2009; Odeku & Akinwande, 2011). 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).

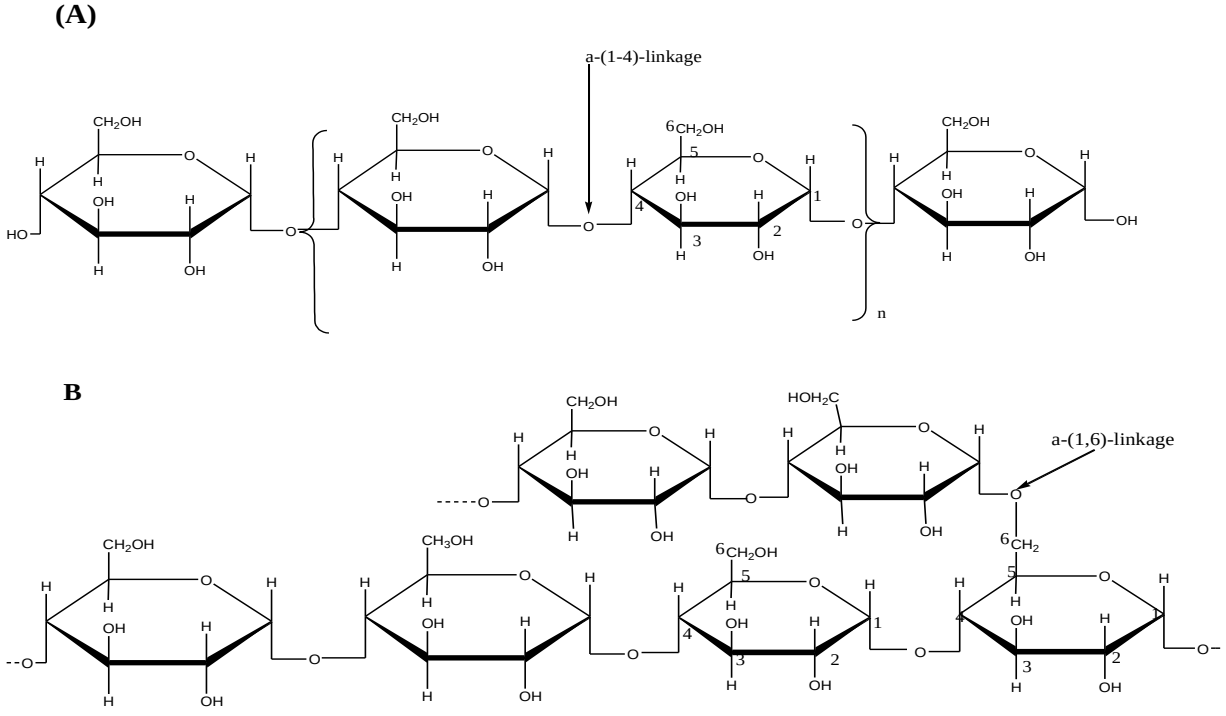


Figure 1.1: The chemical structure of (A) Linear amylose starch molecule and (B) branched amylopectin starch molecule.

Variations in the fine structure, including average degree of polymerization (DP), average number of chains (NC), average chain length (CL), and the chain length distribution profile can lead to different physicochemical properties in starch granules (Lu *et al*., 1997). Structural and physicochemical characteristics of starches are related to their botanical sources. Starch structural characteristics such as amylose content, branch chain length distribution of amylopectin, phosphate monoester, phospholipids and lipid contents affect their functional properties (Peroni *et al.*, 2006).

Starch is a versatile and useful polymer not only because it is a cheap; and natural material but also because of the ease with which its physicochemical properties can be altered through chemical or enzyme modification and/or physical treatment. Hence, a great deal of attention has been devoted to starch and its derivatives mainly in the context of its application in the food, plastics and pharmaceutical industries (Steve, 2004).

1.2. Dioscorea plant and its starch

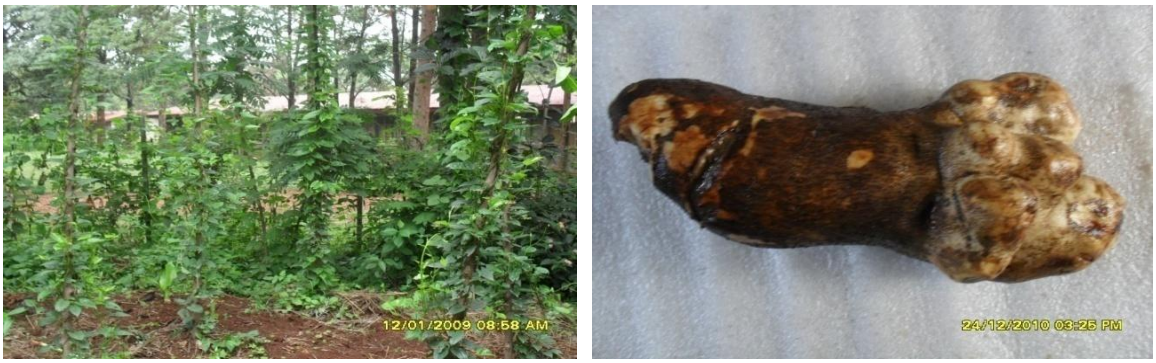
1.2.1 Overview of dioscorea plant

Yam belongs to the genus Dioscorea, representing more than 600 species worldwide (Muluneh *et al*., 2008). Yam (Dioscorea spp) is widely cultivated in the tropical and subtropical regions of the world and is known for its high carbohydrate and medicinal value (Riley *et al*., 2008). Starch is the main carbohydrate reserve in yam tubers, accounting for 70 - 80% of the dry weight (Okunlola *et al*., 2009). Yam starch occurs as granules, consisting of amylose (10–30%) and amylopectin (70–90%) molecules (Riley *et al.*, 2008).

1.2.2 Dioscorea abyssinica

Dioscorea abyssinica (Fam. Dioscoreaceae) is a climber plant twining to the right, with a herbaceous stem and a large tuber. It is cultivated during the raining season in the south, west and the south-west highlands of Ethiopia. Tubers of dioscorea have long been used for food, as they are rich in starch. Locally, dioscorea is commonly known by its vernacular name "Boyna", which is equivalent to the common English name "yam". When the tuber is horizontally directed under the soil, it can grow up to 30 cm in length and 20 cm in thickness (Gebre-Mariam and Schmidt, 1998).

The chemical composition, amylose content and physico-chemical properties of dioscorea starch (*Dioscorea abyssinica*, Fam. Dioscoreaceae) from Ethiopia have been investigated by Gebre-Mariam and Schmidt (1998). The proximate composition of the starch on dry weight basis was found to be 0.1 % ash, 0.5 % protein, 1.0 % fat and 98.4 % starch. The amylose content was estimated to be 29.7%.



A B

Figure 1.2: Dioscorea plant in the garden (A) and tuber (B).

1.3 Modification of starches

Native starches are inherently unsuitable for most applications due to certain undesirable characteristics such as poor solubility, low mechanical properties, and instability at high temperature, pH, and shear during processing (Chiu and Solarek, 2009). The basis of starch modification lies in the improvement of its functional properties by changing the physical and chemical properties of native starch (Omojola *et al*, 2011). Hence, it is always reasonable to modify the starch to meet the demanding technological needs of today (Rudrapatnam, 2005). Starch modification can overcome these shortcomings by means of altering the structure and affecting the hydrogen bonding of amylose and amylopectin in a controllable manner to enhance and extend its application (Kittipongpatana *et al*., 2006; Nattapulwat *et al*., 2009; Wang *et al.*, 2009). Various starch-modification methods: chemical, physical, enzymatic, or a combination thereof, are employed to create new starch products with specific or improved properties (Brouillet *et al.*, 2010).

1.3.1 Physical modification of starches

Starches can be physically modified by various methods in order to enhance their positive attributes and/or to minimize their defects. Pregelatinization (BeMiller & Lafayette, 1997), radiation, sonication (Zuo *et al*., 2009) and heat-moisture treatment (Chung *et al*., 2009) are some of the physical methods used for starch modification.

1.3.2 Chemical modification of starches

Chemical modification involves alteration of functional groups the starch molecule, resulting in markedly altered physico-chemical properties (Chiu and Solarek, 2009). 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 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), acid-thinning, or cross-linking (Bemiller, 1997).

1.4 Acid modified starch

1.4.1 Acid modification of starch

The technique of acid hydrolysis has been used extensively in the food, textile and paper industries for many years to produce soluble thin-boiling starch. Acid modified starches are produced commercially by hydrolyzing the starches with hydrochloric or sulfuric acid at temperatures below the gelatinization temperatures of the starch for a period of time (Wang *et al.*, 2007). The extent of hydrolysis depends on the starch consistency, acidity of the medium, hydrolysis temperature and duration of hydrolysis **(**Omojola *et al.*, 2011). Acid hydrolysis of starch involves the cleavage of the glucosidic bonds between the monomeric units which involves both protonation of the glycosidic oxygen and addition of water to yield the reducing sugar end group (D-glucose) of the starch (Odeku & Akinwande, 2011).

It was reported that the acid hydrolysis on all starches occurred in two steps: the first one, with high hydrolysis rate, was characterized by a quick degradation of the amorphous part; whereas the second step, with lower hydrolysis rate, was characterized by a higher resistance of the

ordered structure of the granules (Franco *et al.*, 2002, Srichuwong *et al.*, 2005). As acid-ethanol quickly permeates into the amorphous areas of the starch granules acting on both 1-6 α -bond and 1-4 α -D-linkage and the more organized areas are slowly hydrolyzed (Jayakody & Hoover, 2002).

1.4.2 Properties of acid modified starch

Wang and Wang (2001) studied the physicochemical properties of acid tinned corn, potato and rice starches. They found that acid modification changed the physicochemical properties of starches without destroying its granule structure. Acid hydrolysis diminishes the molar mass, increases the solubility and relative crystallinity of starch since acid preferentially attacks the amorphous regions, while the crystalline regions remain intact (Omojola *et al*., 2011).

1.5 Tablet excipients

1.5.1 Direct compressible excipient

The term "direct compression" is used to define the process by which tablets are compressed directly from the powder blends of active ingredient/s and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved (Shangraw, 1988). It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets (Gohel, 2005). The direct compression process is mainly influenced by the properties of the excipients (Mukesh *et al*., 2011). The properties of excipients that ensure a robust and successful directly compressible adjuvant are good flowability (Chowdary *et al*., 2012), good compressibility (Odeku *et al*., 2008), low lubricant sensitivity (Odeniyi *et al*., 2008; Timuçin *et al.*, 2010), and high dilution potential (Philip *et al*., 2010). Due to bad flowability and high lubricant sensitivity of natural starches they are not suitable to serve as dry binders during direct compression (Jivraj *et al*., 2000). In order to improve the tableting properties of starches, various modified starches have been prepared, for example by acid modification (Atichokudomchaia *et al*., 2004).

1.5.2 Tablet disintegrants

Several mechanisms have been proposed to rationalize the action of disintegrant and these include porosity and capillary action, rate of water uptake into the tablet, swelling of

disintegrant particles (Nachaegari & Bansal, 2004; Lateef & Kolawole, 2009) gas release whenever the tablet contacts aqueous fluids (effervescent tablets) (Jones, 2008).

Starch was the first disintegrating agent widely used in tablet manufacturing. Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation (Debjit *et al*., 2010). 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" (Gebre-Mariam *et al*., 1996b). These super-disintegrants are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength (Debjit *et al*., 2010). But due to the higher cost of super-disintegrants, pharmaceutical formulators are looking for alternative cheaper disintegrants. Thus disintegrant characteristic of acid modified starch from various botanical sources have been examined in tablet formulation (Odeku & Akinwande, 2011).

1.6 The present study

Ethiopia has variety of plant species which can be used as a source of starch for various purposes including *Enset* (Gebre-Mariam and Schmidt, 1996a), *Dioscorea abyssinia* (Gebre-Mariam and Schmit, 1998), Godare (Adane *et al*., 2006) and Cassava (Paulos *et al*., 2009). Hence, in countries which import starch for industrial applications such as Ethiopia, it is desirable to exploit starch from cheaper indigenous sources.

The choice of excipients becomes critical in terms of its functionality as regards direct compression and rapid disintegration abilities (Philip *et al*., 2010). Only few polymers possess multiple functionalities especially in terms of good flow, direct compression and enhanced disintegration abilities. Thus, novel polymer biomaterials with effective multifunctional properties are continually being sought for drug delivery purposes (Watering *et al*., 2005). Many pharmaceutical scientists have focused their attention on the production of

multifunctional excipients with enhanced performance to meet the needs of formulation experts in terms of costs of production, enhanced excipient functionality and quality of tablets. The development of new excipients to date has been market driven to achieve the desired set of functionalities (Moreton, 1996). The development of new excipient having multi-functionality, directly compressible and disintegrant functionality based on domestically and abundantly available materials, such as starch, proposes a way to decrease the amount of imported materials and cost of production. It also benefits the cultivators of starch-containing plants.

In the present work *Dioscorea abyssinica* starch was isolated and modified with hydrochloric acid and evaluated as a potential pharmaceutical directly compressible excipient and disintegrating agent in paracetamol tablets. 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.

1.7 Objective of the study

1.7.1 General objective

To prepare and characterize Acid Modified Dioscorea Starch (AMDS) and evaluate its potential as directly compressible excipient and disintegrant in tablet formulation.

1.7.2 Specific objectives

- To prepare AMDS and to determine its acid recovery yield;
- To characterize some physico-chemical properties of AMDS;
- To assess the suitability of AMDS as directly compressible excipient;
- To formulate and evaluate tablets containing AMDS by direct compression and wet granulation methods;
- To compare the properties of tablets prepared with AMDS with those of NDS and Starch 1500®.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Plant materials

Dioscorea abyssinica (boyena) tubers were collected from local boyena cultivating farmer in Sawula, Gamo Gofa Zone, SNNPR.

2.1.2 Chemicals and solvents

Croscarmellose sodium, NF (Ac-Di-Sol®) (FMC Corporation, USA), distilled water, hydrochloric acid, magnesium stearate (Bulvinos Chemicals Ltd, England), paracetamol powder (China Associate Co Ltd, China), potassium dihydrogen phosphate (Sörensen, Leuren, Denmark), povidone (China associate Co. Ltd, China), sodium metabisulphite (Guangzhou Jinhaunda Chemical Reagent Co. Ltd, China), sodium chloride (Oxford Laboratory, Mumbai, India), and Starch 1500® were used as received.

2.2 Methods

2.2.1 Starch isolation

Starch isolation was carried out following the method described by Gebre-Mariam and Schmidt (1996a, 1998). Yam tubers were washed, peeled and trimmed to remove defective parts. The tubers were then sliced, diced and blended. The flesh was suspended in large quantities of distilled water containing 0.075 % (w/v) of sodium metabisulphite. The material was allowed to settle, and the sedimented starch was repeatedly washed with sodium metabisulphite solution until the supernatant was free from colouring materials and the suspension was 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 Acid modification of *Dioscorea abyssinica* starch

Two grams (dry basis) of native dioscorea starch was hydrolyzed by suspending in 10 ml of 6% (w/w) HCl solution at room temperature for 1, 2, 4, 8, 16, and 32 days. After hydrolysis, the suspension was neutralized with 10 ml of 10% (w/v) sodium hydroxide solution to terminate the hydrolysis. The starch slurry was washed several times with distilled water until the pH value of the filtrate was 7. The resulting acid hydrolyzed starch was dried in a hot air oven at 40 $^{\circ}$C for 24 h and then powdered using mortar and pestle. All the starches were passed through a 224 μm mesh sieve and packed in closed plastic bags until use (Odeku & Akinwande, 2011).

2.2.3 Preparation of spray dried native and acid modified starches

Starch solutions of native and acid modified starches were prepared and transferred through a peristaltic pump and feed to the spraying nozzle at pumping rates of 7.5 ml/min into the drying chamber of the apparatus (BÜCHI, B-290, Switzerland). A flow of heated air (105 ^{o}C) set at 25 m^3/h aspirated by a pump induces the quick evaporation of the solvent from the drops, leading to the formation of solid particles. The spray dried particles were collected in a reservoir attached to a cyclone, cooled down to room temperature and stored in sealed vials (Bilancetti *et al*, 2010).

2.2.4 The recovery yield of the starch after acid hydrolysis

The recovery yield of the starch after acid hydrolysis was calculated using the following equation:

$$Recovery\ yield\ (\%) = \left(\frac{W_a}{W}\right) X100 \quad \ldots\ldots\ldots (2.1)$$

Where; W and W_a are weight of starch (dry basis) before and after acid hydrolysis, respectively.

2.2.5 Measurement of starch crystallinity

The starch samples were oven dried at 50 $^{\circ}$C overnight and sieved with 160 µm mesh size sieve (Louis & Peter, 2011). The samples were then placed in the cavity of a disc sample holder of the diffractometer. The measurements were done using a Bruker AXS diffractometer (Bruker-AXS, Advanced D8, Germany) operating in the 2Θ modes using computer software

(Operational Soft Diffract^{+} 2000). A Cu target tube operated at a setting of 40 kV (35 mA) in the range of 4 - 64^{o} of 2Θ with single crystal graphite monochromator was used.

2.2.6 Infrared spectroscopy

Possible drug-excipient interaction was investigated by Fourier Transform Infrared (FTIR) spectroscopy. The FTIR spectra of paracetamol powder, AMDS and physical mixture of paracetamol powder and AMDS (1:1) at 500 – 4000 cm^{-1} wave length were recorded using FTIR-8400S, Shimadzu, Japan.

2.2.7 Characterization of starches and Starch 1500®

2.2.7.1 Determination of density and related properties

Thirty grams of starch were transferred into 250 ml measuring cylinder. The volume occupied by the starch powder 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 2.2 and Hausner ratio using Equation 2.3 (Schüssele and Bauer-Brandl, 2003).

$$Carr's\ index\ (\%) = \left(\frac{\rho_T - \rho_B}{\rho_T} \right) X100 \quad \text{..... (2.2)}$$

$$Hausner\ Ratio = \left(\frac{\rho_T}{\rho_B} \right) \quad \text{..... (2.3)}$$

Where, ρ_B is bulk density and ρ_T is tapped density.

2.2.7.2 Flow rate and angle of repose

Flow rate and angle of repose of the starch powders were determined using the funnel method. Starch powder (30 g) was allowed to flow through funnel having a 15 mm aperture from a 10 cm height. The duration of flow was recorded in seconds. The average diameter and height of the powder piles formed were recorded (Olayemi *et al*., 2008). The determination was done in triplicate. Flow rate was determined using the relationship; Flow rate = m/t; where m is mass in gram and t is time in sec. Angle of repose was calculated according to Equation 2.4.

$$\textit{Angle of repose } (\Theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{..... (2.4)}$$

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

2.2.7.3 Swelling power and solubility

Swelling power and solubility were determined in accordance with the methods described by Daramola *et al* (2006). Starch (0.5 g) was weighed directly into a pre-weighed centrifuge tubes, and 10 ml distilled water was added in each tube. The tubes were then kept in a thermostatically controlled water bath (GFL®, D3006, Germany) at temperature of 25, 35, 45, 55, 65, 75, and 85 ^{o}C for 30 min with frequent mixing at 5 min intervals. The tubes were then cooled to room temperature and centrifuged at 3000 rpm for 15 min, and the supernatant was carefully decanted and the weight of the residues (Ws) obtained were weighed. The supernatants were dried to constant weight (W_1) in an oven (Kottermann® 2711, Germany) at 105 ^{o}C for 12 h. All determinations were done in triplicate. The water solubility index (WSI) and swelling power (SP) were calculated as follows:

$$WSI = \left(\frac{W1}{0.5}\right) X 100\% \quad \text{..... (2.5)}$$

$$SP = \left(\frac{W_S X 100}{0.5X(100 - WSI)}\right) \text{..... (2.6)}$$

2.2.7.4 Moisture content

The moisture content was determined as per the methods described by Olayemi *et al* (2008). Accordingly, 2 g of the starch was weighed into weighed, dried petridish and heated in an oven (Kottermann®2711, Germany) at a temperature of 130 ^{0}C for about 2 h. The sample was then taken out of the oven, weighed and the moisture content was reported as percentage. It was determined in triplicate.

$$\textit{Moisture content (\%)} = \left(\frac{W_i - W_f}{W_i}\right) X 100 \quad \text{..... (2.7)}$$

Where W_i and W_f are the weight of starch before and after drying, respectively.

2.2.7.5 Moisture sorption pattern

The moisture sorption properties of the starches were determined in triplicate based on a method described by Riley *et al.* (2006). Pyrex desiccators containing distilled water, saturated solution of sodium chloride to prepare 80% relative humidity and appropriate concentration of sodium hydroxide to prepare 20, 40 and 60% relative humidity were prepared at room temperature. Dioscorea starches (NDS and AMDS) and Starch 1500® were pre-dried in an oven (Kottermann® 2711, Germany) for 4 h at 120 °C. Two grams of the pre-dried starches were placed on dried and weighed petridish and transferred to a particular RH chamber. Samples were equilibrated for one month at room temperature. The weights after a month were recorded and the moisture sorption of each was calculated as the weight difference of the starches before and after equilibration under a given RH.

2.2.8 Compaction property of starches

The compaction property of starches was evaluated following the method described by Atichokudomchai & Varavinit (2003). Compacts of NDS, AMDS and Starch 1500® were produced by compressing 99.5% starches (as filler) and 0.5% magnesium stearate (as lubricant). The mixture was blended for 5 min in a Turbula® mixer (Willy A. Bachofen AG, Turbula® 2TF, Basel, Switzerland) then, 10 mm flat surfaced compacts of the starches were produced with 400 mg size by compressing the powder blends at different compression force adjusted to give tablets (formulated using the standard unlubricated Starch 1500®) of crushing strength 40, 60, 80, 100 and 120 N on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany). The compacts were evaluated for crushing strength, tensile strength, percent friability and disintegration time.

2.2.9 UV calibration curve of paracetamol

A stock solution containing 200 µg/ml of paracetamol in phosphate buffer of pH 5.8 was prepared. From this stock solution, seven different concentrations (3, 4.5, 6, 7.5, 9, 10.5 and 12 µg/ml) were prepared. The UV absorbance readings of these solutions were measured at 243 nm using UV/Visible spectrophotometer (Cecil, CE1021, England). Phosphate buffer (pH 5.8) was used as a blank. The absorbance versus concentration of the solutions was plotted and a calibration curve with a linear regression equation of: $Y = 65.12X + 0.00532$ (where Y is the

absorbance and X is the concentration in mg/ml) and correlation coefficient of 0.9991 were obtained (Figure 2.1). The procedure was repeated three times.

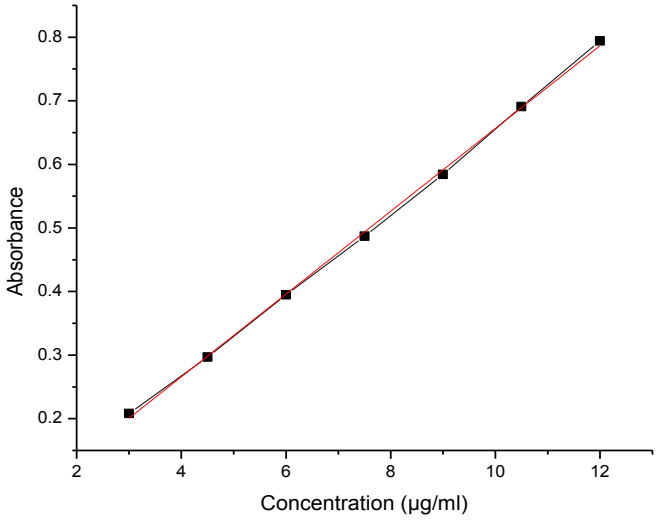


Figure 2.1: Absorbance of paracetamol in phosphate buffer (pH 5.8) at 243 nm with 95% confidence bands for the mean; (r^2 = 0.9991).

2.2.10 Granulation

Batches of paracetamol granules were prepared by conventional wet granulation method as per the formula given in Table 2.1. To each batch of paracetamol granulation, paracetamol and an appropriate quantity of povidone solution was added as a granulating agent and mixed for 20 min in mortar to form dough mass. The wet mass was then passed through wet granulator with 1.6 mm sieve and dried in an oven (Kottermann® 2711, Germany) at 40 °C for 18 h. Then, the dried granules were dry screened by passing them through a 1 mm sieve. The dried granules were stored in glass container until compressed into tablets.

Table 2.1: Paracetamol tablet formulations containing NDS, AMDS or Starch 1500® as disintegrant.

Ingredients	**Formulations**											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paracetamol	91%	88.5%	87%	83.5%	91%	88.5%	87%	83.5%	91%	88.5%	87%	83.5%
PVP	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%
NDS	5%	7.5%	9%	12.5%	-	-	-	-	-	-	-	-
AMDS	-	-	-	-	5%	7.5%	9%	12.5%	-	-	-	-
Starch 1500®	-	-	-	-	-	-	-	-	5%	7.5%	9%	12.5%
Magnesium stearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

2.2.11 Tablet compression

2.2.11.1 Compression of granules into tablet

For evaluation of the starches (native and acid modified) as disintegrant, the starches were mixed with the granules for 10 min in a Turbula® mixer (Willy A. Bachofen AG, Turbula® 2TF, Basel, Switzerland) at 49 rpm, the mixing was further continued for 5 min by adding magnesium stearate, which was pre-sieved with a sieve having pore size of 224 µm. The mixture were compressed into tablets at a fixed compression force (adjusted to give tablets with a crushing strength 70 ± 2 N) on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. The tablets were stored for 24 h at room temperature in glass containers to allow for elastic recovery and hardening before characterization.

2.2.11.2 Direct compression

Lubricant sensitivity of spray dried NDS and spray dried AMDS was evaluated according to the method described by Parrott (1989). Tablets containing spray dried NDS, spray dried AMDS or Starch 1500® were compressed with magnesium stearate at concentrations of 0, 0.5%, 1%, 1.5%, 2% (w/w). Fifty grams batch of each mixture was blended for 5 min in a Turbula® mixer (Willy A. Bachofen AG, Turbula® 2TF, Basel, Switzerland) then, 10 mm flat surfaced compacts of the starches were produced with 400 mg size by compressing the powder

blends at a fixed compression force (adjusted to provide tablets with crushing strength 70 ± 2 N for the standard unlubricated Starch 1500®) on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany).

Dilution capacity of spray dried NDS and spray dried AMDS was evaluated as per the method described by Mitrevej *et al* (1996). All the components (Table 2.2) except magnesium stearate were blended in a Turbula® mixer (Willy A. Bachofen AG, Turbula® 2TF, Basel, Switzerland) for 10 min followed by addition of lubricant (magnesium stearate) and further blended for 5 min. The blend was then compressed into tablets with 400 mg size at a fixed compression force (adjusted to provide tablets with crushing strength 70 ± 2 N for the standard unlubricated Starch 1500®) on eccentric tablet machine (EK0 Korsch, 7891, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches.

Table 2.2: Paracetamol tablet formulations spray dried NDS, spray dried AMDS or Starch 1500® as filler-binder.

Ingredients	**Formulations**											
	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Paracetamol	20%	30%	40%	50%	20%	30%	40%	50%	20%	30%	40%	50%
Ac-Di-Sol	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%
S.D NDS	75.5 %	65.5 %	55.5 %	45.5 %	-	-	-	-	-	-	-	-
S.D AMDS	-	-	-	-	75.5 %	65.5 %	55.5 %	45.5 %	-	-	-	-
Starch 1500®	-	-	-	-	-	-	-	-	75.5 %	65.5 %	55.5 %	45.5 %
Magnesium stearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%

S.D Spray dried

2.2.12 Evaluation of tablets

2.2.12.1 Weight, thickness and diameter

From each batch, 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 and diameter (fixed 10 mm) were measured using sliding caliper scale (Nippon Sokutei, Japan).

2.2.12.2 Crushing strength

After 24 h of production, ten tablets were taken from each batch and the crushing strengths of the tablets were determined using hardness tester (Schelinguer, 2E/205, Switzerland).

2.2.12.3 Tensile strength

The radial tensile strength was calculated using the data obtained from crushing strength, diameter, and thickness of tablets using Equation 2.8.

$$\sigma_x = \frac{2F}{\pi \mathrm{DT}} \qquad \text{(2.8)}$$

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

2.2.12.4 Friability

Ten tablets of known weights 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 25 rpm for 4 min. The tablets were then dedusted and weighed, and the percent loss in weight was calculated as friability.

2.2.12.5 Disintegration test

Disintegration test was carried out according to USP30/NF 25 specification (2007). Six tablets of known weight from each batch 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.

2.2.12.6 Dissolution test

The dissolution test was done according to the USP/NF specification using dissolution apparatus Type II (ERWEKA, DT600, Germany), stirred at a rate of 50 rpm with 900 ml phosphate buffer (pH 5.8) as the dissolution medium at 37 ± 0.5 ^{o}C. Ten ml aliquots of the dissolution medium were removed at 5, 10, 15, 20, 30, 45 and 60 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 a sink condition. One ml of the filtered samples was diluted to 25 or 50 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.

2.2.12.7 Statistical analysis

Statistical analysis was carried out using Analysis of Variance (ANOVA) with statistical software Origin 8 (OriginLab^{TM} Corporation, USA). Tukey multiple comparison test was used to compare the individual difference in the physicochemical 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 & DISCUSSION

3.1 Acid recovery yield

The recovery yield of the acid-hydrolyzed starch is presented in Fig. 3.1. The recovery yield of acid-hydrolyzed starch decreased gradually with increasing acid hydrolysis time. Hydrolysis was rapid for about the first 8 days and much slower from 8 to 32 days. The initial rapid hydrolysis phase was mainly attributed to the hydrolysis of the amorphous phase, and the later slower phase to the hydrolysis of the crystalline phase. The amorphous areas of the starch granules have a looser structure than the crystalline regions which is easier for attack by the hydrogen ions (Wang & Wang, 2001; Franco *et al.*, 2002; Jiang *et al.*, 2011). Based on the result hydrolysis of day eight was selected for further studies since hydrolysis of starch for the first eight days is rapid but beyond day eight is very slow and can be considered as constant.

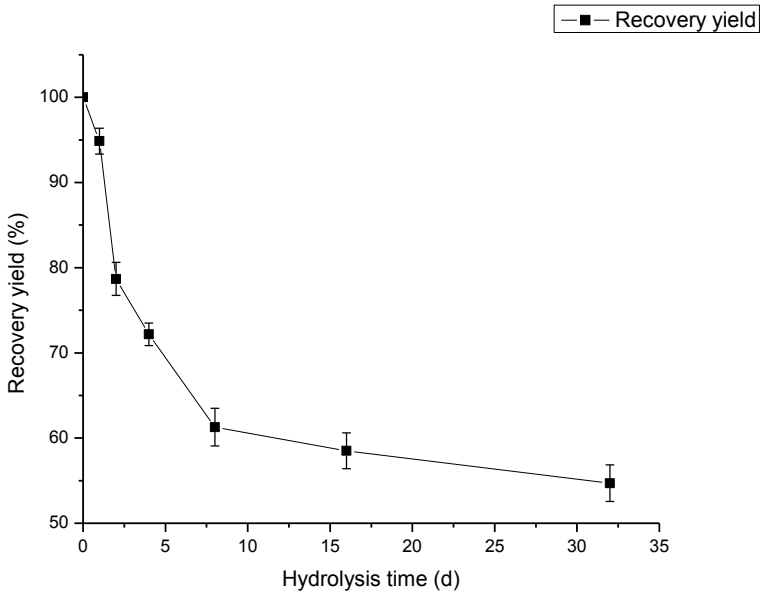


Figure 3.1: Recovery yield of dioscorea starch after acid hydrolysis.

3.2 Crystallinity of the starches

The X-ray diffraction patterns of starch allow a characterization of the crystal packing in the native granules (Wang *et al.*, 2007). The X-ray diffraction patterns of native and acid modified dioscorea starches are shown in Figures 3.2a & b, respectively. The diffractograms showed that both NDS & AMDS exhibit maximum peaks at 17.5° 2Θ. The other significant peaks of NDS were at 5.2°, 15.5°, 17.8°, 22.7° and 24.2° 2Θ. In similar fashion, AMDS also showed significant peaks at 5.3°, 15.6°, 17.5°, 22.7° and 24.3° 2Θ which correspond to the expected B-

type pattern (Wang *et al.*, 2007). No significant difference was observed between the X-ray diffraction patterns of unmodified and acid modified starches, which indicated that acid modification did not induce transition of the crystal type.

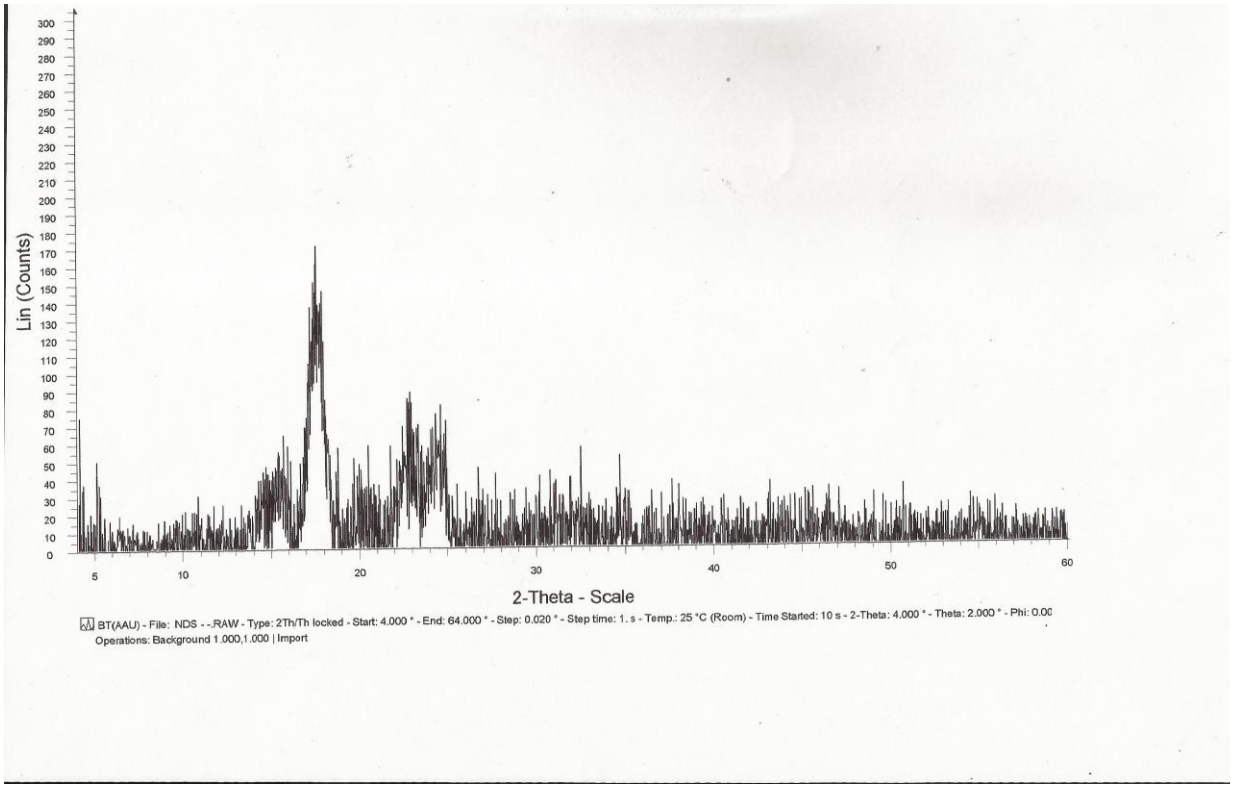


Figure 3.2a: X-ray diffractogram of native dioscorea starch.

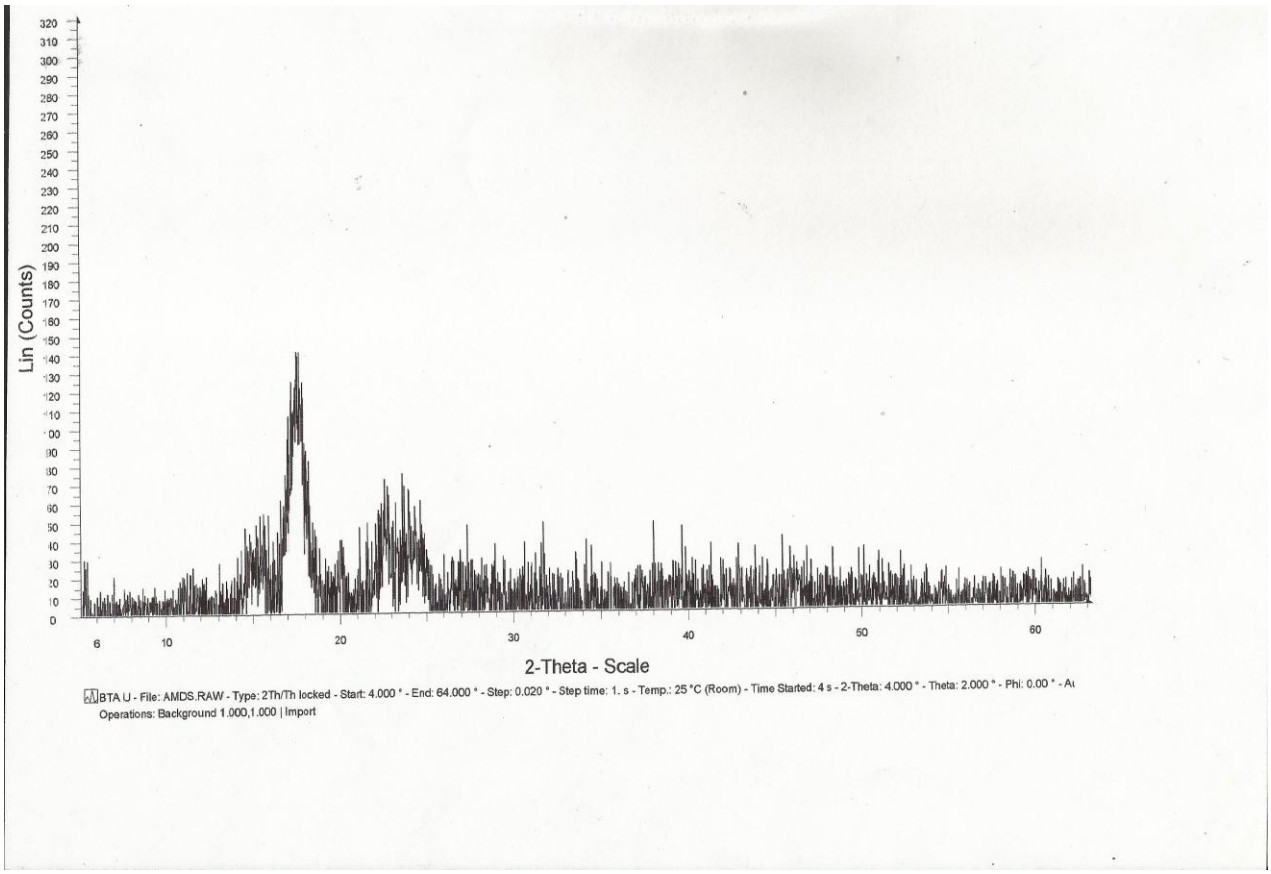


Figure 3.2b: X-ray diffractogram of acid modified dioscorea starch.

3.3 FTIR

FTIR spectroscopy is a quick and simple technique for identifying compounds. The IR spectrum of a given compound is unique and characteristic. This is because IR spectrum distinguishes between the different kinds of bonds in a molecule (Philip *et al.*, 2010). The FTIR spectral results are displayed in Figs. 3.3a, b & c. FTIR spectra of paracetamol, showed characteristic O-H, N-H, C=O (amide) stretching bands at 3323.12 cm^{-1}, 3157.25 cm^{-1}, 1654.81 cm^{-1}, respectively. Whereas, amide II band, C-N-H group and para-disubstituted aromatic rings at 1562.23 cm^{-1}, 1259.43 cm^{-1} and 837.05 cm^{-1}, respectively, were also observed (Bashar, 2010).

The FTIR spectra (Fig.3.3b) of the AMDS sample showed characteristic broad band at about 3350 - 3500 cm^{-1} which is associated with hydroxyl groups stretching vibration. The band at 2727 and 2686 cm^{-1} are characteristics of -CH_2 stretching vibration. A prominent band at 1631

cm^{-1} was present, which can be assigned to deformation vibrations of the hydroxyl groups (CH_2OH) in water. The characteristic peaks appeared between 1261 and 1203 cm^{-1} attributed to -CO and C-C bond stretching. The two peaks of 1155 and 1080 cm^{-1} were associated to represent the C-O-H bending, whereas, bands at 979, 933 and 862 cm^{-1} represent (C-O-C) skeletal mode vibration of glycosidic linkage. The bands between 765 and 520 cm^{-1} represent skeletal mode of pyranose ring (Sekkal *et al.*, 1995, Kemas *et al.*, 2012). All characteristic peaks of paracetamol were observed in the FTIR spectra of physical mixture of paracetamol & AMDS. These results suggest that there were no possible interactions between paracetamol and AMDS indicating compatibility of the paracetamol with AMDS.

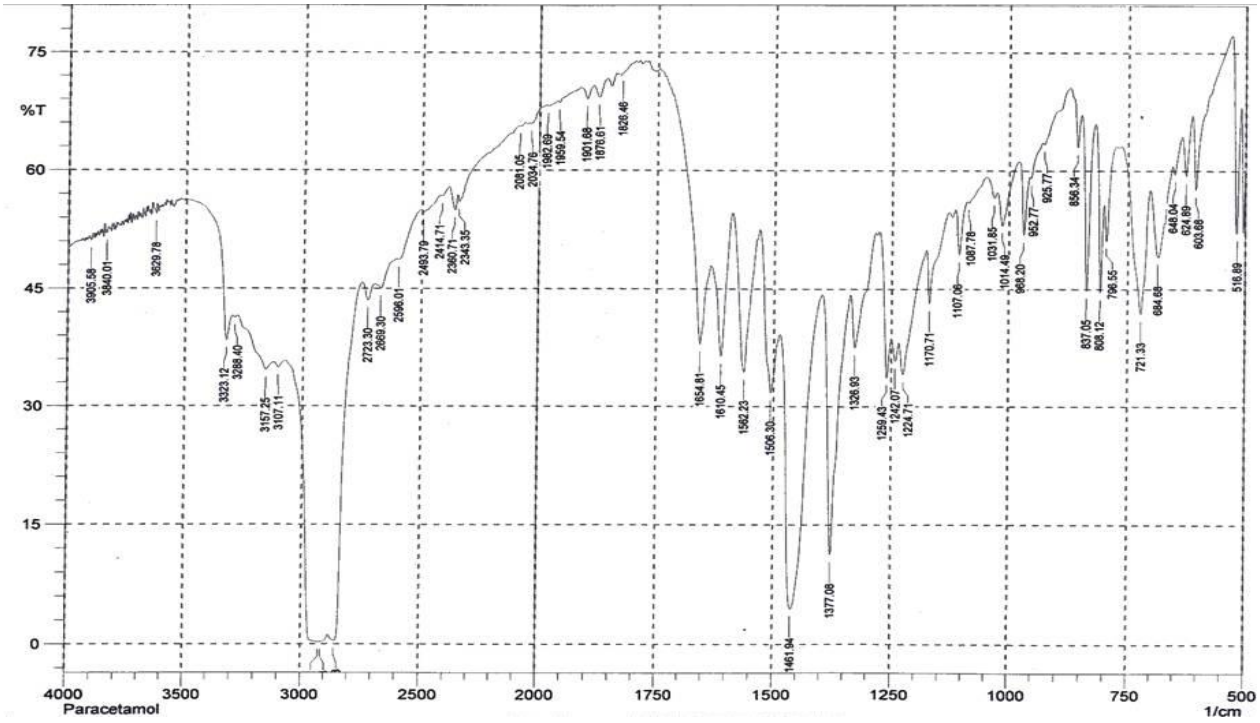


Figure 3.3a: FTIR spectra of paracetamol powder.

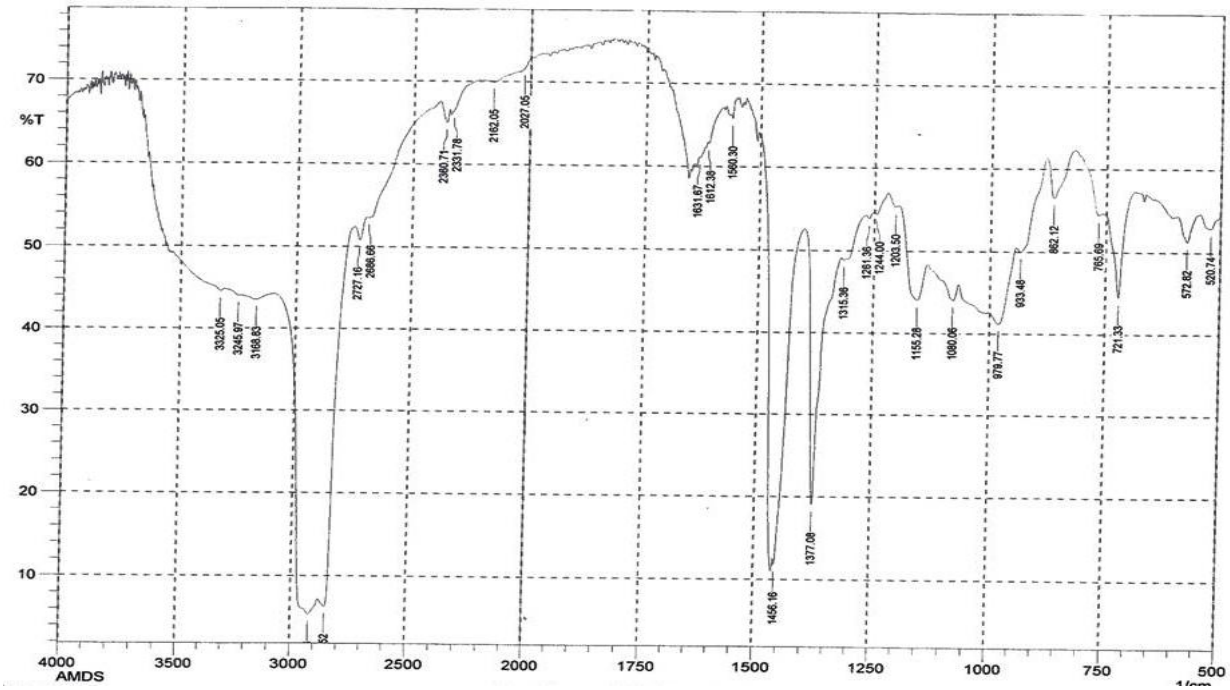


Figure 3.3b: FTIR spectra of AMDS.

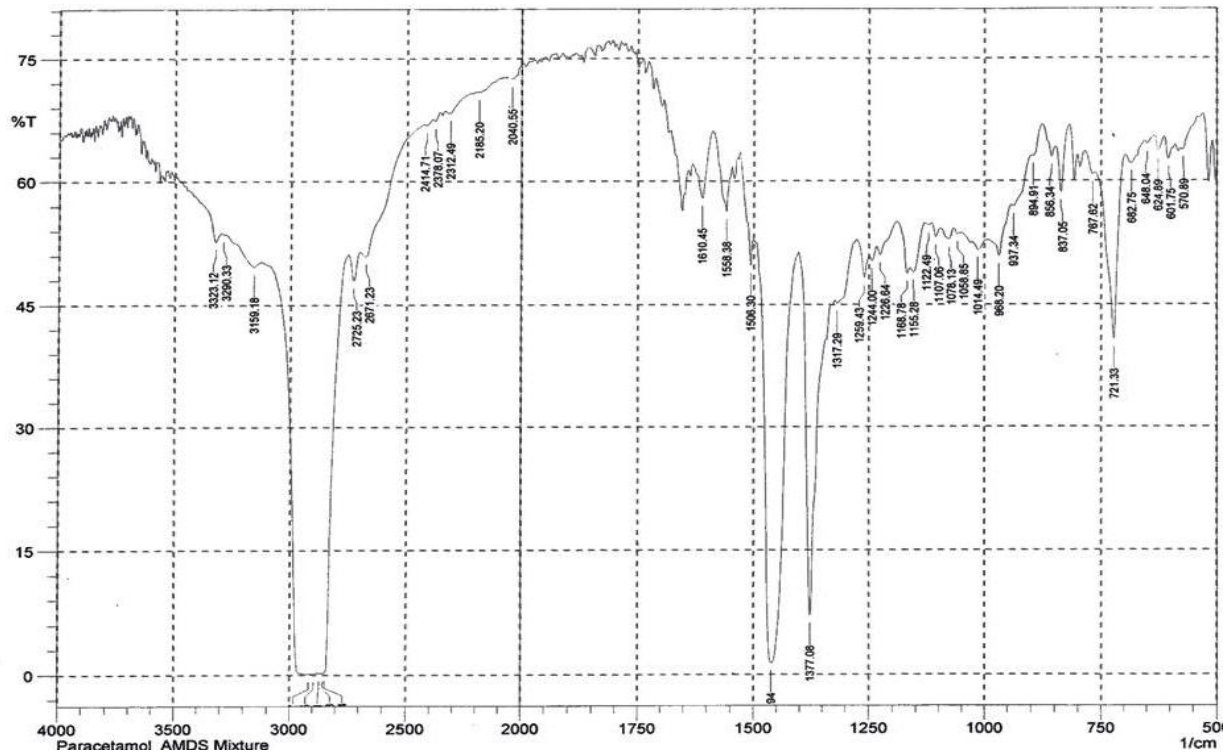


Figure 3.3c: FTIR spectra of physical mixture of paracetamol & AMDS.

3.4 Powder properties of starches

Table 3.1**:** Powder properties of dioscorea starches and starch 1500®.

Powder property	NDS	S.d NDS	O.d AMDS	S.d AMDS	Starch 1500®
Moisture content (%)	15.33 ± 0.09	9.86 ± 0.11	11.53 ± 0.14	9.37 ± 0.10	11.07 ± 0.05
Bulk density (g/ml)	0.61 ± 0.02	0.60 ± 0.02	0.65 ± 0.01	0.67 ± 0.01	0.67 ± 0.02
Tapped density(g/ml)	0.72 ± 0.14	0.71 ± 0.05	0.75 ± 0.00	0.76 ± 0.01	0.77 ± 0.18
Hausner ratio	1.19 ± 0.03	1.18 ± 0.02	1.16 ± 0.23	1.13 ± 0.15	1.14 ± 0.24
Carr's index (%)	15.37 ± 0.15	15.5 ± 0.08	13.23 ± 0.39	11.95 ± 0.06	11.99 ± 0.13
Angle of repose (degree)	*	25.93 ± 0.89	*	21.37 ± 1.39	20.13 ± 1.02
Flow rate (g/sec)	*	7.13 ± 0.94	*	13.24 ± 0.76	12.23 ± 0.93

Mean ± SD (n = 3), * angle of repose & flow rate could not be determined, S.d spray dried, O.d oven dried

The powder properties of NDS, Spray dried NDS, Oven dried AMDS, Spray dried AMDS and Starch 1500® are presented in Table 3.1. The rank order of the moisture content is NDS > oven dried AMDS > Starch 1500® > spray dried NDS > spray dried AMDS. The NDS appears to have the maximum moisture content this might be because it was air dried in comparison to oven dried AMDS (at 40 °C) and spray dried NDS and AMDS. In this study, all of the starches have moisture content within the limits recommended for commercial starches of 10-20 % (Soni *et al*., 1993). Reduction in moisture content reduces chances of microbial spoilage and hydrolysis thereby increasing the stability and shelf-life of the derivatives (Lateef & Kolawole, 2009; Kemas *et al.*, 2012).

Bulk and tapped densities give an insight on the packing arrangement of particles and the compaction profile of a material (Russel and Lantz, 2005). The bulk density of a powder describes its packing behavior during the various unit operations of tableting such as die filling, mixing, granulation and compression. Higher bulk density is advantageous in tableting due to reduction in the fill volume of the die (Okunlola & Odeku, 2009). In this study, the rank order of bulk and tapped density was Starch 1500® > spray dried AMDS > oven dried AMDS > NDS > spray dried NDS. The particle size and shape of the starches may be responsible for the differences in the density values which affect the packing arrangement of the powder particles. AMDS (both oven & spray dried) showed comparable bulk and tapped density with that of

Starch 1500® ($p > 0.05$). Spray drying did not bring statistically significant change on the bulk and tapped densities of AMDS and NDS ($P > 0.05$).

The flow properties of a powder are essential to determine its suitability as a direct compression excipient. Hausner ratio and Carr's index are considered as indirect measurement of powder flowability (Lateef & Kolawole, 2009). The Hausner ratio previews the degree of densification which could occur during tabletting, the lower the Hausner ratio, the lesser the tendency for densification to occur (Jubril *et al*., 2012). Carr's index is affected by the particle shape, surface characteristics, particle size, size distribution and the packing configuration adopted by the powder during the bulk densities determination (Achor *et al*., 2010). 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). NDS showed significantly higher Carr's index and Hausner ratio than AMDS and Starch 1500® ($P < 0.05$) indicating poor compressibility and flow property of NDS. The Carr's index of spray dried AMDS showed a value comparable to that of Starch 1500® ($P < 0.05$). The Hausner ratios of spray dried AMDS and Starch 1500® were found to be comparable ($P < 0.05$). The above results indicated that spray drying improves the flow property of dioscorea starch.

Formulations which exhibit good flow characteristics have potentials of ensuring short production time and uniform drug content, which are some of the desirable qualities in tabletting (Itiola & Pilpel, 1991; Chowdary *et al.*, 2012). The angle of repose θ could be used as a qualitative measure of the cohesiveness or the tendency of powdered or granulated materials to flow. Such uniformity of flow will minimize weight variations in produced tablets (Okunlola & Odeku, 2009). The angle of repose is affected by the particle size distribution and it usually increases with a decrease in particle size (Podczeck & Sharma, 1996). Flow is graded as excellent, good, fair and passable for angle of repose 25-30°, 31-35°, 36-40° and 41-45° respectively (Mukesh *et al*., 2011). Comparable angle of reposes were recorded for spray dried AMDS (21.37 ± 1.39) and Starch 1500® (20.13 ± 1.02) ($P < 0.05$); characteristics of material with excellent flow property (Mukesh *et al*., 2011). Moreover, direct measure of the flow property showed that spray dried AMDS and Starch 1500® have comparable flow rates of 13.24 ± 0.76 and 12.23 ± 0.93, respectively ($P < 0.05$). Better flow properties of the spray dried

AMDS might be attributed to spray drying process since the method is known to produce free flowing spherical particles (Limwong *et al.*, 2004). On the other hand, both air NDS and oven dried AMDS did not flow through the funnel and thus, angle of repose and flow rate could not be determined. The poor flowability might be due to the presence of greater amounts of fines in its particle structure and irregular non-spherical shape of particles (Olowosulu1 *et al.*, 2011).

3.5 Solubility and swelling power

The solubility and swelling power measurements were carried out at different temperatures between 25 and 85 °C (Figures 3.4 and 3.5). As clearly indicated in Figure 3.4 there is rapid increase in the swelling power of all the starches studied as the temperature increases up to 75 °C, and of slower rates above 75 °C. This might be due to the loss of granules structures of the starch at higher temperature resulting in a slower swelling capacity (Chang *et al.*, 1995). This type of behaviour was also observed by Iromidayo *et al.* (2010). It can be seen that the swelling profile of AMDS (both oven & spray dried) is significantly lower than that of the native starch ($p > 0.05$). These could be due to acid hydrolysis which reduces polymer chain length and hydrolyse the amorphous of the starch granules (Wang & Wang, 2001; Odeku and Picker-Freyer, 2009; Himjyoti *et al.*, 2011). Significant change was not observed in the swelling power of NDS and AMDS before and after spray drying ($p < 0.05$).

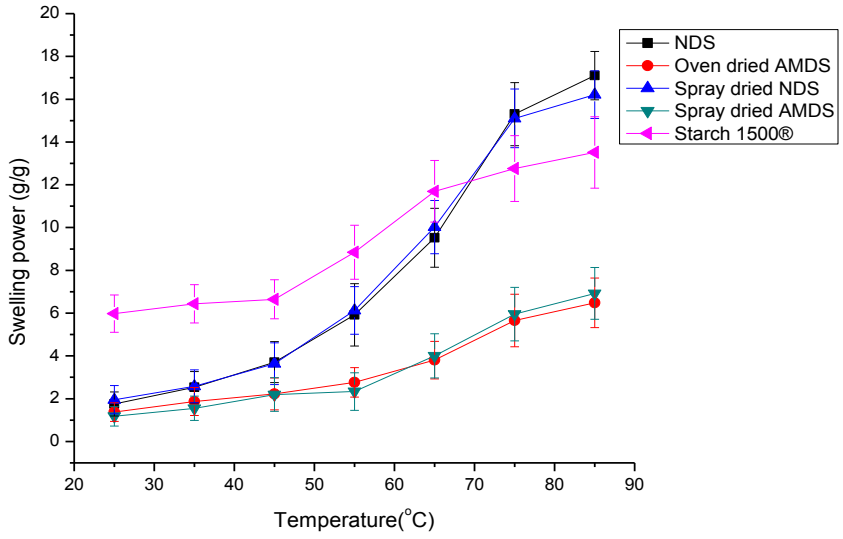


Figure 3.4: Swelling power of dioscorea starches (native and acid modified) and Starch 1500® at different temperatures.

As depicted in Figure 3.5, the AMDS (both oven & spray dried) are more soluble than native starches. The increase in solubility values may be due to shortening of the chain lengths of the starch, corresponding to the weakening of the hydrogen bonds (Osunsami *et al.*, 1989). It has also been reported that the high solubility of acid modified starch with increasing temperature may be due to the loss of granular structure and release of amylose fraction of the starch, as the amylose molecules are preferentially solubilized and leached from swollen granules (Stone *et al.*, 1984). Similar results were also reported by Odeku & Picker-Freyer (2009) and Mutungi *et al.* (2010). NDS and Starch 1500® showed slight solubility increase as compared to AMDS ($p < 0.05$). The solubilities of NDS & AMDS were not affected by drying method since comparable solubilities were found between air and spray dried NDS as well as between oven and spray dried AMDS ($P > 0.05$).

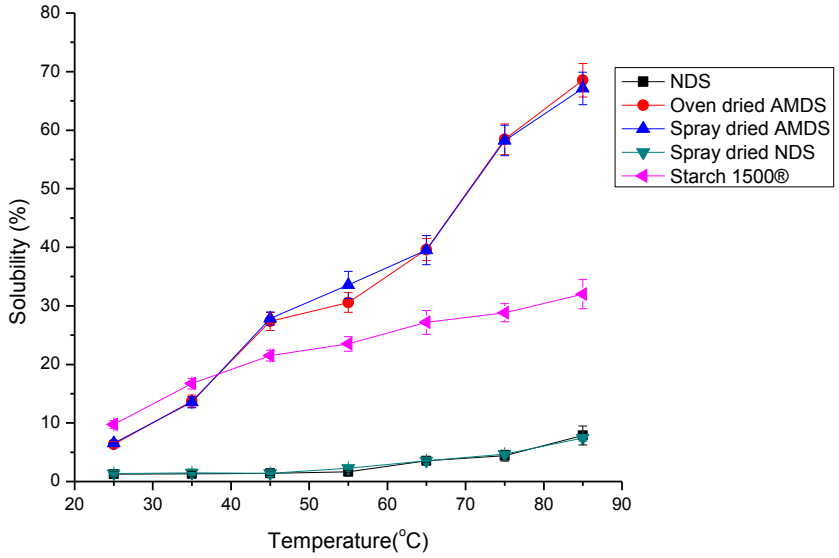


Figure 3.5: Solubility of dioscorea starches (native and acid modified) and Starch 1500® at different temperatures.

3.6 Moisture sorption property

The interaction of moisture with pharmaceutical solids is highly crucial to an understanding of water-based processes especially as it relates to their physicochemical and functional properties (Hancock and Zografi, 1997; Mangel, 2000). Moisture sorption profiles of starches are shown in Figure 3.6. Generally, all the starches showed gradual increase in moisture

sorption between 20 and 80% RH followed by a sharp increase reaching a maximum at 100% RH. The gradual increase between 20 and 80% RH may be due to the gradual saturation of the monomolecular layer of the polymer powder beds at these RHs. The sharp increase in moisture uptake occurred between 80 and 100% RH which corresponds to the saturation of monomolecular layer and subsequent diffusion of excess moisture (absorption) into bulk powder bed (York, 1981). Percent moisture sorbed ranged between 9.36 ± 1.87% at low (20 %) RH to over 47.67 ± 2.11 % at high (100 %) RH. The moisture sensitivity order with 100 % RH was Starch 1500® > Spray dried AMDS > Oven dried AMDS > Spray dried NDS > Air dried NDS. The moisture sorption profiles of NDS (air & spray dried) and AMDS (oven & spray dried) equilibrated at various humidity levels were similar ($P < 0.05$). Both acid modification and spray drying process did not affect the moisture sensitivity of dioscorea starch. 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).

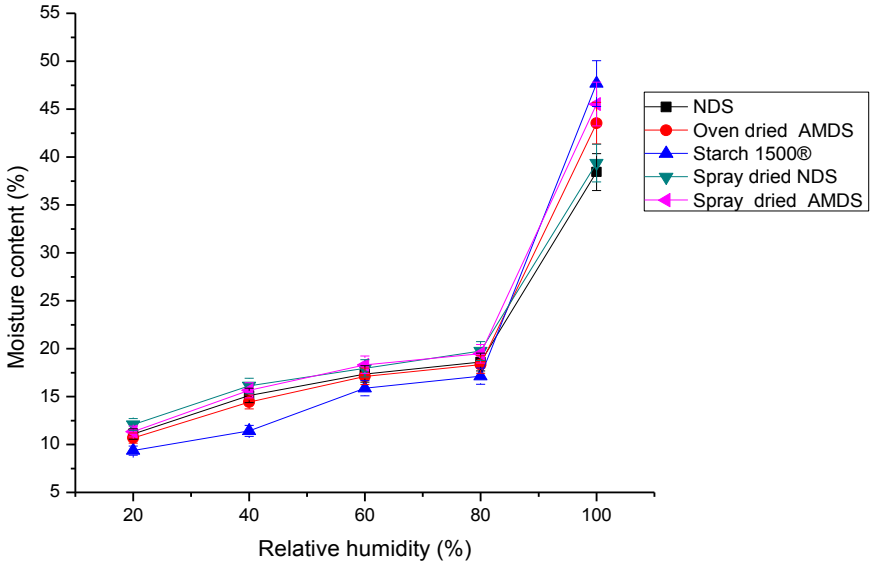


Figure 3.6: Moisture sorption patterns of dioscorea starches (native and acid modified) and Starch 1500®

3.7 Compaction property of starches

Compactibility is the ability of a powder bed to form a mechanically strong tablet. Compaction property of starch has been 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 different compression forces were adjusted indirectly using crushing strength of tablets formulated using the standard unlubricated Starch 1500®.

Table 3.2: Compaction properties of NDS, AMDS and Starch 1500®

Excipients	Parameters	CF1	CF2	CF3	CF4	CF5
NDS (lubricated with 0.5%)	Crushing strength (N)	21.2 ± 3.9	32.4 ± 4.8	39.3 ± 3.5	44.7 ± 5.1	49.7 ± 4.9
	Tensile strength (Kg/cm^2)	2.6 ± 0.5	4.2 ± 0.6	5.2 ± 0.45	5.9 ± 0.65	7.0 ± 0.7
	Friability (%)	*	*	3.21 ± 0.6	2.86 ± 0.4	1.92 ± 0.2
	Disintegration time (min)	1.18 ± 0.5	2.53 ± 0.8	3.05 ± 0.6	4.1 ± 1.1	4.3 ± 1.3
AMDS (lubricated with 0.5%)	Crushing strength (N)	37.3 ± 3.1	58.2 ± 4.6	72.5 ± 3.5	85.7 ± 3.9	93.5 ± 4.7
	Tensile strength (Kg/cm^2)	5.3 ± 0.25	8.1 ± 0.65	10.5 ± 0.50	12.7 ± 0.6	14.5 ± 0.75
	Friability (%)	1.57 ± 0.3	0.92 ± 0.2	0.85 ± 0.1	0.64 ± 0.2	0.51 ± 0.1
	Disintegration time (min)	3.34 ± 1.1	4.93 ± 0.8	5.72 ± 1.3	6.35 ± 0.9	6.93 ± 1.2
Starch 1500® (lubricated with 0.5%)	Crushing strength (N)	34.1 ± 2.7	53.3 ± 4.2	67.8 ± 3.8	81.2 ± 4.1	88 .1 ± 4.5
	Tensile strength (Kg/cm^2)	4.7 ± 0.35	7.4 ± 0.6	9.8 ± 0.55	12.2 ± 0.6	13.4 ± 0.91
	Friability (%)	1.65 ± 0.4	0.96 ± 0.2	0.89 ± 0.3	0.76 ± 0.2	0.62 ± 0.1
	Disintegration time (min)	6.18 ± 1.4	7.79 ± 1.5	9.85 ± 2.0	12.5 ± 1.4	14.6 ± 2.1
Starch 1500® (unlubricated)	Crushing strength (N)	42	61	78	101	118

* tablet breaks CF- Compression force

The data of crushing strength, tensile strength, friability and disintegration time of compacts of AMDS, Starch 1500®, NDS are shown in Table 3.2. The results showed that the crushing strength of tablets increased as compression force increases across the formulations. Crushing strength of AMDS is significantly higher than that of NDS ($p < 0.05$) across the formulations. This might be attributed to the high compressibility of AMDS. No significant difference was observed between the crushing strength of AMDS and Starch 1500® ($p > 0.05$).

Tensile strength is indicative of the bonding strength and may provide information about the laminating and capping tendencies of the material (Jain, 1999). As clearly indicated in Table 3.2 tensile strength increases as compression force increases. The rank order of tensile strength of the compacts in this study is AMDS > Starch 1500® > NDS. The high tensile strength of AMDS is attributed to acid hydrolysis of the amorphous regions resulting in a stronger packing under the application of compression force. Thus, the crystalline region would be forced closer together during compression which results in an increase in tablet strength. Study by Odeku and Picker-Freyer (2007) showed that native starch with high amylose content exhibited poorer compressibility and Atichokudomchai *et al*. (2001) reported that the crushing strength of starch compact/tablet increases due to the leaching out of amylose.

Regarding the percent friability, friability declined with increase in compression force of the compact. The compact of NDS formulated at CF1 and CF2 were broken during the test, moreover all of the friability results are greater than 1 % indicating the tablets were too soft to withstand the abrasion. The friability results of both AMDS and Starch 1500® were less than 1.0 % except formulation formulated at CF1. The relatively low value of friability of the starch compacts could be attributed to the higher strength of their compacts. The disintegration time increased with increase in compaction force for all the starches. Starch 1500® showed prolonged disintegration time than both NDS and AMDS which might be due to gelatinized starch impedes the penetration of water into the tablet.

3.8 Lubricant sensitivity of native and acid modified starches

In tablet compression, lubricants are used in powder form to reduce frictional forces at the interface between powder, granule and tablet surface with the die wall (Aoshima *et al.*, 2005). Without external lubricant addition tableting operations cannot be carried out. Inadequate lubrication due to friction and adhesion among powder particles leads to troubles in the manufacturing process and deterioration of productivity (Roberts *et al*., 2004; Aoshima *et al*., 2005). Because of the aforementioned reasons, determining level of lubricant is among the critical parameters in direct compression. The type, concentration, method of incorporation, time and conditions of mixing, and efficiency of lubricants affect many properties of the produced tablets such as tablet weight, crushing strength, friability, and disintegration time (Mollan & Celik, 1996; Otsuka *et al*., 2004). A good excipient should have low lubricant sensitivity, and should not adversely affect formulation properties (Hwang & Parrott, 1993). Hence tablets containing spray dried NDS, spray dried AMDS and Starch 1500® were compressed with magnesium stearate at concentrations of 0, 0.5, 1, 1.5 and 2% (w/w) to ascertain the effect of lubricant concentration on the tableting properties of spray dried NDS and spray dried AMDS.

3.8.1 Effect of lubricant concentration on crushing strength and friability

Under certain compression force, tablet strength depends on the area of intimate contact between particles of the tableting materials and the attractive forces between the particles over the entire contacting area (Jennifer *et al.*, 2010). The fine lubricant particles can interfere with the interactive bonding forces between the particles to be compressed thus interfering with the eventual strength of the resulting tablet (Jarosz & Parrott, 1984). The crushing strength and friability of tablets produced from spray dried NDS, spray dried AMDS and Starch 1500® at different lubricant concentrations are depicted in Figure 3.7 and 3.8, respectively. As shown in the figure the crushing strength values decreased as the concentration of lubricant increased. This might be due to the altered physical properties caused by the lubricant that created a waxy covering and prohibited inter-particulate forces from bonding (Mollan & Celik, 1996). The crushing strength of spray dried AMDS tablets were significantly higher than that of spray dried NDS and Starch 1500® tablets at all level of magnesium stearate concentrations. As clearly indicated in the figure addition of magnesium stearate up to 1% (w/w) the spray dried

AMDS powder provided hard tablets with an average crushing strength of 50.9 N. Hence, AMDS is able to accommodate up to 1% (w/w) of magnesium stearate concentration. However, it is noted that there is a significant decrease in tablet crushing strength for spray dried NDS and Starch 1500® with increasing magnesium stearate concentration. Moreover, spray dried NDS at 2% of magnesium stearate could not be formulated into tablet at the compression force used for tablet preparation. The above result indicated that spray dried AMDS has lower lubricant sensitivity as compared with both spray dried NDS and Starch 1500®, which make it suitable candidate for directly compressible excipient.

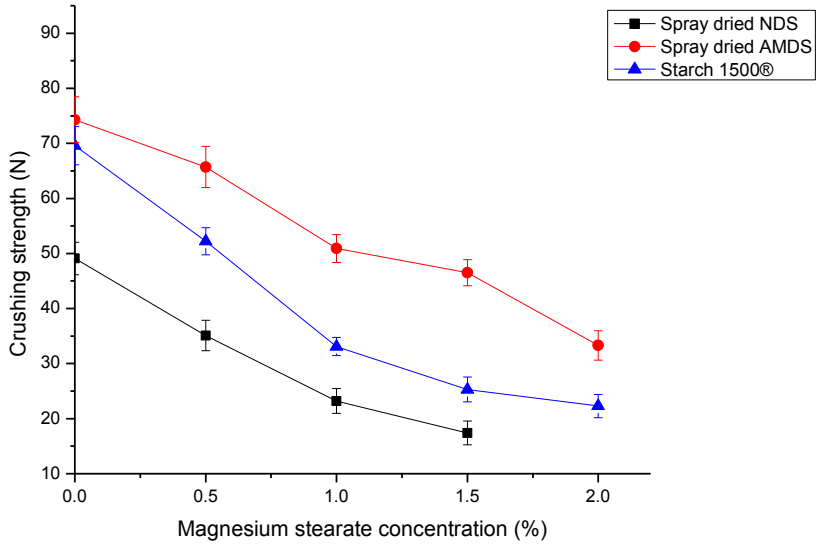


Figure 3.7: Crushing strength of spray dried NDS, AMDS and Starch 1500® tablets at different concentration of magnesium stearate.

Friability is the ability of a tablet to withstand the movement of shipping and handling without breaking or chipping (Sheskey *et al.*, 1995). Friability value less than 1% is considered acceptable (BP, 2009). Figure 3.8 shows friability profiles of spray dried NDS, spray dried AMDS and Starch 1500® at different magnesium stearate concentration. As clearly indicated in the figure tablets formulated from Starch 1500® at 0 and 0.5% magnesium stearate concentration and tablets containing spray dried AMDS at magnesium stearate concentration of 0 to 1% had acceptable friability values (< 1%) but spray dried NDS showed friability

values of > 1% in all magnesium stearate concentrations; Moreover tablets formulated with 1.5 % magnesium stearate concentration broke during friability evaluation. Furthermore, less friable tablets were obtained from spray dried AMDS than Starch 1500® at all levels of magnesium stearate concentration.

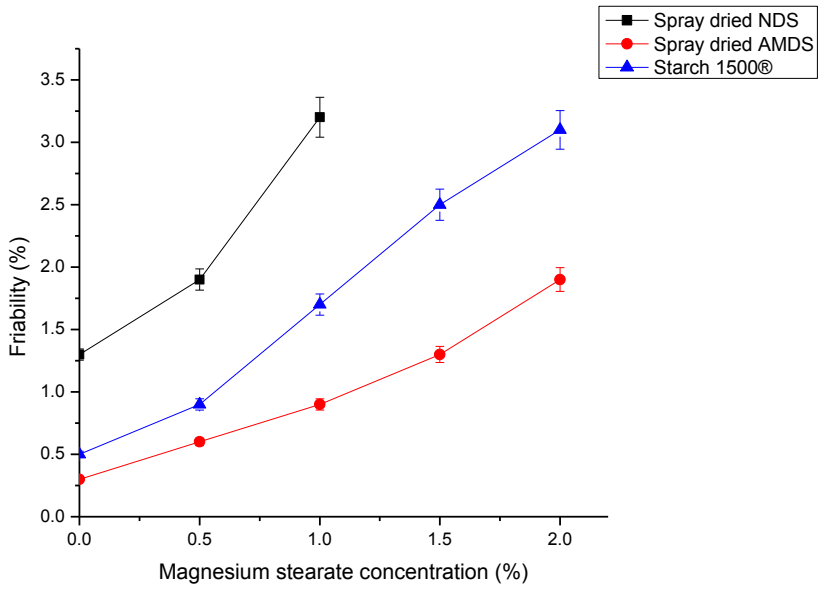


Figure 3.8: Friability of spray dried NDS, AMDS and Starch 1500® tablets at different concentration of magnesium stearate.

3.8.2 Effect of lubricant concentration on tensile strength

The tensile strengths of tablets produced from spray dried NDS, spray dried AMDS and Starch 1500® at different concentrations of magnesium stearate are presented in Figure 3.9. Generally, the tensile strengths decreased as the concentration of lubricant increased. This is attributed to the high extensibility of magnesium stearate; it spreads over the surface of the powder particles. This in turn prevents bonding among powder particles, giving low tensile strength and decrease in tablet hardness with increase in the concentration of magnesium stearate (Aoshima *et al.*, 2005). The tensile strengths of the tablets formulated from spray dried AMDS were higher than those of spray dried NDS and Starch 1500® at all levels of magnesium stearate concentration ($p < 0.05$).

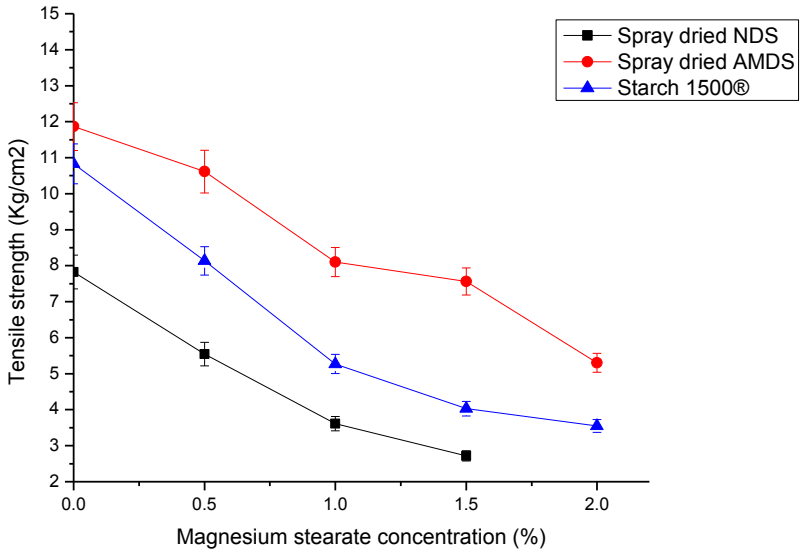


Figure 3.9: Tensile strength of spray dried NDS, spray dried AMDS and Starch 1500® tablets at different concentration of magnesium stearate.

3.8.3 Effect of lubricant concentration on disintegration time

Figure 3.10 shows the relationship between the lubricant concentration and disintegration time of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500®. One of the undesirable side effects of lubricant addition to pharmaceutical formulation is the prolongation of tablet disintegration time (Timucin &Murat, 2008). Generally, disintegration time increased with increased concentration of magnesium stearate. These results are in agreement with the result of Aoshima *et al*. (2005). This delayed disintegration might be due to the hydrophobic membrane that magnesium stearate forms on the surface of the powder particles which limits the hydration of tablets (Sameer *et al*., 2009). Tablets formulated from spray dried AMDS possess a markedly shorter disintegration period than Starch 1500®, though their strength is much higher. Relatively increased disintegration period of tablets formulated from Starch 1500® might be attributed to the formation of gel-like layer which is formed in combination with water (Jitka & Irena, 2011).

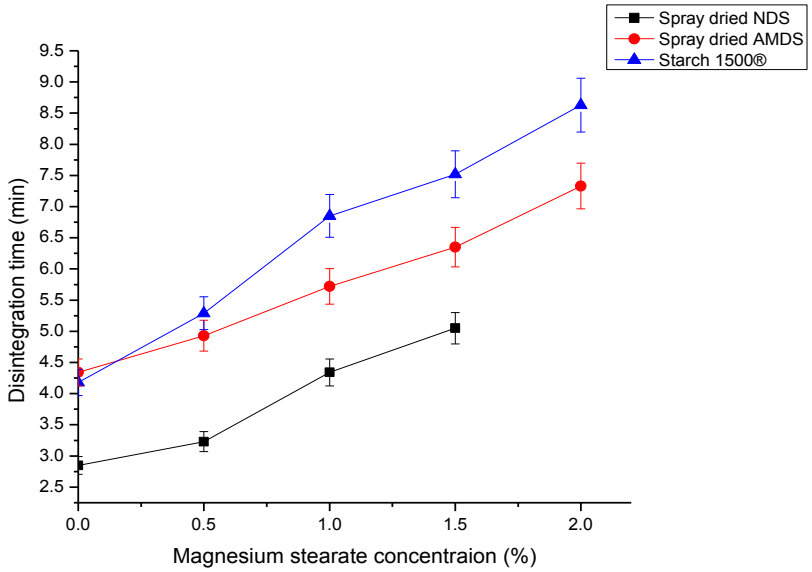


Figure 3.10: Disintegration time of spray dried NDS, spray dried AMDS and Starch 1500® tablets at different concentration of magnesium stearate.

3.9 Dilution potential

Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed into tablets with a given directly compressible excipient (Gohel, 2005). A directly compressible adjuvant should have high dilution potential so that the final dosage form has a minimum possible weight (John *et al*., 2013). In general, the dilution potential can be an indicator of the maximum amount of active pharmaceutical ingredient that can be compressed with the excipient, while still obtaining tablets of acceptable quality, i.e., acceptable crushing strength average of > 50 N, friability < 1.0 %, good disintegration time < 15 min, and must meet the requirement of Pharmacopeia weight variation limit test (Shittu *et al*., 2012). The model drug tablet formulations were designed to evaluate its dilution potential using 20%, 30%, 40%, 50 % paracetamol in 400 mg tablet formulation with spray dried NDS, spray dried AMDS and Starch 1500®. Due to the poor flowability, air dried NDS and oven dried AMDS were not selected for paracetamol formulation.

3.9.1 Weight variation and thickness

Table 3.3: Weight and thickness of paracetamol tablets formulated by direct compression method at different paracetamol concentrations.

Formulations	Paracetamol content (%)	Weight (g)	Thickness (mm)
F13	20	0.397 ± 0.00	3.81 ± 0.05
F14	30	0.401 ± 0.00	3.84 ± 0.10
F15	40	0.397 ± 0.00	3.89 ± 0.03
F16	50	0.400 ± 0.00	3.91 ± 0.05
F17	20	0.397 ± 0.00	3.75 ± 0.09
F18	30	0.401 ± 0.01	3.77 ± 0.03
F19	40	0.396 ± 0.00	3.79 ± 0.01
F20	50	0.402 ± 0.00	3.85 ± 0.01
F21	20	0.401 ± 0.00	3.79 ± 0.08
F22	30	0.398 ± 0.01	3.81 ± 0.07
F23	40	0.400 ± 0.00	3.85 ± 0.02
F24	50	0.398 ± 0.00	3.88 ± 0.03

Mean ± SD (n = 20)

It is a well-known fact that weight variation has a direct impact on the assay of the tablets. Moreover, it indicates homogenous distribution in the formulation (Rabia *et al*., 2008). The weight variation and thickness of tablets formulated by direct compression method is summarized in Table 3.3. The tablets are within acceptable range of weight variation (± 5%) which is the limit of the percentage deviation allowed by BP (2009) for tablets weighing 250 mg or more.

The mean tablet thickness of all the formulations did not show any significant variations ($p > 0.05$). However, there was slight weight variation and tablet thickness between the various batches of formulations; this might be related to the variations in powders density as well as compression behavior of the compacted material.

3.9.2 Crushing strength, tensile strength and friability

Crushing strength, tensile strength and friability of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500® at different concentrations of paracetamol are presented in Fig. 3.11, Table 3.4 and Fig. 3.12. Figure 3.11 shows the relationship between tablet strength and the amount (in percentage) of paracetamol that the starches can accommodate while still maintaining tablet properties. It can be seen that tablet strength declined with increasing amount of paracetamol until it reaches a point where the tablet strength, friability and the physical structure failed to meet tablets with acceptable properties (a minimum of 50 N crushing strength and < 1% friability) (Shittu *et al*., 2012). The crushing strength of spray dried AMDS tablets were hard enough up to 40% of paracetamol. In case of Starch 1500® tablets, crushing strength measurement was possible up to 40% of paracetamol concentration; but tablets with acceptable properties were obtained for formulations containing 20 and 30% of paracetamol concentration. Contrarily spray dried NDS doesn't meet tablets with acceptable properties in all the formulations. The crushing strength of spray dried AMDS tablets was significantly higher as compared to spray dried NDS and Starch 1500® tablets ($p < 0.05$) at all levels of paracetamol concentration. This might be due to the reduction of amylose content through acid hydrolysis possibly enhancing the close packing of amylopectin (Atichokudomchai *et al*., 2001).

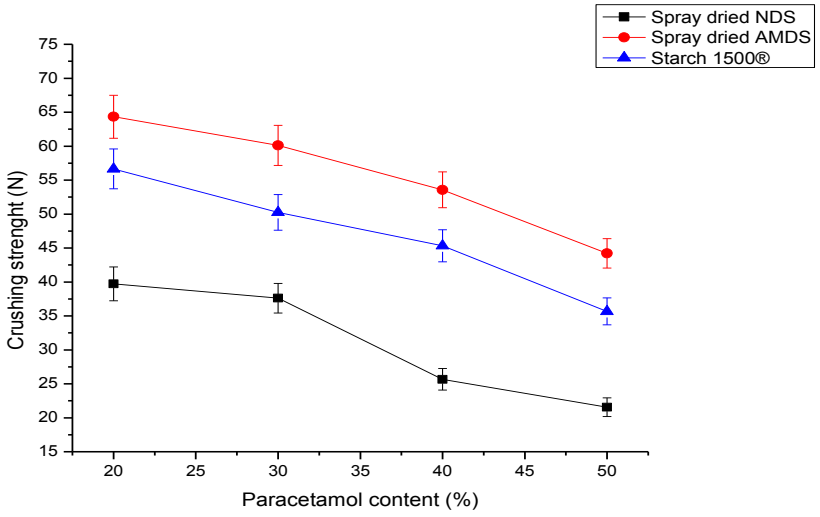


Figure 3.11: Crushing strength of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500® at different paracetamol concentrations.

Tablet tensile strength is an important property for safe transportation and handling. Insufficiently hard tablets, in addition to exhibiting the effects of excessive friability, are prone to breakage and chipping particularly during transportation (Gohel and Jogani, 2002). Tensile strength of spray dried NDS, spray dried AMDS Starch 1500® tablets are given in Table 3.4. Tensile strength decreases with increasing the concentration of paracetamol in all the formulations. Spray dried AMDS tablets showed highest tensile strength as compared to that of spray dried NDS and Starch 1500® at all levels of paracetamol concentration; as related to the high crushing strength of spray dried AMDS.

Table 3.4: Tensile strength of spray dried NDS, spray dried AMDS Starch 1500® tablets at different paracetamol concentration.

Formulations	Paracetamol content (%)	Tensile strength (kg/cm^2)
F13	20	7.24 ± 0.98
F14	30	6.21 ± 0.83
F15	40	4.62 ± 0.77
F16	50	3.93 ± 0.81
F17	20	12.61 ± 0.75
F18	30	11.26 ± 0.67
F19	40	10.61 ± 0.69
F20	50	8.97 ± 0.72
F21	20	10.36 ± 0.58
F22	30	8.97 ± 0.76
F23	40	8.16 ± 0.62
F24	50	6.98 ± 0.71

Figure 3.12 indicates all the friability values of spray dried AMDS tablets except for formulation that contain 50% of paracetamol were in the acceptable friability values. Whereas

Starch 1500® tablets showed acceptable friability values for formulations having 20 and 30% of paracetamol concentration. All of the formulations of spray dried NDS tablets showed friability values that are not acceptable. Moreover, formulations containing 40 and 50% of paracetamol concentration broke during friability testing. The low hardness values coupled with poor compressibility of paracetamol might contribute to high friability of spray dried NDS tablets. In general, a decrease in tablet hardness causes an increase in the friability of tablets. Conventional tablets that lose less than 1.0% of their weight are generally acceptable (BP, 2009).

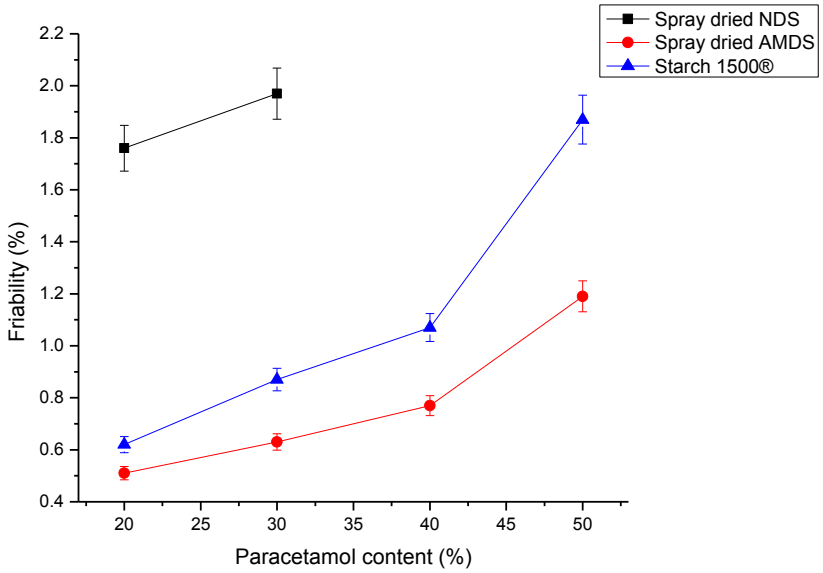


Figure 3.12: Friability of spray dried NDS, spray dried AMDS and Starch 1500® at different paracetamol concentrations.

3.9.2 Disintegration time of directly compressed paracetamol tablets

Disintegration exposes a greater surface area of tablets to the dissolution medium; hence it plays an important role in a tablet's dissolution before the active drug substance is finally released from the tablet's structure into the body (Lateef & Kolawole, 2009). Figure 3.13 shows the declining disintegration time of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500® with increasing paracetamol concentration. Reduction of disintegration time might be explained on the basis of tablet weakness with paracetamol content increment. Generally the disintegration time is related to hardness. When the hardness

increases, the disintegration time increases and the dissolution rate also decrease (Adenuga *et al*., 2008). In this study, the disintegration times of all paracetamol tablets were much lower than the Pharmacopeal limit (<15 min) USP 30/NF 25, 2007).

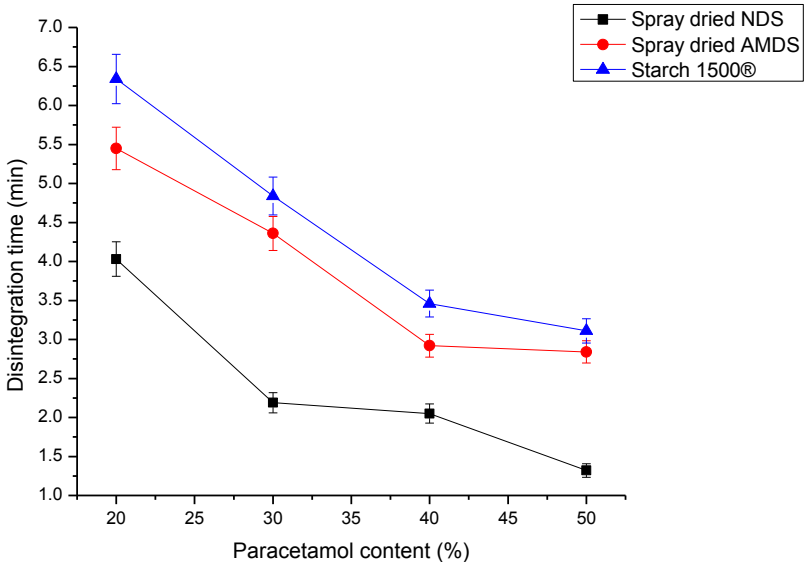


Figure 3.13: The disintegration time of tablets formulated from spray dried NDS, spray dried AMDS and Starch 1500® at different paracetamol concentrations.

3.9.3 Dissolution of directly compressed paracetamol tablet

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 (Parrott, 1989). Figure 3.14 shows the dissolution profiles of F13, F16, F17, F20, F21 and F24. The amount of paracetamol released from the tablets was increased as the concentration of paracetamol increased; however, the variation was not significant ($p > 0.05$). This might be attributed to reduction of tablet hardness upon increasing paracetamol concentration which results in faster dissolution rate. The amounts dissolved from formulations at lower amount of paracetamol concentration (20% w/w) in 30 min were in the order of spray dried NDS (95.1 %) > spray dried AMDS (94.3 %) > Starch 1500® (91.5 %); however, the variation was not significant ($p > 0.05$). All formulations fulfilled the specification of the USP 30/NF (2007) ie., > 80% of the tablet content should be released within 30 min.

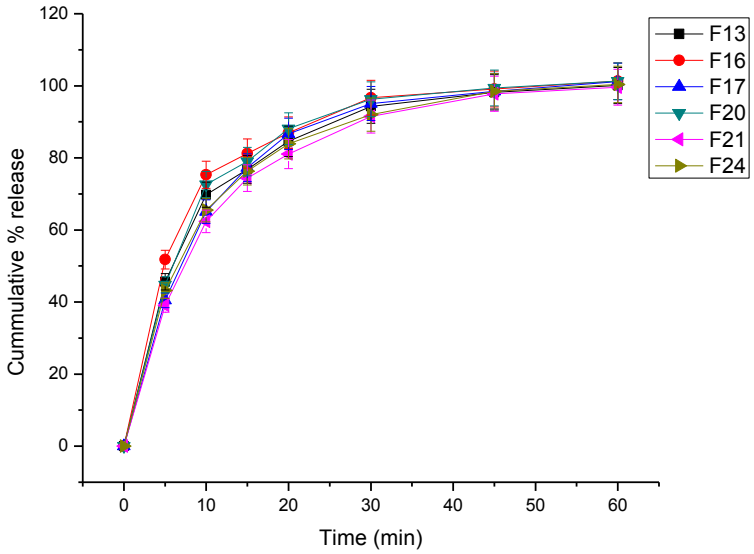


Figure 3.14: Dissolution profiles of spray dried NDS, spray dried AMDS & Starch 1500® at 20 & 50% paracetamol concentrations.

3.10 Evaluation of paracetamol tablet at different disintegrant concentrations

3.10.1 Weight variation and thickness

Table 3.5: Weight and thickness of paracetamol tablets formulated by wet granulation method at different disintegrant concentrations.

	NDS		AMDS		Starch 1500®	
DC (%)	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)	Weight (g)	Thickness (mm)
5	0.44 ± 0.00	4.84 ± 0.02	0.44 ± 0.00	4.84 ± 0.02	0.44 ± 0.01	4.81 ± 0.06
7.5	0.45 ± 0.00	4.89 ± 0.01	0.45 ± 0.01	4.87 ± 0.01	0.45 ± 0.00	4.83 ± 0.06
10	0.46 ± 0.01	4.94 ± 0.03	0.46 ± 0.01	4.89 ± 0.02	0.46 ± 0.01	4.85 ± 0.08
12.5	0.47 ± 0.01	4.97 ± 0.03	0.47 ± 0.00	4.94 ± 0.01	0.47 ± 0.00	4.88 ± 0.04

Mean ± SD (n = 20), DC: disintegrant concentration

The weight variation and thickness of paracetamol tablets formulated by wet granulation method at different disintegrant concentration is summarized in Table 3.5. The tablets are

within acceptable range of weight variation (± 5%) which is the limit of the percentage deviation allowed by BP (2009) for tablets weighing 250 mg or more.

The mean tablet thickness of all the formulations did not show any significant variation ($p > 0.05$) in the formulations. However, there was slight weight variation and tablet thickness between the various batches of formulations; this might be related to the variations in powders density as well as compression behavior of the compacted material.

3.10.2 Crushing strength, tensile strength and friability

The relationship between disintegrant concentration and crushing strength, tensile strength as well as friability for all formulations are shown in Fig. 3.15, Table 3.6 and Fig. 3.16, respectively. The effect of starches as disintegrant on the crushing strength and percent friability differ significantly. In the case of native dioscorea starch when the disintegrant concentration increases there was 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 AMDS and Starch 1500® increased, indicating better compressibility and binding activity of these starches. This might be due to acid hydrolysis of the amorphous regions of the starch resulting in the more crystalline acid modified starch granules being forced closer together during compression which will result in stronger packing of the granules and an increase in the tensile strength of the tablets (Atichokudomchai *et al.*, 2001; Odeku and Picker-Freyer, 2009).

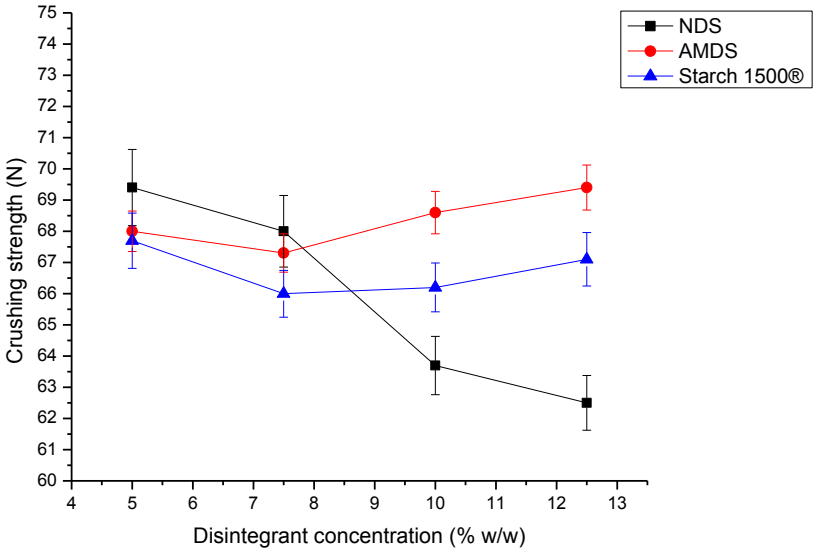


Figure 3.15: The crushing strength of tablets formulated from NDS, AMDS and Starch 1500® at different concentrations of disintegrant.

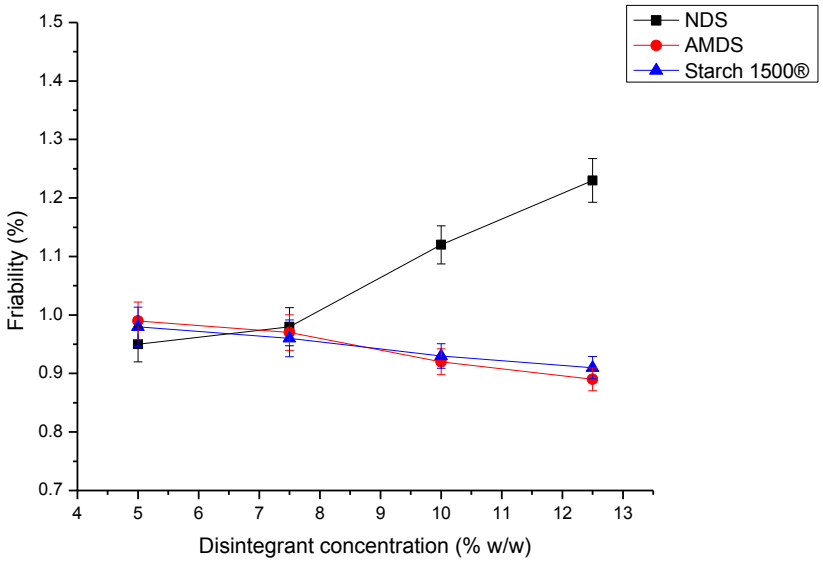


Figure 3.16: The friability of tablets formulated from NDS, AMDS and Starch 1500® at different concentrations of disintegrant.

The tensile strengths of tablets formulated from NDS, AMDS and Starch 1500® are shown in Table 3.6. The tensile strength increases with increase in disintegrant concentrations in the case

of AMDS. This might be due to acid hydrolysis has been shown to remove the amorphous regions of the starch resulting in the more crystalline acid modified starch granules being forced closer together during compression which will result in stronger packing of the granules and an increase in the tensile strength of the tablets (Atichokudomchai *et al.*, 2001; Odeku and Picker-Freyer, 2009). Contrarily the tensile strength of NDS decreases with increase in disintegrant concentrations. This is because of the softening effect of native dioscorea starch.

Table 3.6: Tensile strength of paracetamol tablets formulated from NDS, AMDS and Starch 1500® at different disintegrant concentrations.

DC (% w/w)	Tensile strength (kg/cm^2)		
	NDS	AMDS	Starch 1500®
5	9.13 ± 0.73	8.95 ± 0.61	8.95 ± 0.67
7.5	8.86 ± 0.68	8.81 ± 0.63	8.70 ± 0.68
10	8.21 ± 0.67	8.94 ± 0.72	8.69 ± 0.62
12.5	8.01 ± 0.73	8.95 ± 0.78	8.76 ± 0.87

DC- Disintegrant concentrations

3.10.3 Disintegration time

The disintegration time of tablets formulated from NDS, AMDS and Starch 1500® at different concentrations of disintegrant is depicted in Figure 3.17. All formulations generally passed the official disintegration test for uncoated tablets i.e. <15 mins (USP 30/NF 25, 2007). As clearly indicated in the figure the disintegration time of paracetamol tablets decreased with increase in the concentration of excipients as disintegrant for NDS, AMDS and Starch 1500®. At all concentrations, tablets formulated with AMDS disintegrated faster than those formulated with Starch 1500® but slower than tablet containing NDS. Slightly higher disintegration time of AMDS might be due to decrease in swelling capacity of AMDS whereas relatively longer disintegration time of Starch 1500® might be due to the gelatinized starch which impedes the penetration of water into the tablet (Atichokudomchai & Varavinit, 2003).

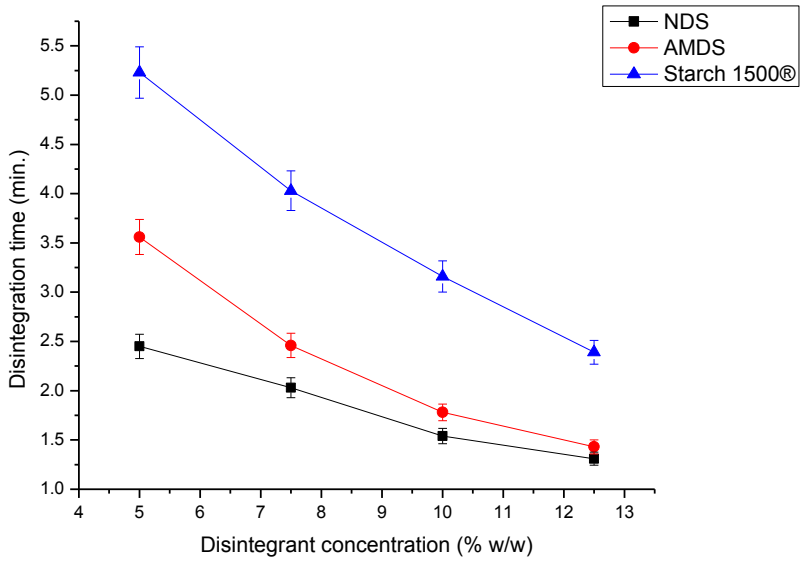


Figure 3.17: The disintegration time of tablets formulated from NDS, AMDS and Starch 1500® at different disintegrant concentrations.

3.10.4 Drug dissolution

The dissolution profiles of paracetamol tablets at low (5 % w/w) (F1, F5, F9) and high (12.5 % w/w) (F4, F8, F12) starch disintegrant concentrations are shown in Figure 3.18. The dissolution pattern agrees with the disintegration-dissolution theory which indicates that 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 (Oyi *et al*., 2009). All the batches of the tablets formulated passed the USP 30/NF (2007) dissolution test for tablets which specifies that at least 80% of the drug should be in solution after 30 min. There was no significant difference between the dissolution rates of paracetamol from the tablets containing 5 &12.5% of the disintegrants ($p > 0.05$). The amount of paracetamol released from tablets when Starch 1500® was used as a disintegrant was relatively lower than those of NDS and AMDS. The gel like layer formed by pregelatinized starch 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).

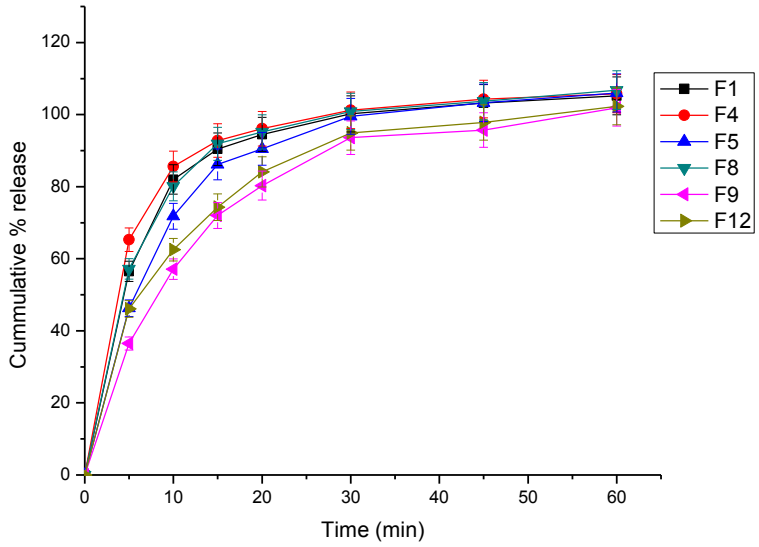


Figure 3.18: Dissolution profiles of paracetamol tablets at low (5% w/w) and high (12.5% w/w) disintegrant concentrations.

4. CONCLUSION

Dioscorea starch modified with hydrochloric acid and some of its properties were investigated. The physicochemical properties of AMDS compared well, in many respects, with those of Starch 1500®. No significant difference was found in powder moisture content, tapped & bulk densities and moisture sorption. Acid modification increases the solubility but decreases the swelling power of the native starch. The results also revealed that acid hydrolysis did not change the crystalline type of the native starch. Moreover, the FT-IR spectra of AMDS show compatibility with the model drug. Spray dried AMDS showed excellent flow property and compactibility, which indicates its potential use as a directly compressible excipient.

The lubricant sensitivity test revealed that spray dried AMDS showed less lubricant sensitivity than that of spray dried NDS and Starch 1500® by yielding tablets with higher crushing strength and acceptable friability values up to 1% magnesium stearate concentrations. Compared to AMDS, Starch 1500® could only accommodate 0.5% magnesium stearate with acceptable properties. Moreover, spray dried AMDS revealed high dilution potential than that of spray dried NDS and Starch 1500® accommodating up to 40% of paracetamol concentration with acceptable pharmacopoeial range of friability, disintegration time and drug release rate; whereas Starch 1500® accommodates only up to 30% of paracetamol concentration. The higher compressibility, lower lubricant sensitivity and good dilution potential make AMDS a good candidate for directly compressible excipient.

Formulation studies on paracetamol tablets containing NDS, AMDS and Starch 1500® as disintegrants, revealed that the starches produced a significant, concentration-dependent reduction in disintegration time of paracetamol tablets. The study showed that AMDS has a better disintegrant efficiency than Starch 1500® in paracetamol tablet formulations. Contrary to native starch, increasing the concentration of AMDS increased crushing strength and reduced percent friability of the tablets.

Spray dried AMDS showed better direct compressibility and oven dried AMDS better disintegrant effect than Starch 1500®.

From the foregoing, it can be concluded that AMDS can be used as an alternative to Starch 1500® as directly compressible excipient and disintegrant in tablet formulation.

5. SUGGESTIONS FOR FURTHER WORK

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

- Detailed characterization properties of the acid modified dioscorea starch such as particle size distribution, pasting property, morphological characterization,
- The application of acid modified dioscorea starch as tablet and capsule filler.

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