# EVALUATION OF MODIFIED FINGER MILLET STARCH (*Eleusinecoracana* L.) AS FILLER/BINDER IN DIRECT COMPRESSION

**BY**

**SHUAIBU, Kurfi Fatima B.Pharm (ABU 2008)**

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## DECLARATION

I declare that the work in this dissertation entitled “Evaluation Ofthe Modified Finger Millet Starch *EleusineCoracana*L.) As Filler/Binder In Direct Compression” has been performed by me in the Department of Pharmaceutics andPhamaceuticalMicrobiology under the supervision of Dr.K. Mshebwala and Dr. A.K.Olowosulu.

The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at this or any other university.

**ShuaibuKurfi Fatima** _____ _____

Name of Student Signature Date

## CERTIFICATION

The dissertation titled 'EVALUATION OF MODIFIED FINGER MILLET STARCH (*Eleusinecoracana*L.) AS FILLER/BINDER IN DIRECT COMPRESSION 'by Shuaibu, Kurfi Fatima meets the regulations governing the award of the degree of Master of Science (PHARMACEUTICS) of Ahmadu Bello University, Zaria, and is approved for it'scontribution toscientific knowledge and literary presentation.

**Dr. K. Mshelbwala BSc: M.Sc: Ph.D----------**

**ChairPerson, Supervisory Committee** Date

Department of Pharmaceutics and Pharmaceutical

Microbiology, Faculty of Pharmaceutical Sciences,

Ahmadu Bello University, Zaria, Nigeria.

**Dr. A.K Olowosulu.BPharm: M.Sc: Ph.D** ----------

**Member, Supervisory Committee** Date

Department of Pharmaceutics and Pharmaceutical

Microbiology, Faculty of Pharmaceutical Sciences,

Ahmadu Bello University, Zaria, Nigeria.

**Prof B. O Olayinka BSc: M.Sc: Ph.D** ----------

**Head,** Department of Pharmaceutics and Pharmaceutical Date

Microbiology, Faculty of Pharmaceutical Sciences,

Ahmadu Bello University, Zaria, Nigeria.

**Prof. S.Z. Abubakar**

**Dean**, School of Postgraduate Studies ----------

Ahmadu Bello University, Zaria, Nigeria. Date

## DEDICATION

This work is dedicated to my parents, siblings, husband and my children.

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## ABSTRACT

Starch modifications are a means of altering the structure and affecting the hydrogen bonding in a controllable manner to enhance and extend their application. There are different methods for modification of starch such as chemical modifications which include stabilization, cross linking, conversions and physical modifications which include annealing and pre-gelatinization. The methods that were chosen to modify *Eleusinecoracana* starch was by pregelatinization and acid hydrolysis, for the formulation of metronidazole tablets by direct compression. Pregelatinization and acid hydrolysisof the native starch (ORS) was carried out by standard procedures. Acid hydrolysis was allowed for 6h,12h and 18h respectively. Acid hydrolyzed starch was labelled as AHS and pregelatinized starch as PGS. Physicochemical characterization of the native and modified forms of the starch was carried out by several tests. The flow properties of the materials were evaluated by determining the angle of repose, flow rate, Carr's index and Hausner's ratio. Compaction studies were carried out using Heckel and Kawakita plots to elucidate the mode of deformation of the materials. Dilution potential was carried out for all modified starches to estimate the optimum drug-excipient ratio. For drug-excipient compatibility studies, analytical technique Fourier Transform Infrared Spectroscopy (FTIR) was used. The Percentage yields of starches hydrolysed for 6,12 and 18 h were%, 62.2 % and 55.6 % respectively. Gelatinization temperature was 66ºC and percentage yield for the Pregelatinized starch (PGS) was 19.4% . Powder characterization indicates that modified starches of *Eleucinecoracana* possessed good flow properties because they had low angle of repose (26˚-30˚) and good flow rate of 2.0 to 7.8 g/s .The values obtained from flow indices suggest that the acid hydrolysed starch(AHS) performed better than PGS which in turn gave a slightly better property than the original native starch (ORS). PGS had the highest hydration and swelling compared to other modified starches. The Phvalue for all modified starches were neutral and this indicated that they are safefor oral

consumption. Decrease in amount of protein and lipids with increase in time in acid hydrolysis indicated that they were denatured by acid hydrolysis. Microscopicalexamations showed all particles were spherical with size ranging from 100-172 µm. Photomicrographs revealed an increase in the size of particle in PGS due to swelling of particles as a result of uptake in water. There was an increase in void spaces between particles with increase in time in acid hydrolysis indicating particles that had been denatured. All modified starches had moisture content within specified limit, tablets containing 40:60 or 50:50 blend of metronidazole starch gave the best physicochemical characteristicsinterms of tablet strength/friability profile.The AHS treated for 12h gave the best tableting characteristics among the acid hydrolyzed starches. From Heckel and Kawakita analysis, the modified starch (AHS &PGS) were found to have low yield values compared to native starch (ORS). The Kawakita parameters were consistent with Heckel analysis as the modified starches performed better in terms of deformation. According to Heckel and Kawakita, all modified starches showed improved compression profile compared with the original starch. FTIR results revealed no interaction of these excipients with the metronidazole tablet. These results suggest that tablets with optimum properties can be formulated by direct compression using AHS modified for 12h as filler-binder.

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## Abreviations, Definations ,Glossary and Symbols

**AHS6H** Acid hydrolyzed starch at 6 hours

**AHS12H** Acid hydrolyzed starch at 12 hours

**AHS18H** Acid hydrolyzed starch at 18 hours

**BP** British Pharmacopoeia

**C** Degree of Volume Reduction

**D** Powder bed's relative density

**$D_0$** Relative density at zero pressure

**$D_A$** Relative density from the value of intercept A

**$D_B$** Describes the phase of rearrangement at low pressures (DA - DB)

**FTIR** Fourier transforms infrared spectrscopy

**HCl** Hydrochloric Acid

**Kgf** Kilogram force

**MET** Metronidazole

**MCC** Microcrystalline Cellulose starch tablet

**STC** Starlac tablet

**NaOH** Sodium Hydroxide

**NS** Native starch

**OH** Hydroxyl Group

**P** Applied Pressure/ Load

**PGS** Pregelatinized starch

**$P_y$** Mean Yield Pressure

**RH** Realtive Humidity

**T** Thickness of Tablet

**T50%**Time taken to release 50% of the drug

**T90%**Time taken to release 90% of the drug

**Ts**Tensile Strength

**USP**United States Pharmacopoeia

**V0**Initial Volume

**V** Volume of Tablet

**Vp**Volume at Applied Pressure

**W**Weight of tablet

**ρs** Particle density

# CHAPTER ONE

# 1.0 INTRODUCTION

## 1.1. Pharmaceutical Excipient

These are additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration of patients (Aulton, 2013). In a tablet formulation, a range of excipient materials is normally required along with the active ingredient in order to give the tablet the desired properties. For example, the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficiently strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients will affect all these properties (Nystrom *et al*,1993).

Starch possesses definite chemical structure and composition. Starch is the most abundant carbohydrate available as an agricultural raw material (Akande,1988). Starch is the main carbohydrate in plants and acts as a reserve food supply for periods of growth, dormancy and germination (Gallant*et al*, 1992).The estimated world production of starch amounts to 58 million tones, extracted from maize (46 million), wheat (4.6 million), potatoes (3.5 million), and the remainder coming from rice and cassava roots (tapioca) (French,1984).

Being a biodegradable polymer with well-defined chemical properties, it has a huge potential as a versatile renewable resource for various material applications in food and non-food areas. The composition and properties of commercially available starches have been studied extensively (Gallant*et al*,1992). The properties of each starch are strongly dependent on plant source.

Starch is a member of the 'polysaccharide' group of polymers. It is laid down as insoluble, compact and microscopic semi-crystalline granules of size 1-100 um. The most important origins of starch are maize, potato, wheat, millet, tapioca and rice, Corn and maize starches are American and European terms that actually refer to the same range of starches (Jivraj, 2000).

Native starches were well explored as binders and disintegrants in solid dosage forms, but due to poor flowability their utilization is restricted. Most common form of modified starch i.e. Pregelatinized starch marketed under the name starch1500 are nowadays most preferred directly compressible excipients in pharmaceutical industry. Modified rice starch, starch acetate and acid hydrolyzed diascorea, were well established as multifunctional excipients in pharmaceutical industry (Bos *et al*, 1992)

### 1.1.1Extraction

The wet milling is the standard method of extracting pure starch from the raw material. After removing the impurities and other debris, separation of pure starch from other undesired components of the raw material like oil, highly-bound proteins and fibers is done through wet milling. When the insoluble starch is collected as its intact granules, it is referred to as native starch. However, at this step, the native starch is washed, dried and kept for subsequent processing in to modified starches (Whistler and BeMeller, 2009)

### 1.1.2 Processing

Unprocessed native starches are structurally too weak and functionally too restricted for application in today's advanced pharmaceutical technologies. Processing is necessary to engender a range of functionality. Processing is a process where new excipients are coming into market without undergoing the rigourous safety testing of a completely new chemical (Russell, 2004). Processing of excipients could lead to the formation of excipients with superior properties compared to the original substance. Excipients can be co-processed to even give products of better properties.

Co-processing is defined as combining two or more established excipients by an appropriate process (Reinmerdes, 1993). The aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. Development of co-processed directly compressible excipients starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physic-chemical parameters (Banker, 1994).

## 1.2Starch Structure

### 1.2.1Starch granule

The starch backbone has numerous 'OH' (hydroxyl) groups projecting into the surrounding space. Hydroxyl groups have a particular affinity for other hydroxyl groups and can serve as a driving force in bringing starch chains together in an ordered manner through hydrogen bonding. Where such ordering occurs, crystalline regions are deposited in the granule. The remaining regions of

unordered starch are referred to as amorphous. It is the crystalline regions that give the granule its structure and facilitate identification of a raw (uncooked) starch. Under a microscope, starch granules illuminated with polarized light, show a characteristic 'Maltese Cross' pattern. This phenomenon is also known as birefringence (Armstrong, 1997).

The microscopic appearance of each granule is diagnostic of its source. Microscopic identification can be enhanced using iodine to stain the amylose to a characteristic blue-black color. This is the result of an association between the two to form a complex in which the amylose forms a helical coil around iodine molecules. Waxy maize starch, which contains negligible amounts of amylose, does not form a complex and as a result takes on the red brown solution color of iodine (Jivraj, 2000).

### 1.2.2 Properties of Starch

It is a tasteless, odorless, white amorphous substance. It is insoluble in cold water and alcohol but a soluble starch can be obtained by heating it with 10% HCl for 24 hours followed by precipitation by addition of alcohol (Amodu, 2011). If a suspension of starch in cold water is added to boiling water with continuous stirring, the opaque granules swell up and eventually rupture to give a translucent solution of substance which on cooling down becomes jelly-like (Light, 1990).

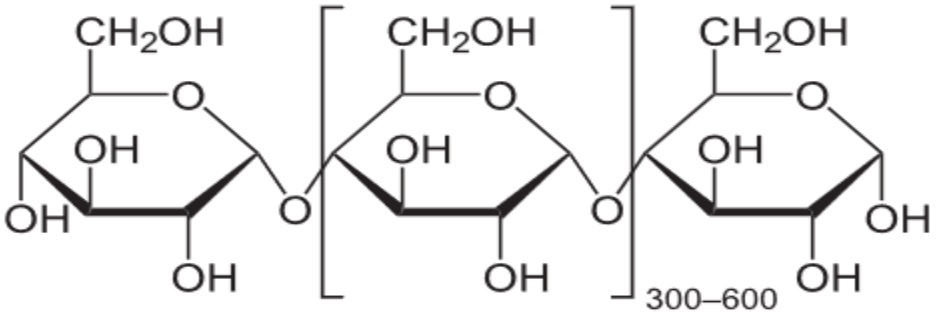



Figure1.1. Linear structure of amylose molecule (Light,1990)

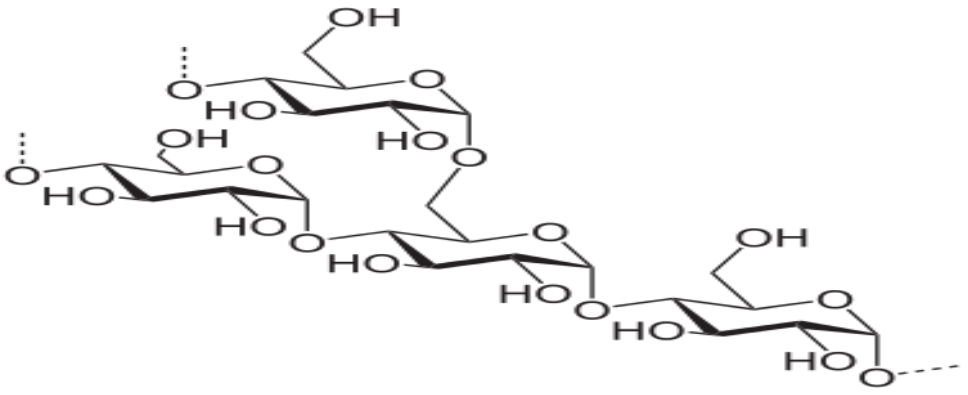



Figure1.2.Branched structure of the amylopectin molecule (Light,1990)

### 1.3 Starch Modifications

Starch modifications are a means of altering the structure and affecting the hydrogen bonding in a controllable manner to enhance and extend their application. The alterations take place at the molecular level, with little or no change taking place in the superficial appearance of the granule. Therefore, the botanical origin of the starch may still be identified microscopicallybelow (Chowhan, 1998).

Each chemical and biochemical modification is described below.

#### 1.3.1Chemical Modification of Starch

**a. Cross-linking**

Cross-linking is the most important chemical modification in the starch industry. It involves replacement of the hydrogen bonding between starch chains by stronger, more permanent, covalent bonds. In this manner, the swelling of the starch granule is inhibited, pre-empting disintegration either by chemical attack, mechanical attrition (shear) or cooking. Simply put, the starch granule is, in the molecular dimension, 'spot welded' at random locations to reinforce it(Le Bail *et al*, 1999).

Commercial cross-linking is often performed by the reaction of bi- or polyfunctional reagents e.g. phosphorous oxychloride, sodium trimetaphosphate. epichlorohydrine, and mixtures of adipic anhydride and acetic acid (Le Bail *et al*, 1999). Cross-linking is often performed in combination with esterification and etherification, to provide appropriate gelatinization, viscosity

and texture properties (Huijbrechts, 2008). Because of the more permanent nature of the covalently bonded bridge or cross-link, only a small degree is necessary to produce beneficial effects: typically one cross-link per 100-3000 anhydroglucose units of the starch. As the number of cross-links increases, the starch becomes more resistant to gelatinization. Consequently, cross-linked starches offer acid, heat and shear stability over their parent native starches (Huijbrechts,2008).

**b. Stabilization**

Stabilization, the second most important modification, is usually used in conjunction with cross-linking. The primary objective of stabilization is to prevent retrogradation and thereby enhance shelf-life through *tolerance* to temperature fluctuations such as freeze-thaw cycles. In this modification, bulky groups are substituted onto the starch in order to take up space and hinder (Steric hindrance) any tendency for dispersed (cooked), linear fragments to re-align and retrograde(Wade and Weller,1994).

The effectiveness of stabilization depends upon the number and nature of the substituted group, of which there are primarily two food-approved types: acetylated and hydroxypropylated. The degree of substitution (DS) is a measure of the number of substituents per 100 anhydrous glucose units. Low DS starches are those with a DS below 0.2 (i.e. 2 substituents per 100 anhydrous glucose units), are the most important commercially. As the DS level is raised, the starch-starch interactions in the granule are weakened and, consequently, hydration and gelatinization by cooking is achievable at lower temperatures. Such starches benefit from easy cooking and are

particularly useful in low-moisture environments and where the moisture level is restricted by competition from co-ingredients (Wade and Weller,1994).

**c.Conversions**

Conversion is a collective term for a range of chain-cleavage reactions of starch such as;

**I.Acid hydrolysis**

Acid-thinned, thin-boiling and fluidity starches are all terms which refer to starches which have been subjected to acid hydrolysis. Acid hydrolysis is an attempt to get starch that will have higher surface area for maximum point of bonding thus achieving more compatibility. This form of hydrolysis differs from dextrinisation in that it is conducted in aqueous conditions. The acid predominantly attacks and depolymerises the amorphous regions of the granule such that when the starch is heated beyond its gelatinisation temperature the granules rupture quickly. The effect on cooking is a lower viscosity and, due to the increase in the ratio of smaller, linear molecules, a stronger gel develops on cooling (set-back) compared to the native parent starch (Jacobs and Plein,1968).

Acid hydrolysis can also be defined as an attempt to get starch that will have higher surface area. This is one of the method of improving the functional properties of native starch. It affects both the chemical and physical nature of starch and improves its suitability for both pharmaceutical and non-pharmaceutical uses(Mullick, 1992).

During acid hydrolysis, glycosidic bonds of the starch are broken leading to the formation of mixtures of anomeric sugars.Acid hydrolysis produced microcrystalline starch (MCS) with improved functional properties in terms of flowability or compressibility (Olayemi, 2009).

**II. Oxidation**

The production of oxidised starches employs alkaline hypochlorite as a reagent.

Two important modifications occur:

a) The relatively bulky carboxyl (COOH) and carbonyl (CO) groups are introduced together with partial depolymerisation of the starch chains.

b) Oxidised starches, like acid-thinned starches, exhibit a significantly reduced hot paste viscosity due to breakdown of the starch beyond its gelatinisation temperature. Unlike acid-thinned starch however, the steric hindrance of the bulky groups disrupts any tendency towards re-association (set back) of the shorter chains thereby significantly reducing the gel strength. This is an advantage of oxidised over acid-thinned starches. 'Bleaching' is, in fact, a milder form of oxidation with less than 0.1 % of carboxyl groups (Jacobs,1968).

**III. Dextrinisation**

Dextrinisation, also known as pyroconversion, refers to two aspects of the structural modification of starch. The first is a partial depolymerisation achieved through hydrolysis. Hydrolysis is the reverse of condensation. It is the addition of water across a bond resulting in cleavage of that

bond. It is usually brought about by dry roasting the starch either alone, making use of its natural 10-20 % moisture content, or in the presence of catalytic quantities of acid. This gives rise to a range of polymer fractions of varying chain length (low conversion)(Jacobs, 1985).

The second aspect involves a recombination of these fragments (repolymerisation) but this time in a branched manner (high conversion). The starches so produced are called dextrins or pyrodextrins. They are typically classified as white dextrins, yellow dextrins or British gums depending on their range of viscosity, coldwater solubility, colour, reducing sugar content and stability (Jacobs,1985).

**IV.Enzyme hydrolysis**

Selective enzyme hydrolysis is a form of biochemical modification. This reaction can result in products with a wide range of functionalities. Depending on the extent of enzyme hydrolysis, a range of chain lengths corresponding to glucose (dextrose), maltose, oligosaccharides and polysaccharides can be produced. A range of enzymes is employed to produce such a spectrum of hydrolysates (Chiu *et al*,1997).

### 1.3.2 Physical Modification of Starch

**a. Annealing**

Annealing of starch is a physical treatment whereby the starch is incubated in excess water (> 60 % w/w) or intermediate water content (40 to 55 %w/w) at a temperature between the glass

transition temperature and the gelatinization temperature for a certain period of time (Tukomane, 2008).

The term, annealing should be applied only where gelatinization does not occur. However, it is noticed that annealing is sometimes associated with partial gelatinization. Annealing increases starch gelatinization temperature and sharpens the gelatinization range. Often annealing is applied unintentionally, such as steeping step used in maize wet-milling process (Tukomane, 2008). Annealing modifies the physicochemical properties of starch without destroying the granule structure. Under the annealing conditions, the amorphous starch molecules become mobile and reorganize to form an enhanced crystalline structure, resulting in an increase in starch overall crystallinity (Tester and Debon, 2000).

**b. Pregelatinization**

Pregelatinization is a physical rather than a chemical modification. Certain starches require cooking to develop their function. These are referred to as 'cook - up' starches and the process of pregelatinization is designed to remove the necessity for cooking. Pregelatinization may be applied to native or modified cook-up starches to achieve a versatile range of cold thickening starches (Amodu, 2003).

Pregalatinized starches are excipients that have been processed chemically and or mechanically. The processes rupture all or part of the starch granules in the presence of water and are subsequently dried. Pregelatinized starches offer a number of benefits both in processing and

performance. They enhance flow and compressibility and can be used as binders in direct compression as well as in wet granulation. They can easily be processed since they swell in cold water and therefore reduce processing time and cost compared to traditional starch paste preparation. The technology employed in the processing of the pregelatinized starch determines its quality such as level of purification, particle size and size distribution, densities and flow properties, which are parameters that cannot be ignored by any formulator (Amodu, 2003).

### 1.3.3Gelatinization Temperature of Starch.

Starch gelatinization is a process that breaks down the intermolecular bonds of starch molecules in the presence of water molecules and heat, allowing the hydrogen bonding sites (the hydroxyl hydrogen and oxygen) to engage more water. Gelatinization temperature is the point at which this transition occurs. While each individual granule sample gelatinize quite sharply, not all granules in a starch sample gelatinizes at the same temperature but rather over a temperature range of ±8 to 10˚C(Okafor *et al,* 1991).This is an indication that there exists a difference in the internal binding forces within the individual granules. Gelatinization temperature indicates the strength of hydrogen bond within the starch granule or the amylose content of the starch. The stronger the hydrogen bond or the amylose content, the higher will be the Gelatinization temperature(Okafor *et al,* 1991).

When an aqueous suspension of starch is subjected to heat, the molecular network within the granules is weakened by disrupting the hydrogen bonds. The more the resistance to the influence of this heat, the higher the hydrogen bond (Burrell, 2003). The higher the amylose content, the

higher will be the gelatinization temperature. The differences in the proportion of gelatinized starch granules may be indicative of the differences in the physicochemical properties of the starch samples (Okafor *et al*, 1991).

### 1.3.4 Application of Modified starches in pharmaceuticals and Medical Industries.

In recent years, pharmaceutical companies around the world widely use modified starches of various kinds at various stages of drug technology and development.Excipients plays a very important role in solid dosage formulation by imparting mechanical strength, stability and tablet disintegration(Preiss and Levi, 1980)..

Native starches are well explored as binder and disintegrant in solid dosage form, but due to poor flowability, there utilization is restricted. Most commonform of modified starch i.e. Pregelatinized starch marketed under the name of starch1500 are now the most preferred directly compressible excipients in pharmaceutical industry.Recently modified rice starch, starch acetateand acid hydrolyzed*diascorea*starchwerewell established as multifunctional excipient in pharmaceutical industry(Preiss and Levi, 1980).

**(a) Tablet Superdisintegrants**: They are generally employed for immediate release tabletformulations, where drug should be available within short span of time to the absorptive area. Sodium carboxymethylate starch, which is well established and marketed as sodium starch glycolate is generally used for immediate release formulation.

Some newer sources ofstarch have also modified and evaluated for the same (Wells and Aulton, 2007*).*

**(b) Controlled/Sustained release polymer**:Two decades earlier modified starch was firstevaluated as sustained release polymer. Modified starches in different forms such as grafted, acetylated and phosphate ester derivative have been extensively evaluated for sustaining the release of drug for better patient compliance(Rudnic and Kottke, 1999).

**(c) Plasma volume expander:**Starch modified with ethylene oxide produces hydroxyethylstarch, which is now mainly used as plasma volume expander. This is mainly useful for the patients suffering from trauma, heavy blood loss and those on cancer treatment (Rudnic and Kottke, 1999).

Official Starches recommended by British Pharmacopoeia (B.P 2009) for pharmaceutical applications include:

- Maize starch obtained from caryopsis of *Zea mays* L.
- Rice starch obtained from caryopsis of *Oryza sativa* L.
- Potato Starch obtained from tuber of *Solanum tuberosum* L.
- Wheat starch obtained from caryopsis of *Triticum aestivum*(T.vulgare).

**1.4 Statement ofthe Research Problem.**

The importance of sourcing of pharmaceutical raw materials locally cannot be over emphasized. Majority of pharmaceutical raw materials are imported. Therefore,it is necessary to research for more raw materials locally.

Starch in its crude form has limited tableting properties. In its native form, it could be used as a diluent, binder and disintegrant.Poor flow,loss of binding and compactibility in the presence of a lubricant make them less suitable for directly compressible tablet formulations (Camphel and Theivagt, 1998).



But when used for direct compression, the size of the grains is small and the flowability is poor, thus making it poorly compressible.Scientist have utilized various physical, chemical and biotechnological means to develop excipients meantfor direct compression. Methods for improving this problem of starch include acid hydrolysis, pre-gelatinization of starch, co-processing. These methods as well as the equipment used for most modification have resulted in products that are relatively expensive and not readily available to local manufacturers.

There is need for local sourcing of pharmaceutical raw materials which are cost effective, hence the evaluation of *E.coracana* starch which is readily available as excipient for direct compression tabletting after modification by thermal pregelatinazation and acid hydrolysis.

**1.5Justification of the Study**

Despite the huge amount of progress achieved in the pharmaceutical world in the area of tablet manufacture, there is an increasing demand for a wide range of different grades of excipients

with better properties that can ensure adequate tablet strength and in-*vitro* bioavailability and also ensure that the drugs comply with the recommended international standards of Current Good Manufacturing Practice (cGMP).

Most of the world's starch supplies are derived from corn, millet, sorghum and major tuber crops. While starches from these various plant sources vary slightly in their chemical and physical properties, they can be substituted for each other across a wide spectrum of end uses. The direct compression method is a preferred method because it is cheap, efficient, and more suitable for thermolabile materials, thus making it the most preferred method of tabletting.Finger Millet is grown in industrial quantities in Nigeria. Hence it can be used to harness home grown excipients for our pharmaceutical Industries.

**1.6 Aim**

The aim of this research is to develop acid hydrolyzed starch and pre-gelatinized starch from finger millet*Eleusine coracana* and evaluate their tabletting propertiesas a directly compressible excipient in the formulation of metronidazole tablet.

**1.7 Objectivesofthe Work.**

The objectives of this work include:

• To produce microcrystalline starch from *Eleusine coracana* starch.

•To determine the physicochemical properties of the starch.

•To Formulate Metronidazole tablets using direct compression.

•To Evaluatethe tableting properties of the modified starch of *Eleusine coracana* compared with tablets formulated with microcrystalline cellulose and Starlac used as standards.

**1.8 Limitation ofthe Research Work.**

The research study is limited to the evaluation of tableting properties of modified starches of *Eleusine coracana* as filler/binder in formulating of Metronidazole 500mg tablet by direct compression.



**1.9 Statistical Analysis.**

**1.9.1 NULL Hypothesis (Ho)**

Modified starches obtained from *Eleusine coracana* will not serve as good direct compression filler/binder in metronidazole tablet formulation.

**1.9.2 Alternate Hypothesis (Ha)**

Modified starches obtained from *Eleusine coracana* will serve as good direct compression filler/binder in metronidazole tablet formulation.

## CHAPTER TWO

# 2.0 LITERATURE REVIEW

## 2.1*Eleusine coracana*



Finger millet is also called African millet. It is an annual plant widely grown as a cereal in the arid areas of Africa and Asia. It is originally native to the Ethiopian Highlands (Akande ,1988) and was introduced in India approximately 400 years ago. It is widely cultivated in tropical Asia and East Africa and on the rainy slopes of the Himalayas up to 2300m elevation. In Nigeria it is cultivated in the northern part of the country and is called "Tamba" in Hausa.Finger millet or Latin *Eleusine coracana* is an annual herbaceous plant widely grown as a cereal crop in the arid and semiarid areas in Africa and Asia. It is a tetraploid and self-pollinating species probably evolved from its wild relative *Eleusine Africana* (French, 1984).

Finger millet is native to the Ethiopian and Ugandanhighlands (Adane,2006).Interesting crop characteristics of finger millet are the ability to withstand cultivation on altitudes over 2000 meters above sea level, its favorable micronutrient contents (high iron and methionine contents

in particular), its high drought tolerance and a very long storage time of the grains(Akande, 1988).

### 2.1.1 Taxonomy/Classification

Kingdom: Plantae

Order: Poales



Family: Poaceae

Subfamily: Choridoideae

Genus: *Eleusine*

Species: *coracana*L. (Amodu,2011)

### 2.1.2Synonyms

Finger Millet ,Pearl Millet, African millet, Coracan, Kura.The Hausa's called it 'Tamba',the French 'Koracan', the Yoruba's 'Ika jero', the Arabians 'Tailabon'and the Indian's 'Ragi'.

### 2.1.3Plant Description

Annual grass; culms erect, laterally flattened, 60-120 cm tall or long, profusely tillering, in addition to branches sent out at the rounded nodes in succession, plants often lodged or prostrate; root system fibrous and remarkably strong, permeating soil thoroughly, inflorescence a whorl of 2-8 (normally 4-6), digitate, straight, or slightly curved spikes 12.5-15 cm long, about 1.3 cm broad; spikelets about 70, arranged alternately on rachis, each containing 4-7 seeds, varying from 1-2 mm in diameter; caryopsis nearly globose to somewhat flattened, smooth or tugose, reddish-brown to nearly white or black (Amodu, 2011).

### 2.1.4 Plant Development



Finger Millet matures 3-5 months after sowing, depending on variety, season and soil properties. Rain fields crops are cut close to ground, stalks are allowed to wither for a day or two in field, and then bundled and stacked for about 2 months before threshing. To separate the grains, dried earheads are beaten with sticks; sheaves are trodden by bullocks or crushed by stone rollers. Separated grains are dried and cleaned. Under irrigated conditions, crop is harvested about 3.5 months after transplanting. Earheads are gathered when they ripen; three or four pickings are usually required to collect all earheads from a field. These are heaped up, and when dry, threshed. Straw from irrigated plants is coarse and thick and is rarely cut. It is grazed down or sometimes turned under as manure for next crop(Amodu, 2011).

### 2.1.5 Chemical Composition

Nutritional value of finger millet per 100g

Protein 7.6g, Fat 1.5g, Carbohydrate 88g, Calcium 370mg, Vitamins - A: 0.48mg,,Thiamine (B1): 0.33mg, Riboflavin (B2): 0.11mg, Niacin: (B3) 1.2mg, Fiber 3g (Amodu,2011).

### 2.1.6 Uses and Consumption

Finger millet is one of the most nutritious of all the world's cereal crops being rich in essential amino acids, iron and calcium. Finger millet also has many medicinal uses.



- Finger Millet is used in Nigeria mainly as food, either as porridge named pap or in local delicacies like Tuwo with soups (Amodu, 2011).
- The main use of finger millet in Africa is to provide malt to make local beer and other alcoholic and non-alcoholic beverages. For example, 'areki' is a popular Ethiopian liquor produced from finger millet (Aiyer, 2005).
- The grains of finger millet can be ground into a flour to be used in porridge or to make 'cakes' which are then wrapped in maize husks or banana leaves and then roasted (Aiyer, 2005).
- Mashing a banana into finger millet flour and then making flat cakes to be fried or baked makes for a delicious treat (Aiyer, 2005).
- Finger millet straw is used as fodder for cattle, sheep and goats. In Uganda by-products of beer are used to feed chickens, pigs and other animals (Aiyer, 2005).

- Medicinally, finger millet seed is used as a prophylaxis for dysentery. In southern Africa the juice of a mixture of finger millet leaves and*Plumbago zeylanica*leaves are taken as an internal remedy for leprosy (Amodu, 2011).
- Finger millet straw is used for thatching and plaiting in China and for paper making. In Sudan,the leaves are made into string (Deshpande and Panya, 1987).



Fig 2.1. Typical seed grains of *Eleusine coracana* obtained from Zaria, Kaduna State.

## 2.2 Literature Review

### 2.2.1 *Eleusine coracana*

Odeku (2005),evaluated the anti-oxidant and nutritional contents of pearl millet (*Pennisatum glaucum*) and concluded that it possed moderate reducing ability and high free radical scavenging activities.

Nindhi and Meenu (2010) evaluated the antimicrobial and anticancer properties of finger millet,it was concluded that finger millet was a natural source of antimicrobials and antioxidants especially for minimizing the risks of disease arising from oxidative deterioration and also cytotoxic effect .

Amodu (2011),evaluated both *Pennisatum glaucum* and *Pennisatum americanum* with comparison to maize starch for their tabletting properties. The result indicated that the millet starches were suitable disintegrants and binders.

Native yam starch and carboxymethyl yam starch (CMS) were evaluated as tablet disintegrants in comparison with various other starches. Tablets with CMS disintegrated in a similar manner to those with native yam starch at a concentration of 9% by weight and disintegration was delayed at higher concentrations (Musa, 2004).

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

The improvement of the crushing strength of tablets prepared from spray dried annealed enzymatic hydrolyzed tapioca starch was reported by Tukomane (2008). This was associated with a significant decrease in amylase after prolonged hydrolysis and a corresponding increase in relative crystallinity.

Adetunji *et al*, (2006) studied the binding properties of trifoliate yam starch, obtained from *Dioscorea dumetorum* (pax), in Chloroquine phosphate tablet formulation in comparison with official corn starch. They analyzed the compressional properties using density measurement and compression equation of Heckel and kawakita. The mechanical properties of the tablet were assessed using the crushing strength and friability of the tablets, while drug release properties of the tablets were assessed using disintegration and dissolution times. They discovered that tablet formulations containing trifoliate yam starch exhibited faster onset and higher amount of plastic deformation during compression than those containing corn starch. The crushing strength, disintegration and dissolution times of the tablets increased with binder concentration while friability value decreased. Trifoliate yam starch produced tablets with stronger mechanical properties and longer disintegration and dissolution times than those containing corn starches. They concluded that trifoliate yam starch could be agood alternative to corn starch in producing uncoated tablets for which high bond strength is essential.

A study was carried out by Anwar *et al* (2006) on pregelatinized cassava starch phosphate as hydrophilic polymer excipients for controlled release tablets. The results obtained showed that

pregelatinized cassava starch phosphate was a suitable material for matrix tablet controlled release.

Sodium carboxymethyl rice starches (SCMRSs) were prepared by Kittipongpatana *et al* (2006) from nine native rice starches with the amylose content between 14.67 - 29.09 %. The modification of native rice starch by carboxymethylation reaction improved several physicochemical properties.

Zhao and Augsburger(2005) reported significant reductions in the rate and extent of water uptake and swelling of sodium starch glycollate in acidic medium (O.1N HCl). This significantly increased tablet disintegration time.

The effects of physical (pregelatinization) and chemical (Acid hydrolysis) modifications on the disintegrants and dissolution properties of *Tacca involucrata* starch was investigated by Ofoefule *et al* (2004). Pregelatinized starch was more effective as a disintegrant than the acid hydrolyzed form of the starch and drug release from the tablets was not retarded.

Peerapattana *et al* (2004) modified glutinous starch (MGS),a hydrophilic matrix substance and studied its release profile in comparison with hydroxypropylmethylcellulose (HPMC) matrix. MGS was able to retard the release of Propranolol HCI to a degree less than that of HPMC.

In studying the tablet properties of spray dried acid modified starches, Puchongkavarin *et al* (2003) observed that the crushing strength and disintegration time of tablets increased with relative crystallinity. In contrast, while friability was reduced.

Alebiowu and Itiola (2003) evaluated the effects of pregelatinization of native sorghum and plantain starches on the mechanical properties of paracetamol tablet formulation in comparison with com starch BP. The tensile strength (TS) and brittle fracture index (BFI) were affected by pregelatinization of the starches.Alebiowu and Itiola (2003) also reported a decrease in disintegration time of tablets when changing from a native to a pregelatinized starch as disintegrants. The use of starch acetate as an excipient for coating multi-particulate beads for controlled drug delivery was investigated by Nutan (2004). Starch acetate was synthesized from native corn starch using the aqueous paste disintegration method followed by acetylation in pyridine. The results obtained showed that starch acetate was suitable as polymeric excipients for controlled drug delivery.The particle and powder properties of starch acetate powder were investigated and found to possess direct compression characteristics (Korhonen *et al*, 2002).

Eihie and Okor (2002) reported that acid treatment of tapioca powder imparted plasticity to tapioca powder which became compressible. In a study carried out by Atichokudomchai *et al* (2001) on some physicochemical properties of high-crystalline tapioca starch, the crushing strength of tablets formulated using high-crystalline acid modified starch increased with increasing crystallinity and a corresponding decrease of amylose content with time.

In a study carried out by Okafor *et al* (1991) on modified starches used in direct compression, they reported a significant effect of the modified starches on the drug release profile (disintegration and disssolution) of the tablets formulated.

Akande (1998), evaluated millet starch as both disintegrant and binder, using maize starch as standard concluded that millet starch can be used as both disintegrant and binder.

Mitrevej *et al*(1996) characterized the compression behaviours of spray dried rice starch (SDRS), as well as pregelatinized starch (PS), and microcrystalline cellulose (MCC) using Heckel analysis. SDRS possessed both good compactability and flowability making it a suitable direct compression excipient.

Pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starches in the formulation of dosage forms (Garr, 1988).

Native starch has been recognized as one of the most commonly used excipients in the manufacture of tablets which can be used as filler, disintegrant or as binder (Banker and Anderson, 1986).

Esezebo and Ambujan (1982) evaluated plantain (*Musa paradisiaca*) starch as tablet binder and disintegrant and compared it with maize starch as standard. They concluded that plantain starch has twice the binding and half the disintegrant property of maize starch.

However, due to the limitations of native starches such as poor compressibility and flow properties, some special starch products have been produced and introduced to the pharmaceutical industry (Davies, 2009).

## 2.3Pharmaceutical Tablets

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer (Sahoo, 2007).It can also be defined as the solid unit dosage form of medicaments with or without suitable diluents and prepared either by molding or by compression. It comprises a mixture of active substances and excipients. The excipients can include diluents, binders or granulating agents, glidants and lubricants to ensure effective tabletting, disintegrants to promote tablet break-up in the digestive tract, sweetners or flavours to enhance taste and pigments to make the tablets visually attractive (Levy and Gumtow, 1963).

Tablets offer advantages over both patients and manufacturers. Tablets are the most popular dosage form due to their simplicity and convenience in packaging, shipping and storage. For the patients, the ease of manufacturing, convenience in administration, accurate dosing and stability compared to oral liquids, tamper-proofness compared to capsules, safe compared to parenteral dosage forms makes it a popular and versatile dosage form (Hwang and Peck, 2001).

**Tablets are formulated for several reasons:**

- The oral route represents a convenient and safe way of drug administration.
- Suitable for large scale production
- Greatest chemical and microbial stability of all oral dosage forms,
- Compared to liquid dosage forms, tablets have better chemical and physical stability.
- The preparation procedure enables accurate dosing of the drug.
- Easy and cheap to package and transport.
- Tablets are convenient to handle and can be prepared in a versatile way with respect to their use and delivery of the drug (Alderborn, 2002).

### 2.3.1 Ideal Qualities Of A Tablet.

According to Alderborn (2007), the quality attributes a tablet must fulfill can be summarized as

Follows:

- The tablet should include the correct dose of the drug.
- It should have an elegant appearance and identity while being free of defects such as chips, cracks, discoloration and contamination.
- It should have strength to withstand the rigors of shocks encountered in its production, packaging, shipping and dispensing.
- It should have the physical stability to maintain its physical attributes over time.

- It must be able to release the medicament (agents) in the body in a predictable and reproducible manner.
- It must have a suitable chemical stability over time so as not to allow alteration of the medicinal agent(s).
- It should be of sufficient mechanical strength to withstand fracture and erosion during handling at all stages of its life time.
- It should be formulated into a product acceptable to the patient.

### 2.3.2 Types of Tablet.

1. Coated tablets
2. Uncoated tablets
3. Effervescent tablets
4. Soluble tablets
5. Dispersible tablets
6. Orodispersible tablets
7. Gastro-resistant tablets
8. Modified-release tablets (Sahoo, 2007)

#### 2.3.2.1 Uncoated Tablets

Uncoated tablets include single layer tablets resulting from a single compression of particles and multi-layer tablets consisting of concentric or parallel layer obtained by successive compression of particles of different composition. The excipients used are not specifically intended to modify

the release of the active substance in the digestive fluid. When examined under a lens, shows either a relatively uniform texture (single-layer tablets) or a stratified texture (multi-layer tablets) but no signs of coating (Aulton, 2013).

#### 2.3.2.2 Coated Tablets

A plain tablet is prepared by compressing a particulate solid in a die by the application of forces via two punches anddie. The coating material should either be sugar coating, film coating or press coating. Advantages of coated tablets include protection of ingredients from the environment, particularly light and moisture. Many drugs have bitter or unpleasant taste. Coating provides an efficient method of masking taste which makes the tablets convenient to swallow. It aids patient compliance with dosage schemes. It aids in rapid identification of product by the manufacturer, dispensing pharmacists and patients. Coating also facilitates handling in high speed automatic filling and packaging equipment. It helps to add mechanical strength to the tablet core. Cross contamination is also reduced in the manufacturing plant as dust from tablet is eliminated (Aulton, 2013).

#### 2.3.2.3Effervescent Tablets

Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates, which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in eater before administration (Aulton, 2013).

### 2.3.2.4Soluble Tablets

Soluble tablets are uncoated or film-coated tablets. They are intended to be dissolved in water before administration. The solution produced maybe slightly opalescent due to the added excipients used in the manufacture of the tablets (Aulton, 2013).

### 2.3.2.5 Dispersible Tablets

Dispersible tablets are uncoated or film-coated intended to be dispersed in water before administration, giving a homogeneous dispersion (Aulton, 2013).

### 2.3.2.6 Orodispersible Tablets

Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed (Aulton, 2013).

### 2.3.2.7Modified Release Tablets

Tablets placed under the tongue sublingually or in the inside of the cheek (buccal) can produce an immediate systemic effect by enabling the drug to be directly absorbed through the oral mucosa. Example is isoprenaline suphate (bronchodilator) and glyceryl trinitrate tablets (Vasodilator).These tablets are usually small and flat; They do not contain a disintegrant and are compressed, lightly to produce a fairly soft tablet. A sweetening agent like sucrose is used to impart sweetness (Aulton,2013).

### 2.3.3.8 Gastro- resistant tablets

Gastro-resistant tablets are delayed-release tablets that are intended to resist the gastric fluid and to release their active substance(s) in the intestinal fluid. Usually they are prepared from granules or particles already covered with a gastro- resistant coating or in certain cases by covering tablets with a gastro- resistant coating (enteric-coated tablets) (Aulton, 2013).

## 2.4 Tabletting Excipients

In a tablet formulation, a range of excipients are normally required along with the active ingredient in order to give the tablet the desired properties. For example, the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficiently strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients will affect all these properties(B.P,2009).

### 2.4.1 Fillers/Diluents

Fillers are used to make tablets of sufficient size for easy handling by the patient and to facilitate production. Tablets containing a very potent active substance would be very small without additional excipients. Good fillers possess good compactibility and flow properties, acceptable taste, non-hygroscopic and preferably chemically inert. It may also be advantageous to have filler that fragments easily, since this counteracts the negative effects of lubricants additions to the formula (De Boer, 1978).

### 2.4.1.1 Type of Fillers

#### 2.4.1.1.1Soluble Fillers

**i. Lactose**

Lactose may appear in different polymorphs depending on the crystallization conditions. Each polymorph has its specific properties. A-lactose monohydrate has very hard crystals and is non-hygroscopic. Lactose is the most widely used filler-diluent in tablets(Lerk,1993).

The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, readily available, bland taste, low hygroscopicity, excellent physical and chemical stability and water solubility (Lerk, 1993) .

Lactose from different suppliers exhibits different properties and are not interchangeable in direct compression formulations. The compaction profile of the lactose samples depends on the machine speed (Whiteman and Yarwood, 1988).

Crystalline lactose mainly consolidates by fragmentation while amorphous lactose consolidates by plastic deformation. Tablets containing amorphous lactose show high crushing strength with increasing water content (Lerk, 1993). Lactose based tablets exhibit better stability than mannitol and cellulose containing tablets at 40°C and 90% relative humidity over a 10 week period (Molokhia *et al*, 1987).The amorphous lactose yields tablets of higher tensile strength than crystalline lactose. Tensile strength increases with reduced particle size (Alderborn, 1988).

### ii. Spray-dried lactose

Spray-dried lactose is produced by spray drying the slurry containing lactose crystals. The final product contains a mixture of crystals of lactose monohydrate and spherical agglomerates of small crystals held together by glass or amorphous material. The former contributes to the fluidity while the latter gives compressibility to the product. It has excellent flow and binding properties. The amorphous portion of the spray-dried lactose is responsible for binding and plastic deformation. Compressibility is affected if it is allowed to dry below a level of 3 % w/w moisture. A disintegrant is required in the formulations containing spray-dried lactose. The tablets require a lubricant, but the lubricant does not affect binding. It has poor reworkability. Spray-dried lactose discolours with certain Active Pharmaceutical Ingredients containing an amine group (Alderborn, 1988).

Gunsel and Lachman (1976) were the first to describe the spray-dried lactose. They reported that the spray-dried lactose produces harder, less friable tablets, which were more susceptible to color development following storage at elevated temperature than tablets containing conventional lactose. Tablets containing spray dried lactose exhibited increase in crushing strength with decrease in the particle size. The spherically shaped spray-dried lactose particles resulted in the strongest tablets than the angular particles (Alvarenz*et al*, 2000). The disintegration time of spray-dried lactose tablets was essentially independent of compaction force (Khan and Rhodes, 1976). The spray-dried lactose undergoes fragmentation (Paronen, 1986).

### iii. Cellulose Derivatives

#### (a) Microcrystalline Cellulose

Microcrystalline cellulose (MCC) is purified partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. It is a white, crystalline powder composed of agglomerated porous microfibers (Shangraw *et al*, 1988). After purification by filtration and spray-drying, porous microcrystals are obtained.

Microcrystalline cellulose occurs as a white odourless, tasteless crystalline powder composed of porous particles of an agglomerated product.

Microcrystalline cellulose is prepared by hydrolysis of cellulose followed by spray drying. The particles thus formed are aggregates of smaller cellulose fibers. Depending on the preparation conditions, aggregates of different particle sizes can be prepared which have different Flowability(Aulton and Kevin,2013).

Apart from its use in direct compression, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. In the pharmaceutical market, microcrystalline cellulose is available under the brand names Avicel, Emcocel etc

**(b) Hydroxypropylcellulose**

Alvarez-Lorenzo *et al* (2000),reported that the difference in flow and compaction properties, the mechanical and microstructure properties of the tablets prepared from various grades of low-substituted hydroxypropylcelluloses are attributed to difference in the specific surface area of the materials.

**(iii)Ethylcellulose**

Ethylcellulose (EC) is a polymer of β-anhydroglucose building blocks joined together by acetal bonding. It is generally considered as a non-toxic, biocompatible and non-biodegradable polymer (Murtaza *et al*, 2009).

Sangekar *et al* (1996) evaluated a new grade of Ethylcellulose in the direct compression of modified release matrix tablets. This new grade of ethylcellulose improved the compactibility and retarded release rates as compared to other grades of EC, while maintaining good manufacturability.

**iii. SUGARS**

**(a) Sucrose**

Sucrose is widely used as filler in chewable tablets and as a binder in wet granulation.Tablets with higher strength, which disintegrates faster can be produced using this material than tablets made with commercially available directly compressible sugars (Bolhuis, 1992).

**(b) Emdex**

Emdex is produced by hydrolysis of starch and consists of aggregates or' dextrose microcrystals intermixed and cohered with a small quantity of higher molecular weight sugars. Emdex occurs as white, free flowing, porous spheres which are water soluble and non - hygroscopic. Emdex is generally used in directly compressible chewable tablets because of its sweet taste. It has good binding properties and slight lubricant sensitivity. It exhibits high moisture sensitivity, at room temperature and at 50 % RH, the crushing strength of tablets decreases dramatically, whereas during storage at 85 % RH tablets liquefy (Bolhuis *et al*, 1996).

**(c) Mannitol**

It is water soluble, non-hygroscopic and produces a semi-sweet, smooth, cool taste. It can be advantageously combined with other direct compression excipients. Sangekar *et al* (1996) reported mannitol as the best sugar for chewable tablet formulation prepared by direct compression out of twenty-four formulations of placebo tablets, made from eight excipients and three disintegrants.

**(d)Starch**

Mullick *et al* (1992) reported that dextrinized rice, corn, wheat and tapioca starches prepared by dextrinization exhibited very good flow, compression properties and disintegration qualities for direct compression tableting.

The directly compressible starch (Starch 1500) is relatively fluid and does not require a lubricating agent when compressed alone. It is more effective as a dry binder and gives equivalent or faster disintegration and dissolution compared to starch USP (Mittal, 1968). Due to improved flowability and compressibility,pregelatinized starch can be used as a binder in direct compression (Itiola, 1991).

**iv. Inorganic Calcium Salts**

**(a) Dicalcium Phosphate Dihydrate**

According to Rees (1978), Dicalcium phosphate is the most common inorganic salt used in direct compression as a filler-binder. The advantage of using dicalcium phosphate in tablets for vitamin and mineral supplement is the high calcium and phosphorous contents. Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.4, which precludes its use with active ingredients that are sensitive to even small amount of alkali (i.e. ascorbic acid). It exhibits high fragmentation propensity. The authors reported that the increase in dwell time had insignificant effect on dicalcium phosphate dihydrate compacts whereas increase in dwell time increased the consolidation of other materials in the rank order sodium chloride, anhydrous lactose, amicrocrystalline cellulose and modified starch.

Panaggio *et al* (1984) studied the effects of varying proportions of dicalcium phosphate dihydrate and modified starch matrices in tablets prepared by direct compression.The authors and observed that at some concentrations, the properties of tablets were intermediate between

those of the pure components and varied linearly with small changes in relative proportions. Water of crystallization of dicalcium phosphate dihydrate could possibly be released during processing and thus chemically interact with hydrolysable drug (Schalack *et al*, 2001).

**(b). Emcompress**

Emcompress consists of aggregates of small primary particles of dicalcium phosphate. Unlubricated Emcompress tablets are difficult to eject from dies, and therefore, require high lubrication. The hardness of tablets containing Emcompress is not affected by the machine speed and lubricant such as magnesium stearate due to the fragmentation behaviour during compression and consolidation. It can be a good directly compressible excipient when used in combination with microcrystalline cellulose or starch (Khan and Rhodes, 1975).

### 2.4.2 Binders

A material with a high bonding capacity can be used as a binder to increase the mechanical strength of the tablet. A binder is usually a ductile material prone to undergo plastic (irreversible) deformation. Table 2.1 shows the classification of binders based on their sources. It shows binders gotten from three main sources mainly sugar polymer, natural and synthetheic sources. Typically, binders are polymeric materials, often with disordered solid state structures. Of special importance is the deformability of the peripheral parts (asperities and protrussions) of the binder particles (Nystrom*et al*, 1993).

Thereby, these groups of materials have the capacity of reducing interparticulate distance within the tablet, improving bond function. However the activity of the binder depends on both its own properties and those of other compounds within the tablet. A binder is often added to the granulation liquid during wet granulation to improve cohesiveness and compactibility of the powder particles, which assist formation of agglomerates or granules. It is commonly accepted that binders added in dissolved form during a granulation process, is more effective than when used in dry powder form during direct compression (Nystrom*et al*, 1993).

**Table 2.1 shows the classification of binders according to Nuten (2004)**

| Sugars Polymer | Natural Binders | Synthetic/Semisynthetic |
|---|---|---|
| Sucrose | Acacia | Methyl Cellulose |
| Liquid glucose | Tragacanth | Ethyl Cellulose |
| | Gelatin | Hydroxy Propyl Methyl Cellulose ( HPMC) |
| | Starch Paste | Hydroxy Propyl Cellulose |
| | Pregelatinized Starch | Sodium Carboxy Methyl Cellulose |
| | Alginic Acid | Polyvinyl Pyrolidone (PVP) |
| | Cellulose | Polyethylene Glycol (PEG) |
| | | Polyvinyl Alcohols |
| | | Polymethacrylates |

### 2.4.3 Disintegrants

A disintegrant is a substance or a mixture of substances added to a tablet formulation to facilitate its breakup or disintegration when the tablet comes in contact with an aqueous fluid.The oldest and most popular disintegrants are corn and potato starches. Starch in the proportion of 5% of tablet weight is suggested, but if more rapid disintegration is desired, the amount may be increased to 10 or 15%.Certain agents called super disintegrants are effective at as low concentration as 2-4%.Examples are:croscarmellose, crospovidone and sodium starch glycolate.Disintegrants have been classified chemically as starches, dyes, cellulose, gums and cross linked polymers(Rudnic, 1999).

It has been postulated that disintegrants work via Four mechanisms;

(a) Promotion of the uptake of aqueous liquids by capillary forces,
(b) Swelling in contact with water,
(c) Release of gases when in contact with water and
(d) Destruction of the binder by enzymatic action (Rudnic, 1999).
(e) Plastic deformation and restoration of original structure of starches.

Fig 2.2 shows the path taken by an intact tablet when in contact with the gastrointestinal fluid. The tablet first disintegrates; then the granules deaggregates into primary particles.Dissolution and absorption occur, causing the drug to appear in the blood.

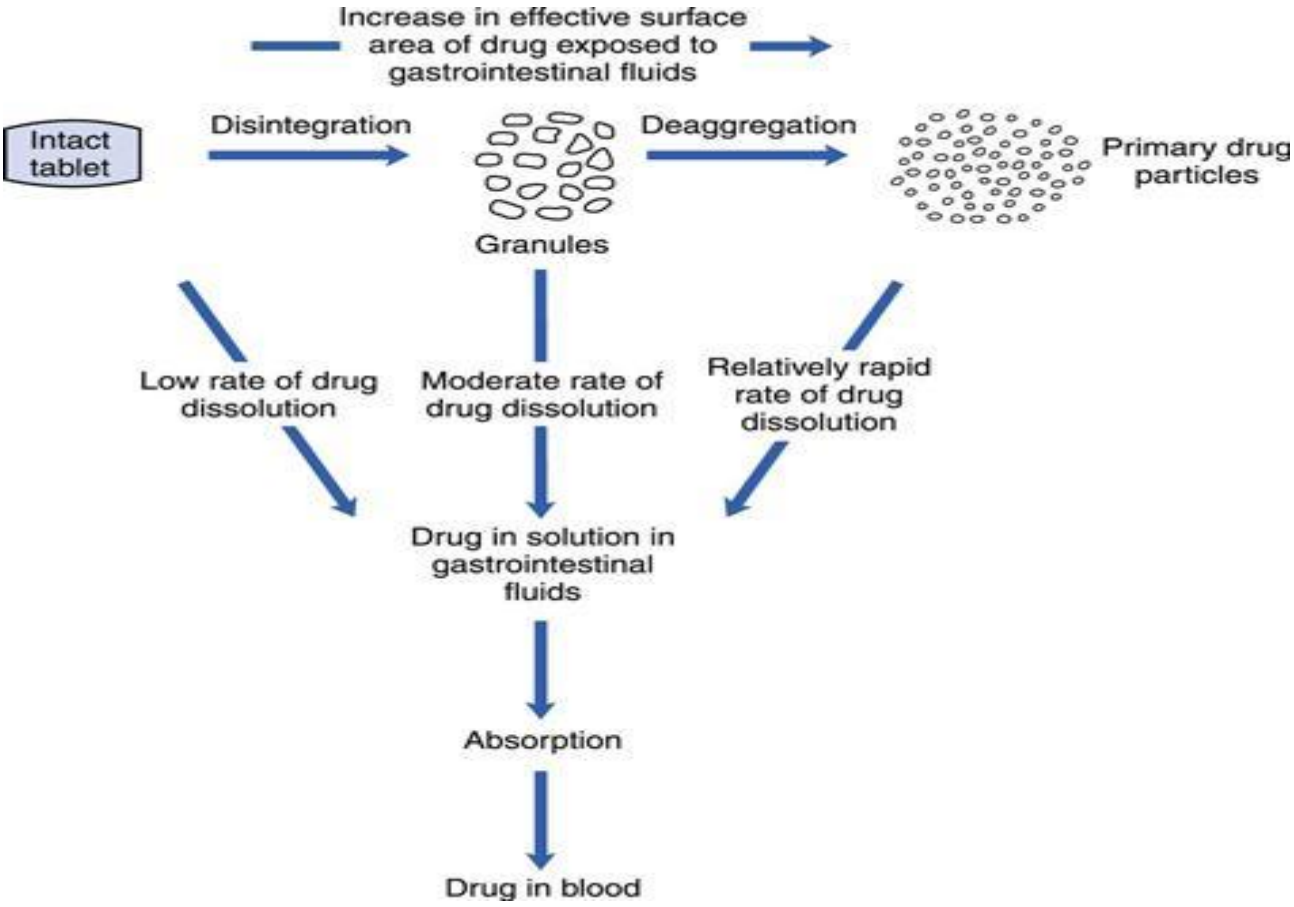



**Figure 2.2 Diagram showing the dissolution of a tablet present in the gastrointestinal fluids.**

### 2.4.4 Lubricants

The function of the lubricant is to ensure that tablet formation and ejection can occur with low friction between the tablet and the die wall.Lubrication is achieved mainly by two mechanisms: Fluid lubrication and boundary lubrication. In fluid lubrication, a layer of fluid is formed between the moving surfaces of the powder thus reducing friction. Liquid paraffin is an example of lubricants utilizing this mechanism. Boundary lubrication is considered as a surface phenomenon. The sliding surfaces are separated by only a thin film of the lubricant,usually fine particulate solid e.g magnesium stearate( Adams, 1994).

Because many lubricants are hydrophobic, tablet disintegration and dissolution are often retarded by lubricants. Because of these effects, more hydrophilic substances have been suggested as alternative to hydrophobic ones. These include: surfactants and polyethylene glycol (Johansson, 1984).

### 2.4.5 Glidants and Antiadherents

Glidants are added to increase the flowability of the powder mass,reduce interparticular friction and improve powder flow in the hopper shoe and die of the tabletting machine. An anti-adherent can be added to decrease sticking of the powder to the faces of the punches and the die walls during compaction, while and a lubricant is added to decrease friction between powder and die, facilitating ejection of the tablet from the die (De Boer *et al*.,1978).

## 2.5 Methods of Tabletting

Tablets are produced through three different methods: These include

- Wet granulation
- Dry granulation
- Direct Compression

### 2.5.1 Wet Granulation

This is the most widely used method of tablet preparation. Its popularity is due to the greater probability that the granulation will meet the physical requirements for the compression of a good tablet. The main advantage is that it involves a lot of separate steps. The steps include: weighing, mixing, granulation, screening the damp mass, drying, dry-screening, lubrication and compression (Itiola, 1991).

During mixing, the active ingredient, diluent and dis-integrant are mixed and blended well. For small scale, stainless steel bowl, mortars or large piece of paper can be used. Patterson-Kelley twin shell blender and double-cone blenders are suitable for large scale while planetary mixers are common in pharmaceutical industries (Itiola, 1991).

A solution of the binding agent is added to the mixed powder with stirring and the wet granulation is forced through a 6-8 mesh screen.While tray drying was the most widely used method for drying in the past, fluid bed drying is now considered the standard. Microwave

drying and infrared drying are equally good methods. After drying, the granulation is further size-reduced by passing it though smaller screen (Itiola, 1986).

This is followed by addition of lubricant as fine powder by screening through 60 or 100-meshnylon cloth to eliminate lumps and to ensure effective covering of the granules. The lubricants is gently blended with the granulation. This is accomplished by compression (Hwang and Peck, 2001).

### 2.5.2 Dry Granulation

When tablet ingredients are sensitive to moisture or unable to withstand elevated temperatures during drying, and when the ingredients have sufficient inherent binding properties, dry granulation is suitable. Phenorbarbitone sodium and vitamin-B complex are produced by this method. The materials are weighed and mixed together. The mixture is then compressed into large tablets called slugs in the process called slugging. The slugs are screened to produce granules and the granules are lubricated before compression. Therefore it is often referred to as double compression(Rudnic and Kottke, 1999).

The method balances the excesses of wet granulation and direct compression. The non-suitability of wet granulation for moisture and heat sensitive drugs are taken care of by dry granulation. Also the non-suitability of direct compression for large-dose drugs are taken care of by this method of tablet production(Rudnic and Kottke, 1999).

It utilizes less equipment and space compared to wet granulation. It eliminates the stage of liquid binding and so improves disintegration. Also, fewer steps are involved compared to wet granulation.The basic challenges of dry granulation includes: involvement of specialized heavy duty tablet machine for preparing slugs and the non-suitability of materials with poor reworking potential(Rudnic and Kottke, 2006).

### 2.5.3 Direct Compression

Over the past hundred years, tablet manufacturers have developed materials and processes that can produce compressed tablets containing a precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost. The development in the field of APIs, excipients and tabletting machines during the past decades has made tablet manufacturing a science and the tablets, the most commonly used dosage form (Resenack and Muller, 2002).

The ease of manufacturing, convenience of administration, accurate dosing, and stability compared to oral liquids; tamper -proofness compared to capsules; safe compared to parenteral dosage forms makes it a popular and versatile dosage form. Experts in the art of tabletting are aware of the basic art of tabletting by the three well-known methods, i.e. wet granulation, dry granulation and direct compression (Resenack and Muller, 2002).

In the early 1960's, the introduction of spray-dried lactose and Avicel had changed the tablet manufacturing process and opened avenues fordirect compression tabletting. Shangraw (1988) conducted a survey of 58 products in the United States of America on the preference of the granulation process. The results were in favour of direct compression. About 41 % of the

companies indicated that direct compression was the method of choice, and 41.1 % indicated that they used both direct compression and wet granulation. Only 1.7% of the respondents indicated that they never used direct compression and 15.5 % indicated that the process was not recommended (Resenack and Muller, 2002).

Previously, the word "direct compression" was used to identify the compression of a single crystalline compound (i.e. sodium chloride, potassium chloride, potassium bromide, etc.) into a compact form without the addition of other substances. Current usage of the term "direct compression" is to define the process by which tablets are compressed directly from the powdered blends of active ingredient(s) and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved. The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques (Shangraw and Dermarest, 1993).

It has been estimated that less than 20 % of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack the flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible excipients may yield satisfactory tablets for such materials (Shangraw and Dermarest, 1993).

#### 2.5.3.1 Directly Compressible Excipients

Excipientscan be defined as "Substances, other than the API in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid

the processing or the manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use. Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of pharmacopoeia unless adequately justified (Robertson, 1998).

Excipients no longer strictly maintain the initial concept of "inactive support" because of the influence they have both over biopharmaceutical aspects and technological factors. In order to deliver a stable, uniform and effective drug product, it is essential to know the properties of the active ingredient alone and in combination with all other ingredients based on the requirements of the dosage form and processes applied. Excipients are usually produced by batch process; hence, there is a possibility of batch-to-batch variation from the same manufacturer (Robertson, 1998).

Excipients obtained from the different sources may not have identical properties with respect to use in a specific formulation. To assure interchangeability in such circumstances, users may wish to ascertain equivalency in final performance or determine such characteristics before use. Such tests are thus related to the functionality, that the excipient impart to a specific formulation (Armstrong, 1997).

In order to manufacture any finished product with consistent quality, standardization of raw materials in the drug formulation is necessary for its acceptance by regulatory authorities and

pharmaceutical formulators. Unfortunately, such performance standards have not been included in pharmacopoeia primarily because their specifications have always been based on chemical purity and because it is not possible to standardize performance criteria. Pharmacopoeia standards do not take into account particle characteristics or powder properties, which determine functionality of excipients (Banker, 1994).

#### 2.5.3.2 Ideal requirements of directly compressible excipients

i. The directly compressible excipient should be free flowing. Flowability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of ± 5 %. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and inaccurate filling (Tester and Debon, 2000).

**ii.** Compressibility is required for satisfactory tableting, i.e., the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible diluent should have good compressibility, i.e. increase in compaction pressure reduces the volume of the compact (Shangraw, 1988).

**iii.** Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed into compact with the given directly compressible excipient. A directly compressible excipient should have high dilution potential so that the final dosage form has a

minimum possible tablet weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient(Shangraw, 1988).

**iv.** A directly compressible excipient should be capable of being reworked without loss of flow or compressibility. On recompression, the excipient should exhibit satisfactory tabletting characteristics. The excipient should remain unchanged chemically and physically. The directly compressible excipient should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat(Shangraw, 1988).

**v.** A directly compressible excipient should have a particle size equivalent to that of the active ingredients present in the formulation (Jivraj *et al*, 2000). The particle size distribution should be consistent from batch to batch. Reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient(s) in order to avoid segregation(Jivraj *et al*, 2000).

**vi.** Filler-binders should not accelerate the chemical and or physical degradation of the API(s) or excipients (Jivraj *et al*, 2000).

vii.Filler-binders should not interfere with the bioavailability of the active ingredient. It should be compatible with all the excipients present in the formulation (Jivraj *et al*, 2000).

**viii**.Filler-bindersshould be physiologically inert (Shangraw, 1988). It should not interfere with: the disintegration or dissolution of the active ingredient. It should be colorless and tasteless. It should be relatively cost effective and available in desired time. It should accept colorants

uniformly. It should show low lubricant sensitivity. It should show batch-to-batch reproducibility of physical and physicomechanical properties(Jivraj *et al*, 2000). .

**ix.**Filler-binders should possess proper mouth feel, which is defined as the feel or the sensation in the mouth, produced when the excipient is used in chewable tablets (Armstrong, 1997).

### 2.5.3.3 Advantages of Direct Compression

**i.** The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets(Pringles*et al*, 2005).

**ii.** Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects (Pringles *et al*, 2005).

**iii.** Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms (Banker, 1994).

**iv.** The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less(Banker, 1994).

**v.** Materials are "in process" for a short period of time, resulting in less chance for contamination or cross contamination, and making it easier to meet the requirements of current good manufacturing practices (Sangekar*et al*, 1996).

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

**2.5.3.4 Limitations of Direct Compression**

**i**. Direct compression is more prone to segregation of the powder mixdue to the difference in density of the API and excipients . The dry state of the material during mixing may induce static charge and lead to segregation. This may lead to the problems like weight variation and content uniformity(Rubinstein, 1998). .

**ii**. Directly compressible excipients are the specialty products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively more costly than the respective raw materials(Eihie, 2002).

**iii.** Most of the directly compressible materials can accommodate only 30 - 40 % of the poorly compressible active ingredients like acetaminophen. That means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing (Eihie, 2002).

**iv.** All the spray-dried directly compressible excipients show poor reworkability sincethe original spherical nature of the excipient particles is lost. API that has poor flow properties and/or low bulk density is difficult to process by direct compression(Rubinstein, 1998).

**v.** Lubricants have a more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch 1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimising the length of blending time to as little as 2 - 5 min (Davies, 2009).

There is lack of awareness in some situations that the excipient behave differently, depending upon the vendor so much so that substitution of one source to another is not possible (Banker, 1994). Hence, there is a need for greater quality control in purchasing the raw material to assure batch uniformity.

### 2.6 Compression and Compaction of Powder

According to Alderborn (2007), "The compressibility of a powder is defined as its propensity when held within a confined space, to reduce in volume when loaded". At a certain load, the reduced space and the interparticulate friction will prevent any further interparticulate movement. The shape may change temporarily until the pressure is removed. This is called elastic deformation.

When there is permanent shape change, it is called plastic deformation. Increasing the load beyond this point will result to brittle fracture or particle fragmentation. The compactability of

powder refers to its propensity to form a coherent tablet and thus represents a critical powder property in successful tablet operation. Powders with high compactability form tablets with high resistance towards fracturing and without tendencies to cap or laminate (Alderborn, 2007).

### 2.6.1 Phases of Powder Compaction

According to Bodga (2002), compaction process has four identifiable phases.

**a.** Consolidation phase (reduction in volume)

**b.** Elastic or reversible deformation. If the force were to be removed in this phase, the powder will recover

**c.** Plastic or irreversible deformation. This is the most critical in tablet formation.

**d.** Brittle fracture which occurs if more pressure is applied after plastic deformation.

### 2.6.2 Factors Affecting Compaction and Consolidation of Powders

The compaction and consolidation of powders are influenced by a number of factors. These factors can be classified into two namely: operational factors and those due to the physical properties of the powder.

**A.** Operational Factors: The operational factors affecting compaction and consolidation of powders are: - pre-compression, compaction pressure, compression speed and duration.

**(i)** Pre-compression: - According to Odeku, (2005), the powder's relative density at the point at which the applied pressure equals zero (Do) describes the initial rearrangement phase of

densification as a result of die filling. This value affects the phase of powder rearrangement at low pressures.

**(ii)** Compaction Pressure: Compaction pressure is the force applied by the upper punch to a powder bed in a die cavity during compression to effect the consolidation and bonding of the powder into a compact mass called tablet. The compaction force is an important parameter that is capable of significantly affecting the tablet properties such as: tensile strength, hardness, friability, specific surface porosity, density, disintegration and dissolution times (Molokhia*et al*., 1987).

The application of a compacting load to a material in a die imparts work to the material in the die. The amount of work applied is a function of the time over which the load is applied. The greater the work done on a material being compacted, the greater is the true area of contact and therefore, potentially, the greater the degree of cohesion or adhesion. The deformation during compaction will be proportional to the applied force. The tolerance range of compaction forces is that range between the critical minimum and critical maximum that produces satisfactory tablets (Alebiowu and Itiola, 2002).

A good formulation should have a wide tolerance range. The variations of machine type and operating compression speed along with adjustments of formulations can change significantly the width of the tolerance range (Camphel and Theivagt, 1958).

At compaction forces below a certain critical minimum, the powder will not form a coherent mass, while at forces above a critical maximum, tablets may be too hard to meet basic requirements such as disintegration and dissolution tests. At the highest pressures, there may be capping and lamination. Different materials have been known to exhibit varying degree of sensitivity to applied compaction pressure. The high sensitivity of some excipients, such as microcrystalline cellulose, to applied force makes it necessary to control the compaction force during production (Copper*et al*., 1962).

**(iii)** Compression Speed and Duration: - Apart from the magnitude of the compacting load, the rate at which it is applied, the duration of the application and the characteristic transmission of the force throughout the compact to which the load is being applied are primary points of importance when compaction force is considered (York, 1978).

**B.**Physical Properties of the Material: - The physical properties of powder that affect the compaction characteristics are: -

**(i)** Particle size: The Particle size may determine the deformation mechanism of a material and thus influences the consolidation and compaction characteristics of elastic and plastic components. Heckel equation (1961) is the most widely used compression equations because it can provide information on the mechanism of consolidation of the powder and allows for the effect of particle size to be readily studied.

Alebiowu *et al* (1985) reported the effect of particle size on the consolidation of powders, and noted that the Heckel treatment facilitated the determination of the influence of particle size - on consolidation. It was possible, from the values of the true density, yield pressure and original packing density to predict the consolidation mechanism and relative compact density at pressures above the material's yield value.

Burell (2003) found that the tensile strength of paracetamol tablets prepared from cassava starch binder increased generally as binder concentration increased. They also found that the angle of repose and Hausner's ratio data for cassava starch indicated an increase in interparticulate frictional and cohesive forces with decreasing particle size. This observation explained the increase in tablet strength with decreasing particle size of starch due to increase in density as a result of the increase in plastic flow and packing with decreasing particle size.

**(ii)** Surface Area: Franco *et al.* (1992) studied the compressional characteristics of four starches namely: barley, corn, potato and wheat using constants obtained from the Heckel plots. They found that potato starch, with the greatest mean particle diameter, formed the densiest column in the die filling stage because it had the least electrostatic forces that could prevent the packing of particles in the bulk state. Barley starch that had the smallest particles had the loosest column because there were mechanical and electrostatic forces prevent packing. They deduced that mechanical and electrostatic forces to prevent packing and also that the values of the packing fraction in the bulk state are strongly dependent on the particle size and shape. The rearrangement of particles occurred more with smaller particle size (corn) and less with large

particle size (potato). This seemed to be particularly responsible for the densification of wheat and barley starches, which have a relatively wide particle size distribution and an irregular particle shape.

**(iii)** Particle Shape: The shape of particles can affect the flow properties of a powder mixture. This is important because pharmaceutical powders could have different shapes due to their chemical identity or the different processes to which they are subjected. Hsu *et al* (1997) found the that angle of repose of powders increased whilst the bulk density and flowability decreased with increasing departure from spherical shape of particles, due to the greater resistance to shear or flow of an assembly of irregular particles compared to those of spherical particles with the same size and density.

Alderborn *et al*. (1985) studied the effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets. The milled powder gave tablets with the highest strength probably due to the increased surface irregularity. This might be because of increased number of points with a close proximity between the particles, increased total bonding surface area, enhanced interparticulate friction and facilitation of plastic flow at the contact points

### 2.6.3 Compaction Characteristics of Pharmaceutical Powders

Compression refers to a reduction in the bulk volume of materials as a result of displacement of the gaseous phase. At the onset of the compression process, when the powder is filled into the die cavity, and prior to the entrance of the upper punch into the die cavity, the only forces that

exist between the particles are those that are related to the packing characteristics of the particles, the density of the particles and the total mass of the material that is filled into the die. When external mechanical forces are applied to a powder mass, there is usually a reduction in volume due to closer packing of the powder particles, and in most cases, this is the main mechanism of initial volume reduction. However, as the load increases, rearrangement of particles becomes more difficult and further compression leads to some type of particle deformation which can be elastic, plastic or brittle fracture (Heckel, 1961).

Many empirical relationships have been proposed to describe the resulting data which may be expressed equivalently in term of stress - strain, pressure - volume or pressure - density. These relationships have been utilized by many researchers to explain the compaction characteristics of powders.

(a) Heckel Equation

According to Heckel (1961),

$Ln\ [1/(1-D)] = kP + A$ ………………………………………….. (2.1)

Where d is the relative density AND (1-D) denotes the pore fraction, and P the applied pressure, A is constant suggested to reflect particle rearrangement and frangmentation, and K the slope of the linear part of the relationship which is suggested to reflect the deformation of particles during compression. A is the intercept of the prolonged linear portion of the plot with the y axis.

Plotting the value of ln [ 1 / (1 - D)] which is porosity against applied pressure, P, yields a linear graph having slope, k and intercept, A. The value of k is the reciprocal of the mean yield pressure, $P_y$ which is inversely related to the ability of the material to deform plastically under pressure. A Low value of P indicates a faster onset of plastic deformation; A is a function of the original compact volume and is related to the densification and particle re-arrangement prior to bonding. D is the relative density of tablet at the applied pressure P.

From the value of A, the relative density, $D_A$, which represents the total degree of densification at zero and low pressures (Mitrevej *et al*., 1996), can be calculated using the equation:

$A = \text{In } 1 / (1 - D_A)$ ……. (2.2)

Thus,

$D_A = 1 - e^{-A}$ …… (2.3)

The relative density of the powder bed at the point where the applied pressure equals zero, $D_0$, is used to describe the initial rearrangement phase of densification as a result of die filling. $D_0$ is determined experimentally and is equal to the ratio of bulk density at zero pressure to the true density of the powder. The loose packing of granules at zero pressure tends to yield low $D_0$ values (Odeku and Itiola, 1998).

The relative density, $D_B$, describes the phase of rearrangement of particles in the early stages of compression and tends to indicate the extent of particle or granule fragmentation, although fragmentation can occur concurrently with plastic and elastic deformation of the constituent

particles (Odeku, 2005). The extent of the rearrangement phase depends on the theoretical point of densification at which deformation of particles begins. $D_B$ can be obtained from the equation:

$$D_B = D_A - D_0 \quad \text{(2.4)}$$

(b) **Kawakita equation**

The Kawakita equation was developed to study powder compression (Kawakita and Ludde, 1971) using the degree of volume reduction, C, a parameter equivalent to the engineering strain of the particle bed and is expressed as:

$$C = (V_o - V_p)/V_o = a\,b\,P / (1+bP) \quad \text{(2.5)}$$

In practice, the Kawakita equation can be rearranged to give:

$$P/C = P / a + 1 / ab \quad \text{(2.6)}$$

Where C is the degree of volume reduction, $V_0$ is the initial volume of the powder bed and $V_p$ is the powder volume after compression; *a* and*b* are constants which are obtained from the slope and intercept of the P/C versus P plots respectively. The constant *a* is equal to the minimum porosity of the bed prior to compression while *b*, which is termed the coefficient of compression, is related to the plasticity of the material. Value of 1 - *a* yield the initial relative density of the material, which has been shown to provide a measure of the packed initial relative density of tablets with the application of small pressure or what may be referred to as tapping (Presscott, 2000). The reciprocal of *b* yields a pressure term, $P_k$, which is the pressure required to reduce the

powder bed by 50 %. The value of $P_k$ is an inverse measurement of plastic deformation. The lower the value of $P_k$, the higher the degree of plastic deformation occurring during compression(Adams, 1994).

The Heckel and Kawakita plots have been employed to evaluatethe compressional characteristics of paracetamol formulations (Odeku and Itiola, 1988). Both plots have their limitations and are believed to generally exhibit linearity for materials at high and low pressures, respectively (Prescott,2008). Thus both plots have been used with the hope of obtaining more accurate information on the compressional characteristics of the paracetamol tablet formulations.

Research has shown that the Heckel and Kawakita plots gave largely different indications for the plasticity of the formulations.

The observed differences between $P_y$ and $P_k$ for the different binders are probably due to the fact that the $P_y$ values relate essentially to the onset of plastic deformation during compression while the $P_k$ values appear to relate to the amount of plastic deformation occurring during the compression process, especially with plastic deformation being a time-dependent phenomenon (Akande , 1988).

### 2.6.4 Types of Deformation

Hall(1973) and York and Pilpel (1972) classified powders into three types A, B and C. The classification is based on Heckel plots and the compaction behavior of the material. The Heckel plots for the three different types of materials are shown in figures 2.3, 2.4 and 2.5.

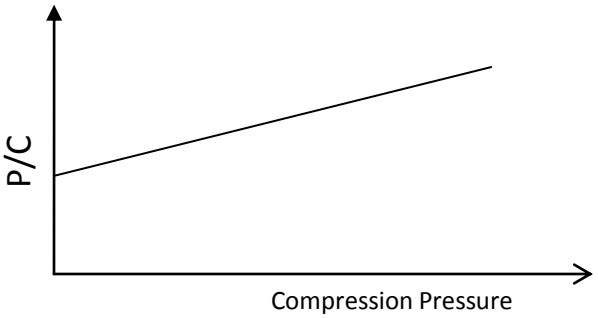



**Figure 2.3 Heckel Plot for Type A Material**

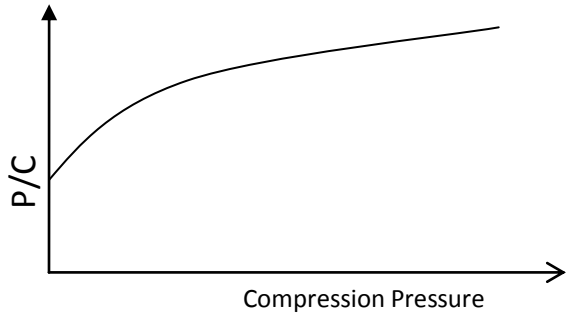



**Figure 2.4 Heckel Plot for Type B Material**

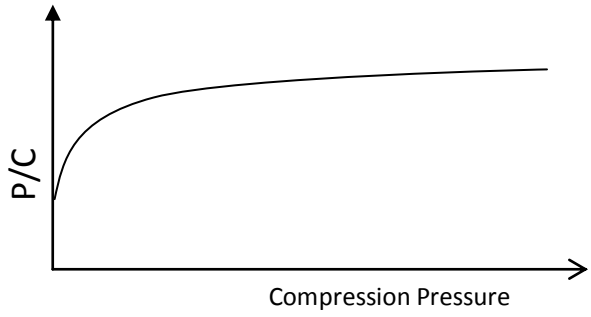


**Figure 2.5 Heckel Plot for Type C Material**
Where Pr is Porosity

With type A material, a linear relationship is observed, with the plots remaining parallel as the applied pressure is increased,indicating deformation apparently only by plastic deformation (Fig. 2.3). An example of materials that exhibit type A behaviour is sodium chloride. Type A materials are usually comparatively soft and readily undergo plastic deformation retaining different degrees of porosity depending on the initial packing of the powder in the die. This is influenced by the size distribution and shape of the original particles (Heckel, 1961).

For type B materials, there is an initial curved region followed by a straight line (Fig. 2.4). This indicates that the particles are fragmenting at the early stages of the compression process i.e. brittle fracture precedes plastic flow. Type B Heckel plots usually occur with harder materials with higher yield pressures which usually undergo compression by fragmentation first, to provide a denser packing. Lactose is a typical example of such materials (Heckel, 1961). .

Type A Heckel plots usually exhibit a higher final slope than type B which implies that the former materials have a lower yield pressure. This is so because fragmentation with subsequent percolation of fragments is less efficient than void filling by plastic deformation. In fact, as the porosity approaches zero, plastic deformation may be the predominant mechanism for all materials (Heckel, 1961).

For type C materials, there is an initial steep linear region which becomes superimposed and flatten out as the applied pressure is increased (Fig. 2.5). York and Pilpel (1973) ascribed this

behavior to the absence of a rearrangement stage and densification is due to plastic deformation and asperity melting. Example gold and silver

**2.7 Metronidazole**

White to pale-yellow crystalline powder with a slight odour.Bitter and saline taste.pH (saturated aqueous solution) about 6.5.

Metronidazole (Fig 2.6) is a synthetic nitroimidazole derivative with antiprotozoal and antibacterial activities. Although its mechanism of action is not fully elucidated, un-ionized metronidazole is readily taken up by obligate anaerobic organisms and is subsequently reduced by low-redox potential electron-transport proteins to an active, intermediate product. Reduced metronidazole causes DNA strand break, thereby inhibiting DNA synthesis and bacterial cell growth (B.P, 1988).

Metronidazole is a medium dose drug and poorly compressible due to its crystalline nature (Olowosulu *et al*,2014).

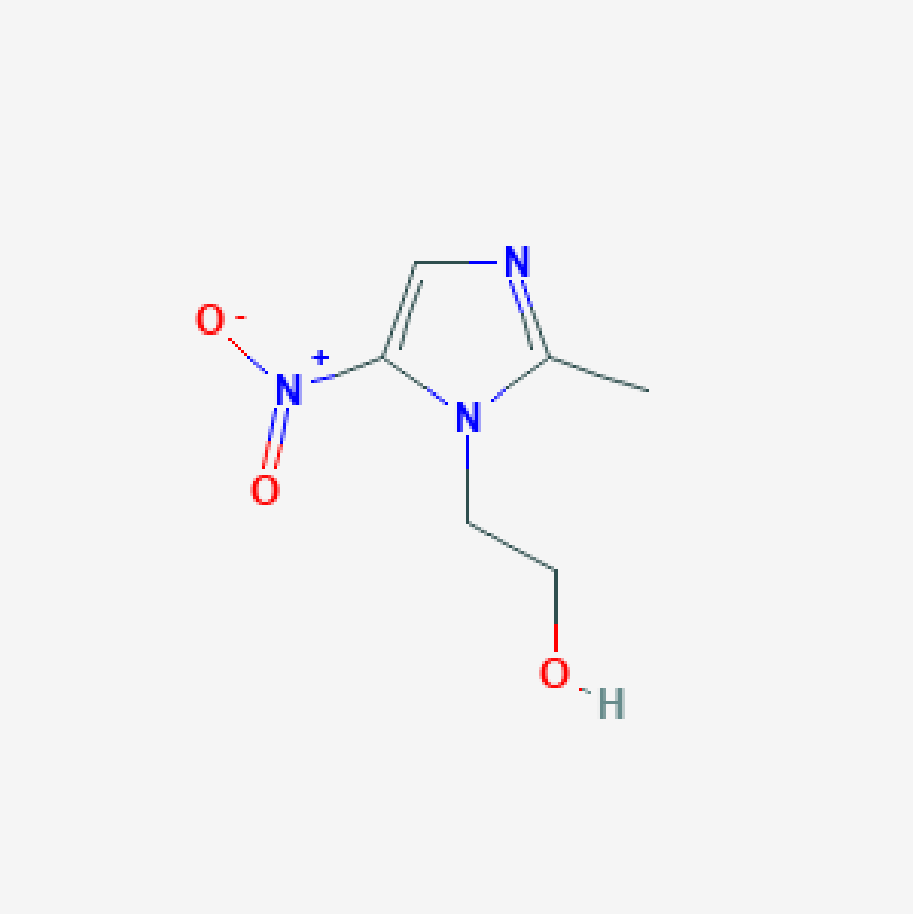



**Figure 2.6 Chemical Structure of Metronidazole**

# CHAPTER THREE

# 3.0 MATERIALS AND METHODS

## 3.1 Materials

### 3.1.1 Experimental Samples

- Finger Millet Starch *Eleusine coracana*obtained from Samaru Market,Zaria.
- Metronidazole Powder (BDH Chemicals Ltd Poole, England)
- Microcrystalline cellulose, AVICEL PH 101 (ATOZ Pharmaceuticals Ltd, India).
- Starlac (BDH Chemicals Ltd Poole, England)

### 3.1.2 Chemicals and Reagents

- Hydrochloric Acid (Sigma-Aldrich laborchemikalien GmbH, Germany)
- Stearic acid powder (BDH Chemicals Ltd Poole, England)
- Talc powder (BDH Chemicals Ltd Poole, England)
- Xylene (BDH Chemicals Ltd Poole, England)
- Ascorbic acid powder (BDH Chemicals Ltd Poole, England)
- Ethanol (Absolute) (BDH Chemicals Ltd Poole, England)

### 3.1.3 Glassware Apparatus

- Beakers, Conical Flasks, Measuring Cylinders, Stirring rods

- Density bottle
- Desiccator
- Pestle and Mortar
- Test tubes



- Whatman Filter Paper 11 cm (Whatman International Ltd Maidstone, England)

### 3.1.4 Equipments

- 79-1 Magnetic Stirrer with water (MSI)
- Compound Biological Microscope (Serial No: B2006-5450-1026, Fisher Scientific Company,China).
- Disintegration Test Unit (Type ZT3, Erweka - Apparatebau - G.m.b.H Heusenstamm, Germany)
- Dissolution Test Apparatus (Type DT, Erweka - Apparatebau - G.m.b.H Heusenstamm, Germany)
- Flow Rate Meter (Type GDT, Erweka - Apparatebau - G.m.b.H Heusenstamm , Germany)
- Single Punch Tabletting Machine ( Type EKO, Erweka - Apparatebau - G.m.b.H Heusenstamm,Germany)
- Tablet Friabilator (Type TA3R, Erweka - Apparatebau - G.m.b.H Heusenstamm, Germany)
- Mettler Analytical Balance (Serial No: 647624, Type P163, Supplied by Gallenkamp, Mettler Instrumente AG, CH-8606 Grefensee - Zurich, Switzerland)

- Electronic Scale (Serial No: XO 27555, Denver Instruments, 6542 Fig Street, Arvada CO 80004,U.S.A)
- Gallenkamp Oven BS Size 3 (Cat No: DVH 200 210W, App No: 7B 9938 D, England)
- Gallenkamp Regulator Hotplate (List No: HL-052, App No: 6B 8547 E,England)
- General Laboratory Centrifuge - 2 (Sorvall Serial 7506180, England)



- Helios Zeta UV - VIS Spectrophotometer (Thermo Fisher Scientific Inc. 19 Mercers Row, Cambridge, CBS 8B2 UK)
- HH-S Digital Thermostatic Water Bath (Mcdonald Scientific International Lagos, Nigeria)
- Monsanto Tablet Hardness Tester (Monsanto Chemical Co., USA)
- Oaklon pH Meter (pH 1100 series) (Serial No: 378486, Eutech Instruments, Singapore)
- Screw Gauge Micrometer (965M, Moore & Wright Sheffield, England)

## 3.2 Methods

### 3.2.1 Collection and identification of *Eleusine coracana*

*Eleusine coracana* grains were obtained from Samaru Market in Zaria, Kaduna State, Nigeria. It was identified by a taxonomist Mr. Bello from the Department of Biological Sciences, Ahmadu Bello University, Nigeria. (Voucher number26234 )

### 3.2.2 Extraction of *Eleusine coracana* starch

For the extraction 500 gm of the grains were weighed and cleaned then soaked overnight in water and grinded. The grinded grains were then sieved with a kaliko cloth. The liquid was then left to settle for another 2 h and then decanted and then centrifuged to remove the protein. It was

then left to dry on a tray inside the laboratory for 3 days. The powder was then micronized using a mortar and pestle and then bleached using 500 ml sodium hypochlorite. The starch cake was then passed through 180um sieve mesh and further dried in the oven at 40˚C for 24 h(Khalid, 2016).

### 3.3 Modification of starch

#### 3.3.1 Preparation of Acid hydrolyzed *Eleusine coracana*starch

Bleached starch (100g) was weighed into a clean beaker. Then 250ml of distilled water was added to disperse it, followed by 15ml of 6N HCl with constant stirring provided by a digital thermostatic water bath set at 54˚C . The reaction was allowed to proceed for 4 h on a water bath at 54˚C. The slurry was then centrifuged at 1000 rpm to regain the starch, which was washed with enough water, and Phwas brought to nearly 7 using NaOH. To the mixture, 100 ml of 95 % ethanol was added and stirred. The slurry was allowed to stand for 1Hr after which it was decanted. The hydrolyzed starch obtained was poured on a tray and air dried for 3 days. The granule obtained was then passed through a 1.6mm sieve and then 1mm.The above procedure was then repeated with reaction times of 6, 12 and 18 h (Khalid, 2016).

The Percentage yield was determined and the starch labelled AHS.

#### 3.3.2 Preparation of Pregelatinized starch/ Determination of gelatinization Temperature

A 100g of thestarch wasweighed on electronic digital scale and transferred into a stainless steel bowl. Then 100ml of water at room temperature 37$^{o}$ Cwas added and stirred to form a

suspension. The suspension was placed on a water bath (Digital thermostatic water bath) set at 90˚C.With continuousstirring, a thermometer was used to monitor the temperature. The dispersion was stirred continuously until it begins to gelatinize at 66˚ C and immediately taken off from the heat at this point. The gel point and the temperature at this point wastaken as the gelatinization temperature. The mucilage was then thinly spread on stainless steel trays and dried in hot air oven at 60˚ C for 24 h. The PGS was dried by dehydration in absolute ethanol at 40˚ C for 24 h. The dried flakes were milled using laboratory blender. This was labelled as PGS and the percentage yield was determined using the equation below.

$Pq = P/P_{\circ}\ X\ 100$……(8)

Where

$Pq$ is the percentage yield, P is the weight of the pregelatinized starch formed and $P_{\circ}$ is the initial weight of the native starch used.This procedure was repeated but instead of drying directly, absolute ethanol was used to dehydrate the starch, and then dried at 40˚C for 24 h, milled and labeled as Pregelatinized starch (PGS).

### 3.4Physicochemical Evaluation OfNative And Modified Starches

#### 3.4.1. Organoleptic Properties

The taste, colour, texture and odour of the starches and the standard MCC were examined and noted.

### 3.4.2. Hydration capacity

This was determined according to the method of Kornblum and Stoopak (1973). One gram (1 g) of each of the powders (Y) was placed in a centrifuge tube and covered with 10 ml of distilled water. The tube was shaken intermittently for about 2 hand left to stand for 30 min before centrifuging at 3000 rpm for 10min. The supernatant was decanted and the weight of the wet powder after water uptake and centrifugation (X) was determined. The Hydration capacity was calculated as (Ochekpel *et al*,2013);



X/Y …….…… (9)

### 3.4.3. Determination of Swelling Capacity

The tapped volume occupied by 2.5 g starch in a measuring cylinder was denoted as Vo. This was dispersed in 50 ml distilled water and left for 24 h. The volume of sediment was then noted as V. The swelling capacity (S.C) was calculated using the equation( Musa *et al*,2011):-

S.C = V/Vo---------- (10)

### 3.4.4. Solubility Test

One gram (1 g) of each powder sample was dispersed in 10 mL each of hot distilled water, cold water and 95 % ethanol, shaken and allowed to stand for 24 h. Then 5 mL of the supernatant was taken in each case and heated to dryness on a hot plate (Gallenkamp hot plate) at 110 ˚C for 5 min. The weight of the dried residue was expressed as a percentage with reference to the volume of the solution. The solubility of the material in solvent was calculated as % w/v (Olurunsola *et al*,2011).

### 3.4.5. Determination of Percentage Moisture Loss

Five grams (5 g) of each powder sample was heated in an oven (BS size 3 Gallenkamp, England) at 105 ˚C, examined every hour until a constant weight was obtained. The percentage moisture loss was calculated as the ratio of loss in weight to the initial weight of the sample (Ochekpel *et al*,2013).

### 3.4.6. Determination of Moisture Sorption Capacity

Two grams (2 g) of each powder sample was weighed and evenly spread over tarred Petri-dish (70 mm surface), and placed in a desiccator containing distilled water in it's reservoir (RH=100%) at room temperature 37˚ C for 5 days after which it was reweighed. The moisture sorption capacity was calculated as the ratio of change in weight to the initial weight (Olurunsola *et al*,2011).

### 3.4.7. Determination of Ash Content

Crucibles were cleaned and dried in the oven. They were cooled in the desiccator and weighed (W1). Two grams (2 g) of the ground powder sample was placed in the crucibles and weighed (W2). They were transferred into the Muffle Furnace at about 550 ˚ C, then removed and cooled in the desiccator and weighed (W3) (Gul,2009).

The % of ash was calculated as:

W3-W1/W2-W1 X 100 ……. (11)

### 3.4.8. Determination of pH

One gram (1 g) of each powder sample was dispersed in 100 mL of distilled water and shaken for 5 mins and allowed to stand for 10 mins. The pH of the supernatant liquid was determined using a pH meter (Oaklon pH 1100 series)(Olurunsola *et al*,2011).

### 3.4.9. Identification Test for Starch

This was done according to BP (2009) specification. One gram (1 g) of the starch sample was suspended in 50 mL distilled water and boiled for a minute and cooled. A drop of iodine solution was added to 1 mL of the starch mucilage formed and observed the color change (B.P, 2009).

### 3.4.10. Microscopy

Little quantity of each powdered sample was suspended in glycerol as the mounting reagent on a slide and covered with a thin slit. The microscope was calibrated using eye-piece and stage micrometer respectively set at X250 magnification. The prepared slides were viewed under the electronic microscope. Then 500 starch granules were counted in each case to determine the mean particle size. A camera was attached and picture of the particles were taken(Olurunsola *et al*,2011).

### 3.4.11. Drug-Excipients Compatibility Studies

Metronidazole and modified starches of *Eleusine coracana* interactions were assessed with Fourier transform infrared spectrophotometer (FT-IR). Initially, pure drug (metronidazole) was crushed with potassium bromide (KBr) and a transparent pellet of about 1mm thickness was prepared .A 1:1 ratio physical mixture of pure drug and excipients were made and the pellets

prepared in the way as described. The prepared samples were analyzed with FT-IR spectrophotometer using KBr as beam splitter. The instrument was operated under dry air at scanning speed of 2.8 mm/sec with a resolution of $4cm^{-1}$ over the region of 4000-400 $cm^{-1}$.

### 3.5. Physicomechanical Characterisation Of The Powder

Determination of Powder Flow Properties

#### 3.5.1. Determination of Angle of Repose

Twenty grams (20 g) of each powder sample was poured inside a glass funnel of orifice diameter,0.8 cm, clamped ata height 10 cm from the table surface and was allowed to flow freely. The angle of repose, Ɵ was calculated from the heap of the powder using the equation:

Ɵ = Tan-1 h/r..... (15)

Where h = height of heap and r is the radius formed by the heap. It was repeated thrice and the mean ±SEM determined(Olurunsola *et al*,2011).

#### 3.5.2. Determination of Flow Rate

Twenty grams (20 g) of each powder sample was placed in a flow rate machine. The time of flow was noted and the flow rate calculated in grams per second (g/s). The mean ±SEM of three determinations was calculated.

Flow Rate (Fr) = W/T…….. (16)Where, W is the weight of the powder in grams (g) and T is the time taken for the powder to flow in seconds (s).

### 3.5.3. Determination of Bulk and Tapped Densities

Ten grams (10 g) of each powder sample was placed in a 50 mL measuring cylinder and the bulk volume noted. The cylinder was dropped on a wooden platform from a height of 2.5cm three times at 2 s intervals. The volume occupied was recorded as bulk volume. The bulk density (BD) and tapped density (TD) were then calculated. The Carr's index (C.I) and Hausner's ratio (H.R) were also calculated using Wells and Aulton (2007) equations:-

Carr's Index (C.I) = (T.D - B.D)/ T.D x 100…… (17)

Hausner's ratio (H.R) = T.D/B.D…… (18)

### 3.5.4. Determination of True Density

The true density (Dt), of each powder sample was determined by the liquid displacement method using xylene as the immersion fluid,according to the following equation:

Dt = Wp [(a +Wp) – b] x SG…… (19)

Where, Wp is the weight of powder, SG is specific gravity of solvent (xylene, 0.86), a is weight of bottle + solvent and b is weight of bottle + solvent + powder(Olurunsola *et al*,2011).

### 3.5.5. Determination of Packing Fraction and Porosity

The packing fraction (Pf) was expressed as the ratio of the bulk density (BD) and the true density (Dt) (Okpanachi *et al*, 2012);

Pf = B.D / Dt ……(20)

Porosity = 1- B.D/Dt x 100…….. (21)

### 3.5.6. Particle Size analysis

Twenty grams of each powder sample was placed in a nest of sieves containing sieves arranged in descending order of aperture size (180, 150, 125, 90 and 75 μm) and the shaker vibrated for 10 mins. The weight of the samples retained on each sieve was taken and percentage cumulative weight oversize was plotted against particle size(Olurunsola *et al*,2011).

### 3.6. Compaction Studies and Determination of Compressibility

Compacts of each powder were made by weighing 500 mg individually and compressing at various compression loads ranging from 28.31 -169.88 $MN^{-}$ on Apex hydraulic hand press .The dwell time of 30 s was allowed for each compression.Before the compression,the 10.5 mm die and flat-faced punches were lubricated with 2 % w/v dispersion of magnesium stearate in acetone .After ejection,the compacts were stored in a dessicator over silica gel for 24 h to allow for elastic recovery and hardening and also to prevent low yield values. The tablet weight (*W*) and the dimensions (thickness and diameter) were then determined to within ± 1mg and 0.01 mm respectively. The relative density (*D)* was calculated using the following equation(Apeji,2010).

$D=W/V\rho s$

……(22)

Where, *V* is the tablet volume (cm3) and ρs is the particle density (g/cm3) of the solid material.Heckel plots of ln (*1/1-D)* against the applied pressure *P* (MNm-2) and Kawakita plots

of P/C versus P were constructed for all the materials. Also compressibility index was determined using plot of compact density (g/cm3) versus log compaction load in mega Newton per meter square (MNm-2)

### 3.7. Evaluation of Dilution Potential

A 500 mg quantity each of the drug and excipient was mixed in the following proportions: 100:400, 150:350, 200:300, and 250:250. It was then compressed at varying compression loads on the Single Punch Tableting Machine. The crushing strength comparison was then made of these parameters for different drug:excipients ratio to evaluate their dilution potential (Apeji,2010).

### 3.8. Tablet Formulation

A batch size of 200 tablets was prepared, and four batches were made by direct compression using metronidazole as the active pharmaceutical ingredient (API). The target tablet weight was 500 mg as indicated in the formula for each batch in Table 3.1. The tablets were formulated by mixing the active drug and the filler/binder to achieve a uniform blend. The calculated quantities of the glidant 0.75 % w/w and lubricant 0.25 % w/w were weighed on an electronic scale and incorporated into the powder mix. Mixing continued for about 10 min and tablets were compressed using a single punch tabletting machine fitted with 12 mm concave – faced punches and die set. Tablets were made at varying compression load between 3.5 – 9.5 MT(Apeji, 2010).

**Table 3.1 Formula for preparing metronidazole tablets containing the modified starch of *Eleusine coracana*as filler-binder-disintegrant.**

| **Ingrediants** | **Qty/tablet** | **Qty/tablet (mg)** | **Qty/batch Of 200 tablet (g)** |
|---|---|---|---|
| Metronidazole | 200mg | 200.00 | 40.00 |
| Filler/binder: PGS/AHS/MCC/STL (58.75%) | q.s | 93.75 | 58.75 |
| Lubricant: stearic acid | 0.5% w/w | 2.5 | 0.5 |
| Glidant: talc | 0.75% w/w | 3.75 | 0.75 |
| **Total** | **500mg** | **500.00** | **100.00** |

**Key**

MCC -Microcrystaline Cellulose

PGS- Pregelatinized starch

AHS-Acid hydrolysed starch

STL –Starlac

### 3.9. Evaluation of Tablets

#### 3.9.1. Uniformity of Weight Test

Twenty tablets from each batch were selected at random and weighed individually using an electronic balance. Their mean weights ±SEM were determined based on BP (2002) method.

#### 3.9.2. Tablet Disintegration Test

The disintegration time of tablet was determined on six tablets in distilled water at 37°C ± 1°C using USP disintegration test apparatus. The time taken for each tablet to disintegrate and pass through the mesh was noted. The data for an average of 6 ±SEM determinations were recorded (BP, 2009).

#### 3.9.3. In-vitro Dissolution Studies

The *In vitro* dissolution studies were conducted on metronidazole tablet formulations using the basket method at 100 rpm in 900 mL of dissolution medium (0.1 N HCl) . The dissolution medium was maintained at 37 ± 0.5° C. Samples (5 mL) were withdrawn at different time intervals 5s, 10s, 15s, 30s, 1min, 1m30sand replaced with equivalent amount of fresh dissolution medium. The samples were diluted (1:9) with the dissolution medium prior to absorbance reading in a UV spectrophotometer at 277 nm. The percentage drug released was determined and plotted against time to generate dissolution profile data.

A calibration curve was first generated by dissolving 50 mg of metronidazole in 100 mL of 0.1 N HCl. A serial dilution was made in the order of 0.5 mg/mL – 0.0078 mg/mL. Absorbance for

each concentration was taken at 277nm. The data were plotted against the various concentrations from which a linear regression equation was resolved. This was used to generate the dissolution profiles(Apeji ,2010).

### 3.9.4. Assay of Metronidazole (Content uniformity)

Five tablets were randomly selected from each batch, weighed and finely powdered using mortar and pestle. The weight of the powdered tablet equivalent to 50mg of metronidazole was dissolved in 100 mL of 0.1 N HCl. A ten fold dilution of the aliquots was further made, filtered and analyzed using UV spectrophotometer for the content of metronidazole at 277nm. Three determinations were made for each batch (B.P,2002).

### 3.9.5. Determination of Tablet Diameter and Thickness

Tablet thickness and diameter were measured using digital screw gauge micrometer. A mean ±SEM of five determinations was obtained and recorded.

### 3.9.6. Friability Test

The friability of ten (10) tablets was determined for each batch using Roche Friabilator at a rotation speed of 25 rpm for 4 mins. The tablets were removed, dusted and re-weighed. The percentage weight loss was determined (Musa,2011).

### 3.9.7. Determination of Crushing Strength

The crushing strength of tablets from each batch was determined using Monsanto hardness tester (Manesty, England). Pressure was applied by turning the knob until the required pressure that

crushed the tablet was read in terms of kilogram force (kgf) on the scale. The results are the mean of five (5) determinations(Musa,2011).

### 3.9.8. Determination of Tablet Tensile Strength

Tensile strength is the stress measured as force per unit area. It is the load required to fracture a tablet by diametrical compression. The load P, needed to fracture the five (5) tablets was determined using Monsanto hardness tester. The mean value was calculated and was used to calculate the tablet tensile strength (TS) from the equation:

$$TS = 2P/\pi dt \quad \text{(22)}$$

Where, P is the load required to crush the tablet, d is the diameter and t is the thickness of the tablet(Musa *et al*,2011).

### 3.10. Statistical Analysis

Data were presented as mean ± standard error of mean (SEM). Differences between means were analyzed by one way analysis of variance (ANOVA) , followed by Dunett's test formultiple comparison using the IBM SPSS version 20 to compare the filler/binder properties of modified starches of *Eleusine coracana* in the formulation of metronidazole tablets as well as the properties of the tablets before and after storage using the student's t-test as a statistical tool. At 95 % confidence interval, $p \leq :0.05$ were considered significant.

# CHAPTER FOUR

## 4.0 RESULTS

### 4.1 Preliminary Results

The yield of native starch (ORS) from the dried seeds of *Eleusine coracana* was 22.5% while the yield of starches obtained after modification were as follows: 19.4% after pregelatinization, 16.4%, 12.6% and 11.6% by acid hydrolysis after 6,12 and 18h respectively.

On physical examination, the ORS, PGS, AHS6H, AHS12H and AHS18H were white in colour and tasteless. The ORS was a smooth white powder, but was brittle in texture. PGS was lightbrown, brittle and coarse in texture after drying. All acid modified starches were white in colour and smooth in texture. The pH of aqueous dispersion of the starches indicates slight acidity. Granules sizes were in the order of 100 -172 µm. The PGS hadlarger particle sizes of 172µm. AHS18 had the smallest particle sizes of 102µm.The results are shown in Table 4.1

**Table 4.1: Results of the Preliminary Investigations of modified starchesof*Eleusine coracana***

| **Properties** | **ORS** | **AHS6H** | **AHS12H** | **AHS18H** | **PGS** |
|---|---|---|---|---|---|
| Taste | Tasteless | Tasteless | Tasteless | Creamy | Tasteless |
| Colour | White | White | White | White | Brown |
| Texture | Smooth | Smooth | Smooth | Smooth | Coarse |
| Odour | Odourless | Odourless | Odourless | Odourless | Odourless |
| Yield (%) | 22.5 | 16.4 | 12.6 | 11.6 | 19.4 |
| pH | 6.9 | 6.5 | 6.3 | 6.1 | 6.8 |
| Iodine Test | Blue-black | Blue-black | Blue-black | Blue-black | Blue-black |
| Particle size(µm) | 142.2 | 136.1 | 130.5 | 102.2 | 172.7 |

**Key**

ORS –Native Starch

PGS- Pregelatinized starch

AHS6H-Acid hydrolysed starch at 6 hours

AHS12H- Acid hydrolysed starch at 12 hours

AHS18H- Acid hydrolysed starch at 18 hours

Particle size distribution was normal for the modified starches and indicating good flow properties as compared to ORS. PGS was averaging 172µm, AHS18H with average particle sizes of 102µm, AHS12H had 130µm and AHS6H had an average particle size 136µm. (Fig 4.1)

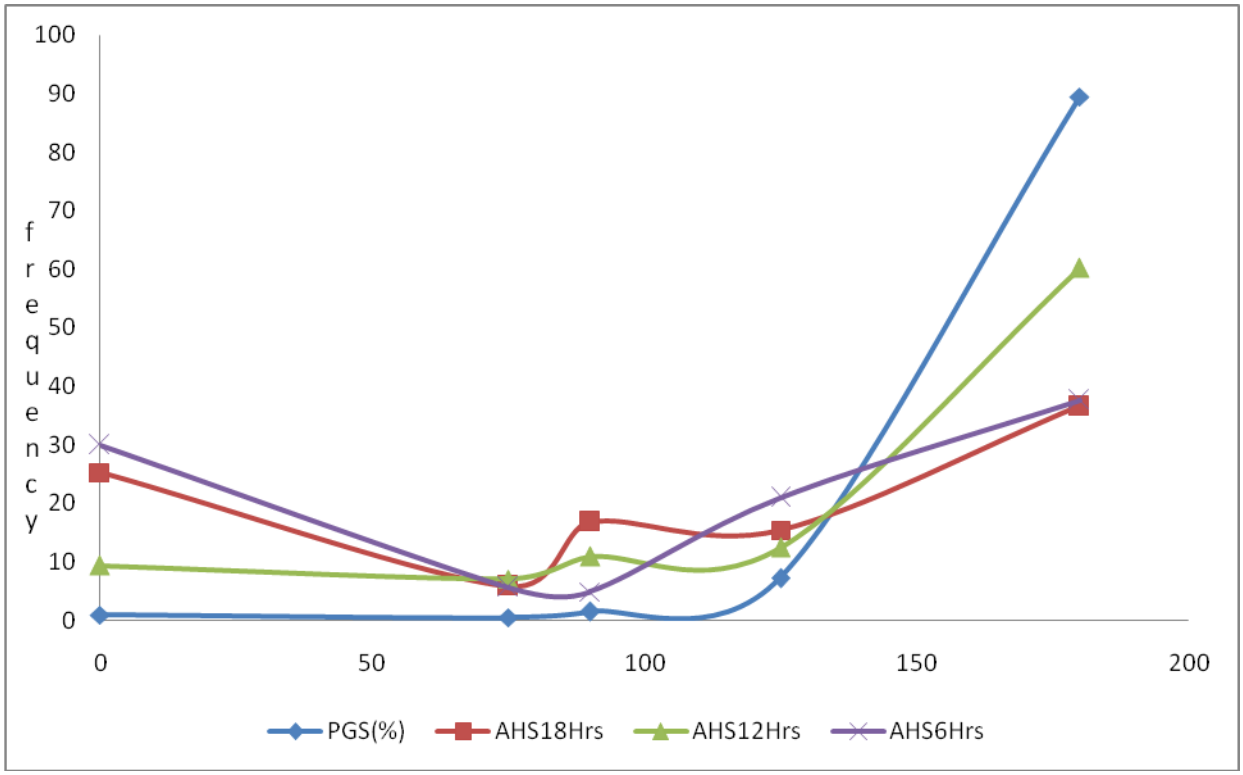



Figure 4.1. Partcle size distribution of PGS, AHS18H, AHS12H, AHS6H

**Key**

PGS- Pregelatinized starch

AHS6H- Acid hydrolysed starch at 6 hours

AHS12H- Acid hydrolysed starch at 12 hours

AHS18H- Acid hydrolysed starch at 18 hours

## 4.2 Physicochemical Properties

The results of angle of repose and flow rate are presented in Table 4.2. The lowest angle of repose (26˚)was obtained with AHS12Hwith a corresponding flow rate and the highest recorded with AHS18H(42˚). Lower angle of repose correspond to faster flow rate.

The Hausner's ratio and Carr's index were computed from the values obtained for bulk and tapped densities. The results show that AHS6H and AHS12H have good flow property while AHS18H and ORS having poor flow property.Powder porosity ranged from 35-71%.

PGS had the highest swelling power and also a high moisture sorption capacity. Modification seems to have reduced moisture carrying capacity of all starches.

**Table 4.2: Physicochemical Propertiesof modified starchesof *Eleusine coracana***

| Parameter | ORS | PGS | AHS6hrs | AH12hrs | AHS18hrs |
|---|---|---|---|---|---|
| Bulk Density (g/cm) | 0.43±0.00 | 0.47± 0.00 | 0.56±0.01 | 0.49±0.02 | 0.45±0.01 |
| Tapped Density (g/cm) | 0.62±0.01 | 0.69±0.01 | 0.71±0.01 | 0.67± 0.01 | 0.69±0.00 |
| Angle of repose (˚) | 41.50 | 30.00 | 28.00 | 26.00 | 42.00 |
| Flow rate (g/s) | 0.72±0.01 | 2.85±0.02 | 7.8±0.1 | 8.6±0.08 | 4.6±0.1 |
| Carr's Index (%) | 32.80 | 15.20 | 17.61 | 18.80 | 34.80 |
| Hausner's ratio | 1.44 | 1.47 | 1.28 | 1.36 | 1.53 |
| Swelling Capacity | 2 .00 | 7 .00 | 1.10 | 1.10 | 1.20 |
| Moisture Sc at 100% RH and 28˚C(%) | 14.80 | 12.40 | 6.60 | 8.80 | 5.40 |
| Moisture Content (%) | 15.00 | 13.00 | 11.50 | 10.70 | 9.20 |
| True Density (g/cm) | 1.28 | 1.62 | 1.38 | 1.36 | 1.34 |
| Packing Fraction (%) | 47.00 | 29.00 | 40.00 | 36.00 | 65.00 |
| Porosity (%) | 53.00 | 71.00 | 60.00 | 64.00 | 35.00 |
| Ash content (%) | 1 | 1 | 0.5 | 0.77 | 0.33 |
| Protein Content (%) | 6.20 | 4.80 | 5.40 | 4.70 | 3.75 |
| Lipid Content (%) | 1.50 | 0.70 | 0.92 | 0.83 | 0.50 |
| CHO contents (%) | 6.65 | 86.02 | 85.69 | 85.22 | 54.16 |
| Particle size (µm | 142±1.5 | 172.7±0.2 | 136.1±2.3 | 130.5±2.5 | 102.2±3.5 |
| Ph of 1% aqueous dispersion | 6.90 | 6.80 | 6.50 | 6.30 | 6.10 |

**Key**

ORS – Native Starch

PGS- Pregelatinized starch

AHS6HRS- Acid hydrolysed starch at 6 hours

AHS12HRS- Acid hydrolysed starch at 12 hours

AHS18HRS – Acid hydrolysed starch at 18 hours

**Table 4.3 Dilution Capacity and tests Modified starches of *E.corocana***

| Drug/Ex | | Friability | | | Crushing strength | | | |
|---|---|---|---|---|---|---|---|---|
| | **PGS** | **AHS6H** | **AHS12H** | **AHS18H** | **PGS** | **AHS6H** | **AHS12H** | **AHS18H** |
| 20/80 | 3.79 | 1.9 | 1.3 | 7.7 | 2.7 | 6 | 8 | 6.8 |
| 30/70 | 3.9 | 7.4 | 1 | 7.7 | 2 | 5 | 9 | 7.3 |
| 40/60 | 5.8 | 8.4 | 0 | 7.5 | 2.5 | 4 | 7.0 | 4.7 |
| 50/540 | 5.2 | 1.8 | 0 | 10.6 | 6.8 | 6 | 6.5 | 4.3 |

**Key**

PGS- Pregelatinized starch

AHS6HRS- Acid hydrolysed starch at 6 hours

AHS12HRS- Acid hydrolysed starch at 12 hours

AHS18HRS – Acid hydrolysed starch at 18 hours

Plates 4.1-4.6 show photomicrographs of the PGS and AHS starches when viewed under the microscope at different magnifications. PGS appears as material with irregular shape that has been fractured irregularly. The photomicrograph reveals the change in polarization of the starch granules as the temperature increases.

With Acid hydrolyzed starches AHS, the granules are spherical in shape and appear close together, but with increase in time of subjecting the starch granules to acid hydrolysis. A lot of the granules were seen to have been destroyed with increase in spaces between the particles.

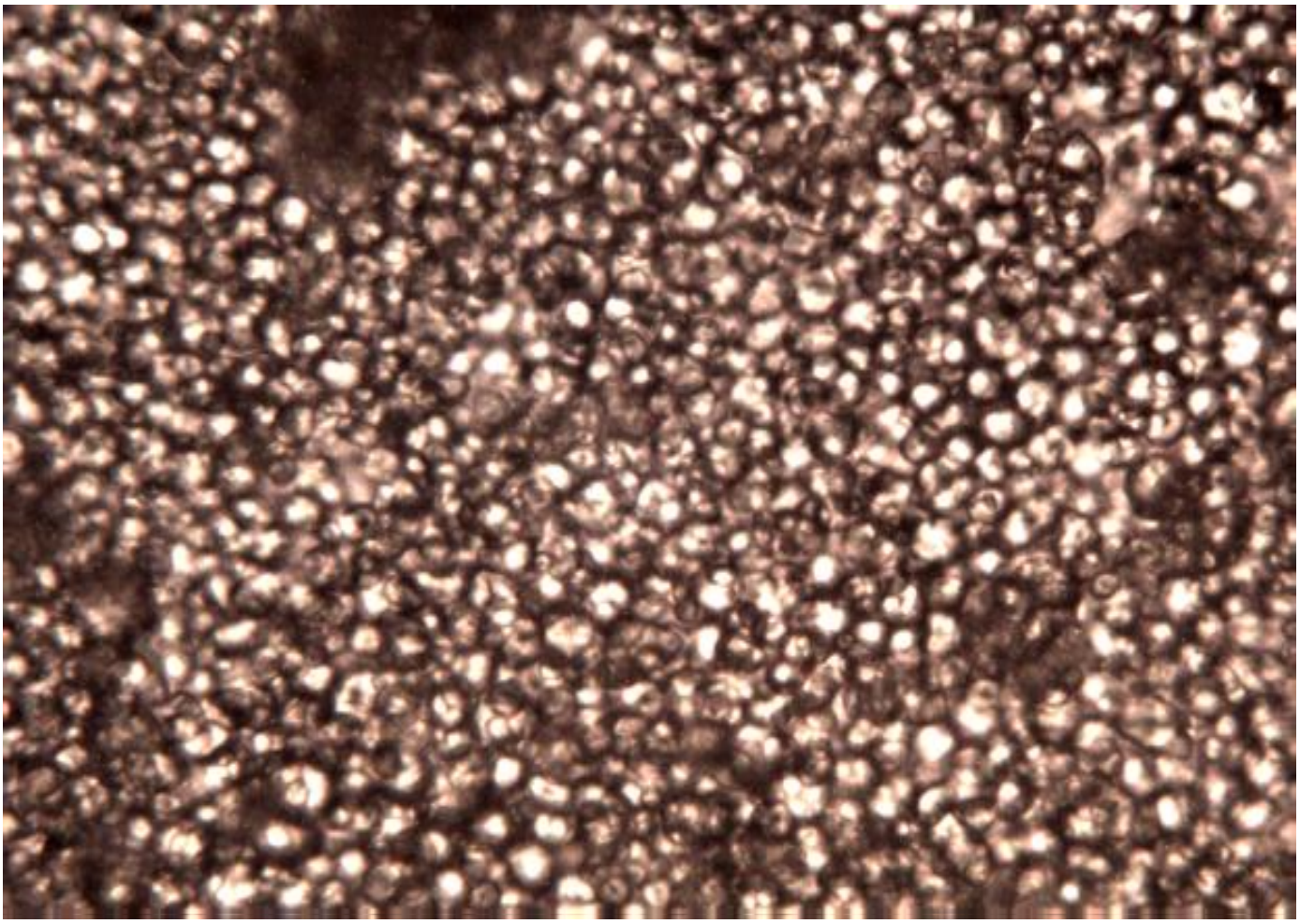


**Plate 4.1. Photomicrograph of Pre-gelatinized starch of *Eleusine coracana* at 45˚C (PGS) X 250 Magnification**

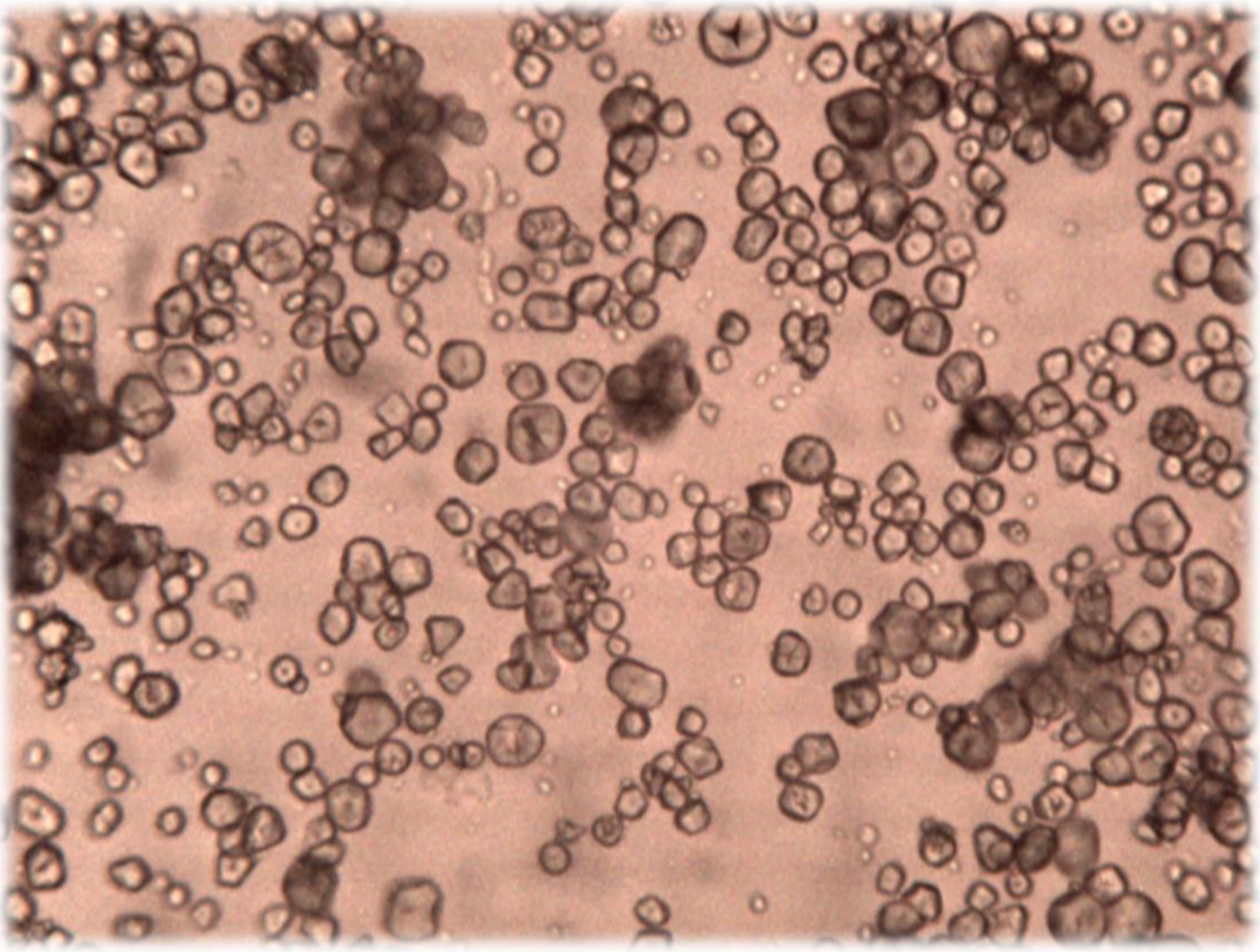


**Plate 4.2. Photomicrograph of Pre-gelatinized starch of *Eleusine coracana* at 55˚C (PGS) X 250 Magnification**

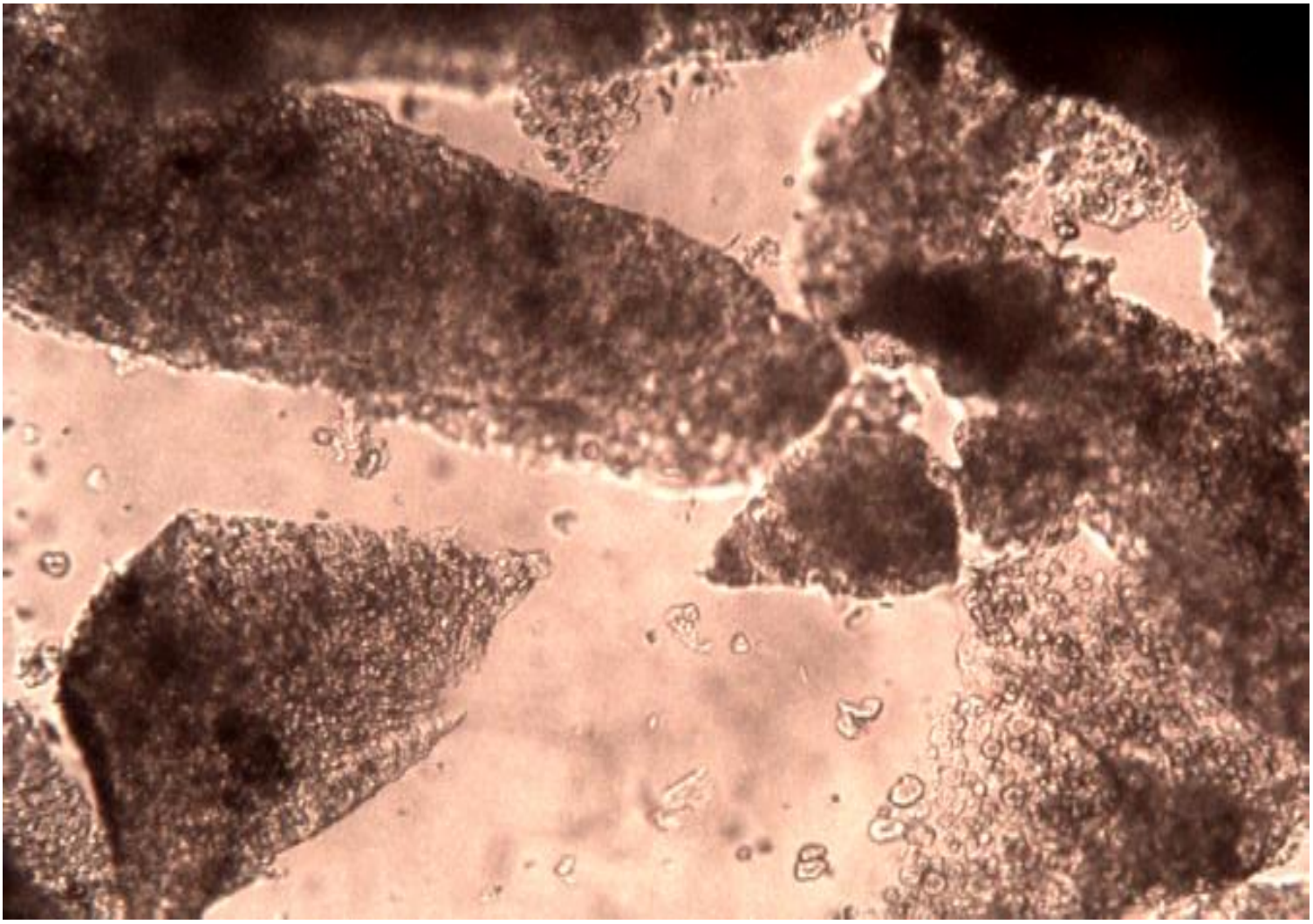


**Plate 4.3. Photomicrograph of Pre-gelatinized starch of *Eleusine carocana* at 66˚C (PGS) X 250 Magnification**

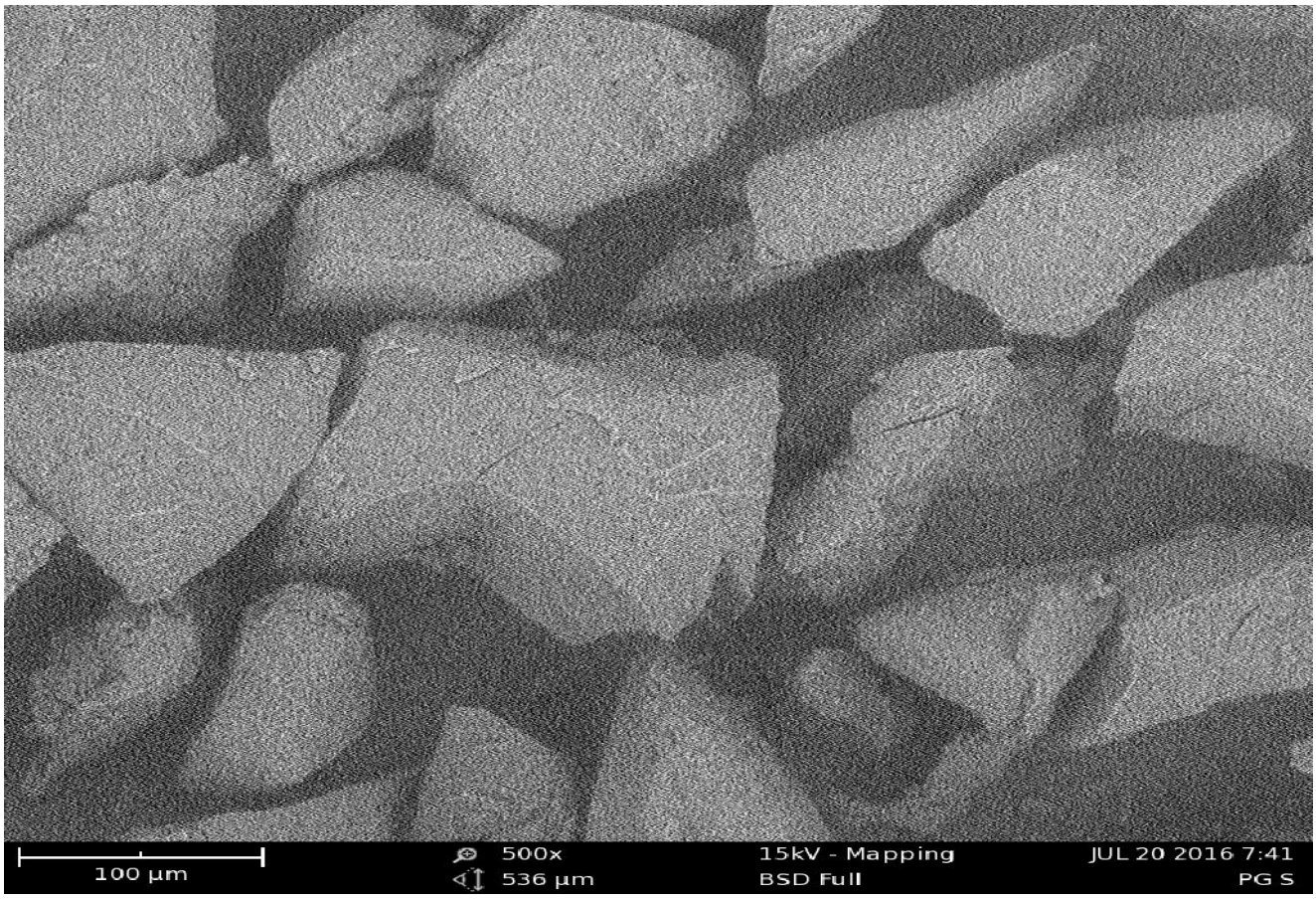



**Plate 4.4 Photomicrograph of pregelinitinized starch of *E.coracana*at gelatitinization temperature of 66 ◦C x500 magnification**

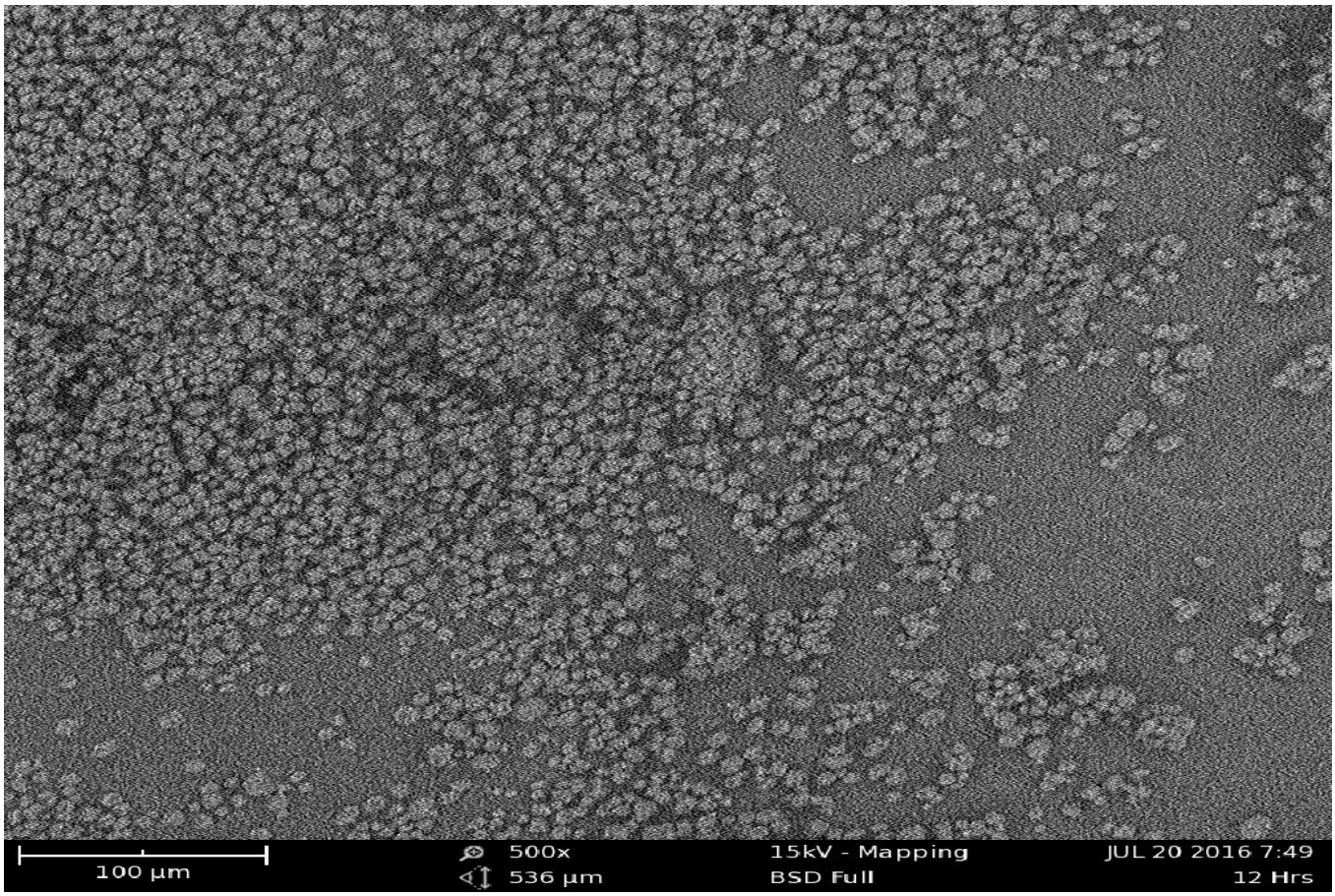



**Plate 4.5. Photomicrograph of Acid hydrolysed starch of *Eleusine coracana* at 12 Hrs (AHS12Hrs) X 500 Magnification**

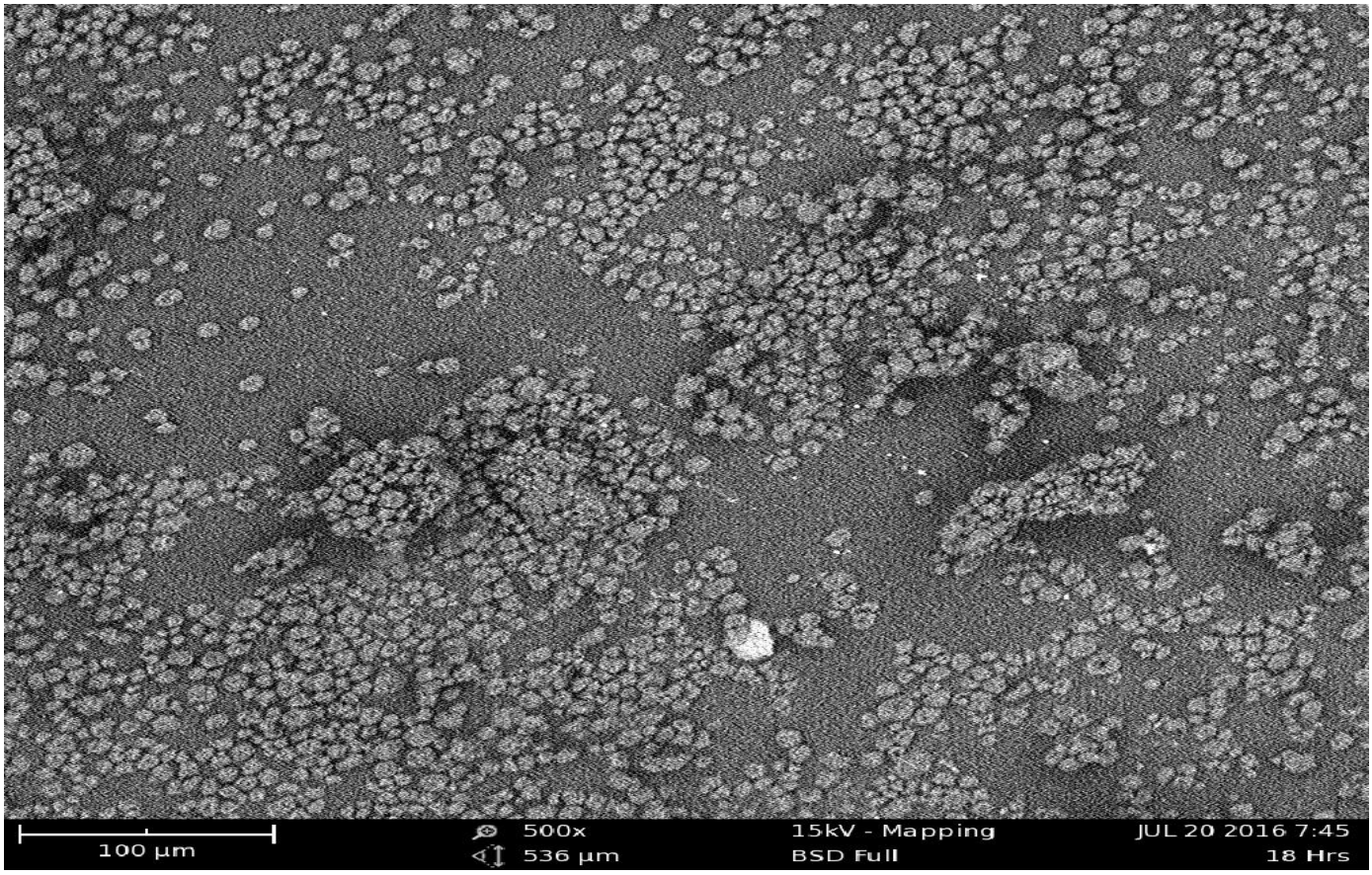



**Plate 4.6. Photomicrograph of Acid hydrolysed starch of *Eleusine coracana* at 18 Hrs (AHS18Hrs) X 500 Magnification**

### 4.3 Compaction Characteristics

The Heckel parameters (Table 4.3) were obtained by extrapolating the linear portion of the curve to calculate the slope and intercept. The yield value ($P_Y$) which represents the pressure at which deformation of the powder bed is initiated during compaction ranged from 237.38 – 609.56 N/m$^2$ with ORS recording the highest value indicating a greater resistance to deformation during compaction. The total amount of deformation was as a result of initial die filling, particle rearrangement and low pressures ($D_A$) ranged from 0.55 – 0.70 with AHS recording the highest value. Densification attributed to particle fragmentation was measured using the $D_B$ parameter and it was seen to be highest with AHS. The extent of deformation occurring as a result of fragmentation was relatively significant when comparing the $D_B$ values of the native starch (ORS) and the modified starches (AHS and PGS).

Kawakita parameters were also determined using the slope and intercept values of the straight line curve (Fig. 4.3). These parameters are displayed in Table 4.3. The minimum porosity (a) of the powder bed during compression ranged from 0.52 – 0.60 with PGS having the highest porosity. The pressure that is required to reduce the powder bed by 50 % ($P_K$) ranged from 2.72 – 33.72 N/m$^2$ with AHS having the least value indicating a faster onset of deformation relative to the other two materials. The $D_I$ values which represent the initial packing density of the powder were higher than their corresponding $D_0$ values as expected. ORS recorded the highest packing density possibly due to a smaller particle size.

Heckel plots of tablet porosity versus compaction pressure which measure plastic deformation of modified starches and native starch of *Eleusine coracana.*is depicted is Figure 4.2. Kawakita plot which relates the increase in tablet compaction pressure with relative increase of degree of volume reduction of compact tablet is presented in Figure 4.3.

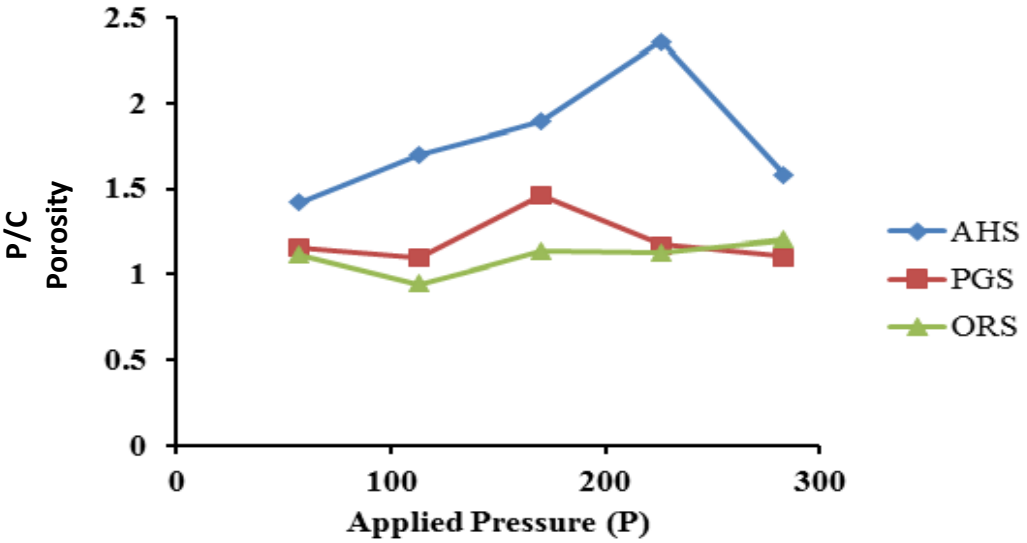



**Fig 4.2.Heckel Plots of AHS,PGS and ORS**

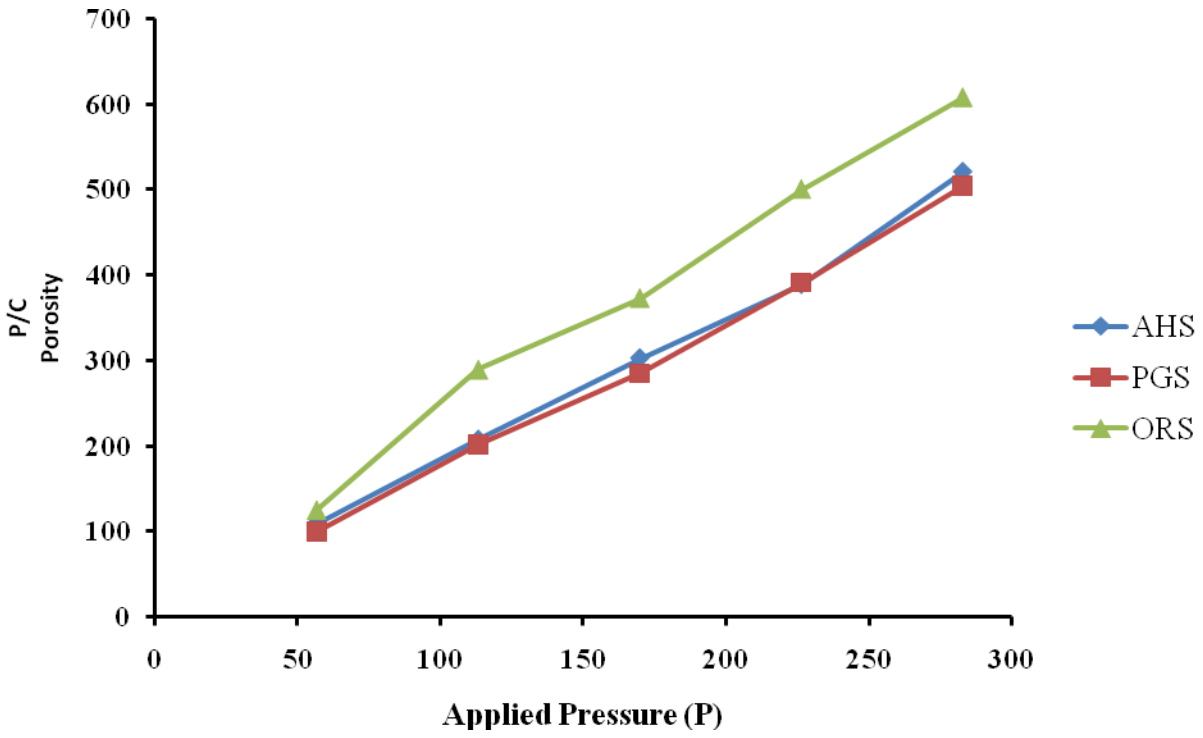



**Figure 4.3: Kawakita plots for AHS,PGS and ORS**

The various parameters generated from the Heckel and Kawakita plotsare presented in Table 4.3

**Table 4.4: Heckel and Kawakita Parameters of AHS, PGS and ORS**

| | **Heckel** | | | | **Kawakita** | | | |
|---|---|---|---|---|---|---|---|---|
| **Material** | $P_Y$ | $D_A$ | $D_B$ | $D_0$ | $a$ | $b$ | $P_K$ | $D_I$ |
| **ORS** | 609.56 | 0.55 | 0.08 | 0.47 | 0.52 | 0.03 | 33.72 | 0.48 |
| **AHS** | 237.38 | 0.70 | 0.33 | 0.36 | 0.56 | 0.37 | 2.72 | 0.44 |
| **PGS** | 371.52 | 0.61 | 0.32 | 0.29 | 0.60 | 0.20 | 4.97 | 0.40 |

**KEY** $P_Y$ is the mean yield pressure; $D_0$ is the relative density at zero pressure; $D_A$ is the relative density from the value of intercept A; $D_B$ describes the phase of rearrangement at low pressures ($D_A$ - $D_0$); a is the minimum porosity before compression; b represents plasticity; $D_I$ is the initial relative density and $P_K$ is the measure of plastic deformation (reciprocal of b)

## 4.4 Tablet Properties

The properties of the tablets formulated with modified starches of *E. coracana*,MCC and STLwere evaluated and the results obtained are displayed in Table 4.5.Four batches of tablets were formulated using metronidazole as active drug using AHS,PGS,MCC or STL as direct compression filler/binders. Tablet weight ranged from 498 -511mg and the thickness range from 4.3 – 4.9mm. Only tablets formulated with MCC and AHS passed friability test. PGS failed friability test and had a low crushing strength as well as tensile strength. Tablets formulated with MCC had the lowest disintegration time followed by AHS.$T_{50}$% was achieved for all formulations within 1 minute while all formulations released 90% metronidazole within 2 minutes. The content of metronidazole in all formulation range between 98-104%.

The plots of *in-vitro* dissolution characteristics of metronidazole tablets formulated with modified starches of *E. coracana*, MCC and STL are presented in Figure 4.4.

**Table 4.5 Physiochemical Properties of Tablets from Modified Starches of *E.coracana*,MCC and STL (Mean±SEM)**

| Parameter | MCC | STLPGSAHS | | |
|---|---|---|---|---|
| Mean Tablet weight (mg) | 498±18 | 511±9.2 | 508±7.8 | 501± 1.5 |
| Thickness (mm) | 4.9±0.5 | 4.32± 0.1 | 4.32±0.1 | 4.3± 0.04 |
| Friability (%) | 0.20 | 7.00 | 5.20 | 0.80 |
| Crushing strength (N) | 66±6.50 | 60±10.00 | 22±2.74 | 66±5.50 |
| Tensile strength ($MNm^{-2}$) | 0.85±0.09 | 0.74±1.14 | 0.27±0.03 | 0.82±0.07 |
| Disintegration time (min) | 0.4±0.03 | 0.85±0.08 | 0.85±0.08 | 0.63±0.1 |
| $T_{50}$% (min) | 1.00 | 0.40 | 0.20 | 0.60 |
| $T_{90}$%(min) | - | 0.70 | 1.20 | 1.80 |
| Content of API(%) | 98.55±2.5 | 99.3±2.3 | 104.4±3.12 | 101.01±3.01 |

**Key**

STL –Tablets formulated with Starlac

MCC- Tablets formulated with Microcrystaline cellulose

PGS- Tablets formulated with Pregelatinized starch

AHS- Tablets formulated with Acid hydrolysed starch at 12 hours

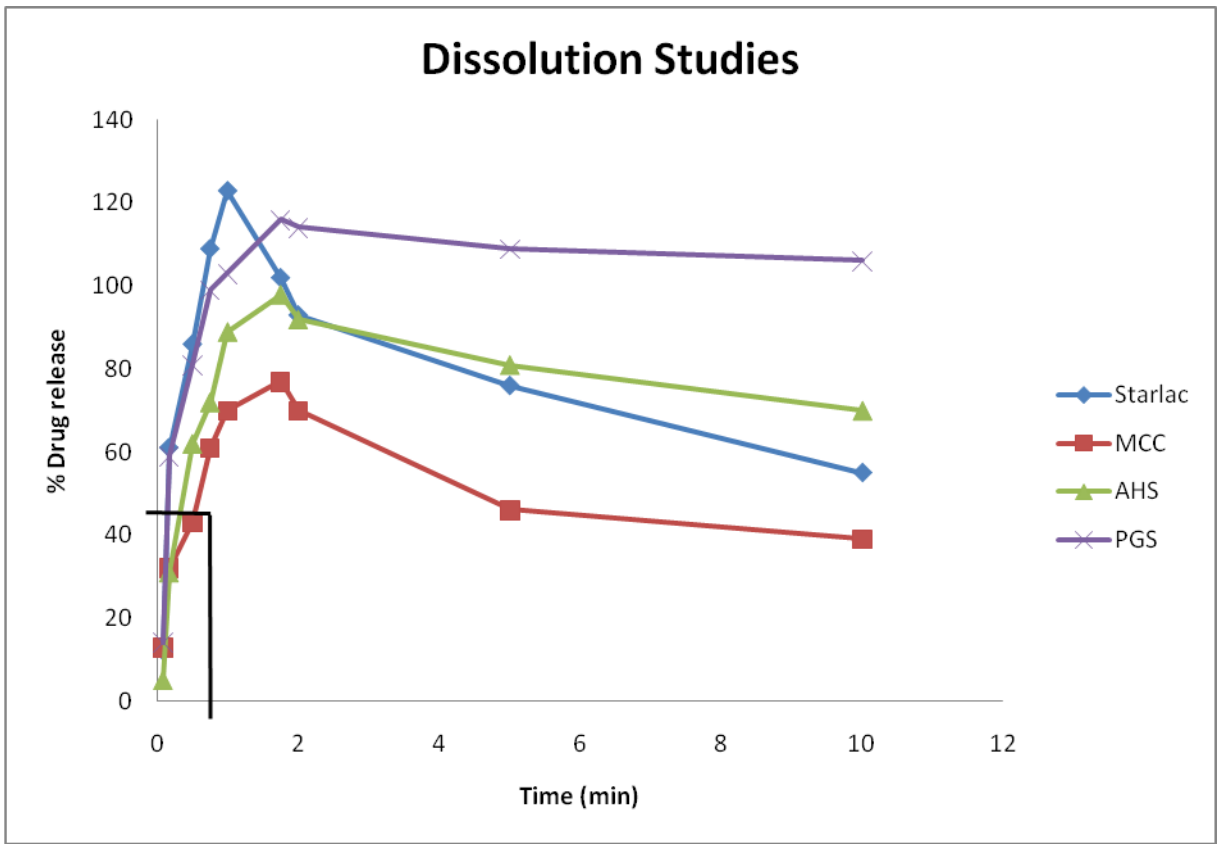



Fig 4.4.*In-vitro* Dissolution profile of metronidazole 200mg tablet formulated with AHS, PGS, MCC and STL

**.Key**

STL –Tablets formulated with Starlac

MCC- Tablets formulated with Microcrystaline cellulose

PGS- Tablets formulated with Pregelatinized starch

AHS- Tablets formulated with Acid hydrolysed starch at 12 hours

## 5.0 DISCUSSION

The yield of 22.5% for native starch from *Eleusine coracana* is in line with the value reported by Bender (1990), who reported 23%.The loss of polarization crosses start at 60-66º C.It shows that gelatinization starts at this temperature range.The gelatinization temperature was at 66˚C.Gelatinization of starch gave a higher yield of about 91.8%.Acid hydrolysed starch at 24h gave the lowest yield and this can be connected to the fact that reaction of starch in 6N HCL for 24 h results in increase in denaturation of the substance(Aiyer, 2005).Loss may also be due to removal of ash and color by several washing (Okpanachi,et al,2012).

The result of organoleptic properties of the modified starches showed that the acid hydrolyzed starches retained the colour,taste and odour while the PGS changed in taste,texture, and odour.This indicates that acid hydrolysis did not change the integrity of the starting material as much as pregelatinization.However,all modified starches gave positive test with iodine.Starch modification retained the integrity of the starch.

The moisture content for nativestarch was 15% and those of modified starches was in the order PGS>AHS6>AHS12>AHS18. None of the starches exceeded the limit 15% specified by the BP (2002).Moisture content plays an important role in the formulation of pharmaceutical as it can also affect properties of the material like flowand stability of the product.A lot of pharmaceutical excipients are affected by moisture.Moisture is also known to modify the flow and mechanical properties of many powders including starches (Adane *et al*,2006).

The values of the angle of repose recorded for all the starches were between 26˚-30˚. The angle of repose was in the order AHS18>>PGS>>AHS6>>AHS12.There is a correlation between the flow rate and angle of repose. Small angles of repose (≤ 30˚) correspond to a faster flow rate of the material. This was seen in the results in Table 4.2 where AHS18 had the highest angle of repose with a corresponding least flow rate. As a general guide,powders with angle of repose greater than50˚ have unsatisfactory flow properties,whereas those with angle of repose close to 25 ˚ correspond to very good flow properties (Davies, 2009).

Particles sizes were in the range of 100µm – 172 µm and were in the order PGS>AHS6>AHS12>AHS16. Large particle size of PGS was as result of swelling due to gelatinization. Particles larger than 250µm are usually free flowing but as the size falls below 100µm,powders become cohesive and flow problems occur. Powders having a particle size less than 10µm are usually extremely cohesive and resist flow under gravity (Staniforth, 2007). This shows why AHS12H had the best physicochemical properties because of free flowing particles.The flow rate of powder during manufacturing indicates the quality of the product in terms of its weight and content uniformity.Weight variation in tablets can be minimized if the formulation exhibits good flow property(Prescott and Barnum, 2008).

The bulk, tapped and particle densities of all three materials were also given in Table 4.2. The values of bulk and tapped densities occur in descending order as follows, AHS6>AHS12>PGS>AHS18. The tapped density is usually higher than the bulk density because of diminished void spaces as a result of a change in bulk volume. This change in bulk

volume was produced by rearrangement of the packing geometry of the particles resulting in a tightly packed powder bed. Also, the bulk density is always less than the true density of its component particles because the bulk powder contains interparticulate pores or voids(Staniforth and Aulton, 2007) .

Carr's index and Hausner ration are parameters used to evaluate the flowability of a powder by comparing the bulk and tapped density of a powder and the rate at which packing occurs. Usually for good flow of powders, angle of repose, Carr's index and Hausner's ratio should not be more than 30˚, 28% and 1.20 respectively (Hausner, 1967). PGS and AHS6 had angles of repose less than 30˚,Carrs index less than 28% but only AHS6 and AHS12had Hausner's ration less than 1.20. Addition of glidant to a powder having hausner ratio between 1.25 and 1.5 normally improves the flow (Wells and Aulton's, 2007)

From the results obtained,after starch modification, Pregelatinization improved the flow properties,Carr's index,Hausner's ratio than Native starch.The acid hydrolysed starch AHS12H gave far better physicochemical properties than the other AHS6 and AHS12 starches because it gave the lowest angle of repose, had the best flow rate, the least Carr's and Hausner's ratio,a good swelling capacity and particle sizes that were greater than 120 µm. These gave it better flow properties than all the other acid hydrolysed starches. The AHS12H was selected among all AHS starches for tabletting studies.

The most common features of all theories of disintegration is that penetration of water must precede disintegration (Prescott and Barnum, 2008). This can be assessed by the hydration

capacity,swelling capacity and porosity.PGS had the highest hydration and swelling capacities and hence disintegrant property as shown in Table 4.2 and 4.5.This was further shown in the disintegration time from the metronidazole tablet made using PGS as the filler.

The Ph values as shown in Table 4.1 are all within approximate neutral region, this finding indicates that when these materials are subjected to an aqueous medium, an acidic or alkaline medium will not turn into an toxic substance and not cause any harm while passing through the gastrointestinal tract.

Table 4.2, also confirmed the prescense of proteins and lipids in these modified starches. Reasonable amount of proteins can cause unwanted coloration in starch and starch hydrolyzed products, although this is regarded as Millard reaction (Chichester, 1986). Surface lipids reduce the diffusion of water into starch granules thereby altering starch properties by reducing water binding capacity and swellin of starches (Aprianita, 2010). For protein contents, the values are PGS>>AHS6>>AHS12>>AHS18, and for lipid content the results are of the order PGS>>AHS6>>AHS12>>AHS18. Acid hydrolysed starches seem to have lower lipid and protein content as a result of acid hydrolysis on the content.

Plates 4.1 – 4.6 show the photomicrographs of the modified starches. The mean particle sizes from Table 4.2 are in the following rank PGS>>AHS6>>AHS12>>AHS18. Due to uptake of water and swelling the particles in PGS appeared to have gotten bigger, while there was an increase in void spaces with increase in time in acid hydrolysis indicating some particles had been destroyed or denatured.

Table 4.3 shows the dilution capacity findings for the various materials. Dilution potential is the amount of active pharmaceutical ingredient (API) that can be satisfactorily compressed into tablets with the given directly compressible excipient. The data obtained were generated from crushing strength, friability and disintegration time of the solid compact of the drug and excipients in varying ratios. The results showed the following ranking AHS12>>AHS6>>PGS>>AHS18. The AHS12 maintained superiority interms of carrying capacity because it was able to accommodate up to 50%of the active drug, Apeji (2010) made a similar finding.

The dilution potential for PGS was estimated at 50% while that of AHS was 40% based on their crushing strength and friability tests.

The Heckel and Kawakitaequations (Heckel, 1961)have been used by many researchers to characterize the compaction behaviour of powders during compression. From the Heckel analysis, the reciprocal of the slope of the straight line portion of the plot translates to the yield pressure ($P_Y$) which is an indicator of the plasticity of the material. A lower yield value is consistent with materials that deform plastically while higher yield values correspond to materials that deform by brittle fracture. Our study has shown that acid modified starch had the lowest yield value compared with the other starches. This suggests that it has the fastest onset of plastic deformation. The modified starches (AHS & PGS) were found to have lower yield values compared to the native starch (ORS). This indicates that a greater degree of bonding occurred as a result of increased particulate contact due to a large bonding area. Also, modification of starch

may have affected particulate properties like particle size and shape that may have contributed to larger bonding area during compaction.

Kawakita analysis was conducted to linearize the compaction data so as to derive a better resolution of a straight line plot. The Kawakita parameters obtained were consistent with Heckel analysis as the modified starches (AHS & PGS) performed better in terms of deformation. A lower $P_K$ constant is a measure of the material's ability to deform easily when little pressure is applied. The degree of volume reduction of the modified starches was found to exceeding that of the native starch. This implies therefore that modification improved the compression profile of native starch. Hence, the modified starches are most likely to form good tablets at low pressure.

The weight range of allthe tablet formulations is 500-510mg. Crushing strength is a measure of tablet hardness.Although there are no official limits for tablet hardness,values ranging from 4-7kgf are generally acceptable. The crushing strength of the tablet is shown in Table 4.5.Results showed that tablets containing AHS, MCC and STL all passed the tablet hardness test and did not exceed the upper limit of 7kgf. Howevertablets made from PGS were below the standard crushing strength and so gave very soft tablets. But the PGS gave better properties when compared to native starch ORS with regard to tabletting properties.This showsthermal modification of starch improves the physical property of the tablets.

Friability of the tablet gives a measure of weakness of the tablet and is also an indication of the likely damage that will occur when the tablets are mishandled during dispensing. The limit is 1%. Batches of tablets made with PGS failed the test with a mean friability of about 5%. Batches

of STL had high value with a mean value of 7%.Batches made from MCC gave the lowest limit of 0.2% while that of AHS 12H gave 0.8%.Thus only tablets made from AHS 12H and those from MCC passed friability test.This agrees with findings of Bastos *et al* (2008) that tablets formulated with microcrystalline cellulose presented a lower friability and higher hardness.

The disintegrationtime and dissolution profile show the drug release profile of the drug.Determination of the time for a tablet to disintegrate when immersed in some test fluid has been a requirement in most compendia for many years and should not normally exceed 15mins for uncoated tablets (BP,2002).All batches of tablets passed the disintegration test as all disintegrated in less than 15 minutes.

It could be seen from the result that there is a correlation between tablet disintegration and dissolution. Disintegration assesses the availability of a drug in solid dosage form for dissolution and absorption into the gastro-intestinal tract and hence onward bioavailability.Faster disintegration time results in a faster drug release.The disintegration time is shown in Table 4.3.However the disintegration time has a greater impact on dissolution properties of the tabletand is considered to be a limiting step in case of tablet designed for immediate release (Hsu *et al,* 1997). The results obtained showed that the tablets containing MCC had the least disintegration time of 43 seconds, followed by AHS with 63 seconds with STL and PGS had the same disintegration time of 85 seconds. The low disintegration time, is attributed to the moderate crushing strength of about 60N.But the high disintegration time of PGS can be attributed to the large particle sizes. It was also observed that during swelling time it formed sticky jelly in

contact with water. This can prevent the entry of water into the tablet during disintegration. This could explain the high disintegration time of PGS despite very low crushing strength of about 22N. All batches of tablets however passed the official disintegration time of <15 minutes.Rapid disintegration is one of the advantages of tablets produced by direct Compression (Olowosulu *et al,*2014)

The dissolution profiles of metronidazole tablets are shown in figure 4.4.All the tablets had maximum percentage drug release within 3 mins. However it can be seen that the dissolution profile follows similar pattern as that of the disintegration and can be ranked in the following order STL> PGS>AHS>MCC.

The official requirement for drug content of active ingredient is met if percentage content of tablets with average weight above 250mg falls within 95%-105 (B.P 2002). All batches passed the pharmacopoeias limit for drug content uniformity test. Dissolution rate for tablets containing PGS were higher because as dissolution occurred the tablets formed a jelly like coat slowing futher penetration of water ,those having higher dissolution rate than those containing PGS.

# CHAPTER SIX

## 6.0 SUMMARY, CONCLUSION AND RECOMMENDATION

### 6.1 Summary

The modification of *Eleusine coracana* sourced freshly was done by acid hydrolysis and pregelatinazation. Acid Hydrolysis was done at 6 h, 12 h and 18 h and physicochemical tests carried out on the hydrolyzed starches. Acid hydrolyzed starch at 12 h(AHS12H) gave the best physicochemical characteristics.Hydrolyzed starches gave better flow properties when compared to the pregelatinized starch.

Dilution potential for the modified starches was estimated to be 40-50% of metronidazole.AHS12H tablet was choosenfrom results obtained for dilution potential because the tablets gave better physiochemical characteristics compared with the other batches of hydrolyzed starches.

Compaction studies further revealed that modified starches (AHS and PGS) were found to have lower yield values compared to the native starch (ORS).

Dissolution tests further revealed that PGS tablets released their active ingredient at a much faster rate within 30 seconds. But AHS gave a steady release of ingredient over time and a decline steady. Dissolution profile of AHS was similar to that of MCC so was their disintegration and crushing test which were all within normal rate.

## 6.2 Conclusion

Acid modified starches of *Eluesine coracana* produced robust metronidazole tablets of good quality compared to the thermally modified pregelatinized starch. Therefore,acid modified starch AH12H could be developed as a good directly compressible filler/binder in conventional tablet formulations.



## 6.3 Recommendations

- Pregelatinized starch of *E. coracana* should be considered for use as tablet disintegrant, or in formulations for orally dispersible tablets.
- Acid hydrolyzed starch of *E.coracana* should be explored in sustained release or modified tablet formulations.

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## APPENDIX

**A1.1: Particle size distribution of Modified starches of*E.coracana***

| Pan size (um) | PGS | AHS18Hrs | AHS12Hrs | AHS6Hrs |
|---|---|---|---|---|
| 180 | 89.5% | 36.6% | 60.2% | 37.6% |
| 125 | 7.52% | 15.4% | 12.4% | 21% |
| 90 | 1.52% | 16.8% | 10.9% | 4.9% |
| 75 | 0.51% | 5.9% | 7.1% | 5.7% |
| Pan | 0.96% | 25.3% | 9.4% | 30% |

Key

PGS- Pregelatinized starch

AHS6Hrs- Acid hydrolysed at 6 hours

AHS12Hrs- Acid hydrolysed at 12 hours

AHS18Hrs- Acid hydrolysed at 18 hours

**A2.1 Parameters for Heckeland Kawakita Plot for AHS**



| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 1.084881 | 133.7702 | 0.248561 | 1.418265 | 109.7399 |
| 113.3 | 1.712989 | 125.5981 | 0.197972 | 1.702738 | 207.7925 |
| 169.9 | 1.844221 | 121.7046 | 0.176578 | 1.895531 | 302.9945 |
| 226.5 | 1.870735 | 115.5145 | 0.128131 | 2.366095 | 389.2922 |
| 283.1 | 1.785069 | 126.5693 | 0.208136 | 1.586415 | 521.258 |

STDEV

| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 0.33823 | 11.70366 | 0.066755 | 0.284251 | 8.86549 |
| 113.3 | 0.363861 | 12.75747 | 0.086226 | 0.530247 | 6.70049 |
| 169.9 | 0.083212 | 6.986047 | 0.046004 | 0.089225 | 13.88907 |
| 226.5 | 0.139721 | 11.69492 | 0.091616 | 1.110132 | 27.49575 |
| 283.1 | 0.056523 | 7.371772 | 0.045948 | 0.224053 | 5.59649 |

**A2.2.Parameters for Heckel and Kawakita Plot for PGS**



| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 0.639017 | 148.1793 | 0.319891 | 1.158553 | 99.71489 |
| 113.3 | 0.656696 | 18.74592 | 0.33599 | 1.096214 | 201.8544 |
| 169.9 | 0.574763 | 138.7475 | 0.273952 | 1.463644 | 285.4125 |
| 226.5 | 1.02572 | 145.099 | 0.309819 | 1.175607 | 391.4673 |
| 283.1 | 1.194806 | 151.0144 | 0.334667 | 1.105423 | 505.1872 |

**STDEV**

| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 0.199449 | 15.87958 | 0.073636 | 0.239001 | 8.056691 |
| 113.3 | 0.142228 | 9.409307 | 0.041945 | 0.127507 | 9.726919 |
| 169.9 | 0.147977 | 14.94389 | 0.074043 | 0.072647 | 21.54923 |
| 226.5 | 0.104062 | 6.748434 | 0.03216 | 0.104585 | 13.23665 |
| 283.1 | 0.25881 | 12.41537 | 0.057379 | 0.181787 | 31.25306 |

**A2.3 .Parameters for Heckel and Kawakita Plot for ORS**



| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 0.11198 | 148.6391 | 0.32697 | 1.118882 | 125.9967 |
| 113.3 | 0.176526 | 164.0763 | 0.389512 | 0.945048 | 289.8612 |
| 169.9 | 0.212185 | 147.1321 | 0.320301 | 1.136517 | 373.3822 |
| 226.5 | 0.231502 | 147.7954 | 0.323124 | 1.130757 | 500.7269 |
| 283.1 | 0.259834 | 143.7016 | 0.302046 | 1.204679 | 607.7343 |

STDEV

| App. Press | TS | 100V | Porosity | ln(1/Ɛ) | P/C |
|---|---|---|---|---|---|
| 56.6 | 0.071883 | 3.593571 | 0.016077 | 0.048616 | 3.787729 |
| 113.3 | 0.085658 | 8.230948 | 0.030371 | 0.077723 | 22.92219 |
| 169.9 | 0.122693 | 1.34538 | 0.006195 | 0.02668 | 4.104367 |
| 226.5 | 0.167307 | 3.607481 | 0.016298 | 0.049774 | 15.03163 |
| 283.1 | 0.03533 | 9.75521 | 0.045684 | 0.146123 | 49.0386 |

**A3Calibration for Metronidazole**

| Concentration mg/mL | Absorbance (A) |
|---|---|
| 10 | 0.533 |
| 5 | 0.329 |
| 2.5 | 0.233 |
| 1.25 | 0.180 |
| 0.625 | 0.157 |
| 0.3125 | 0.141 |

**A4.1: Dissolution studies for AHS**

| Time (mins) | Abs (nm) | Amount dissolved (mg/100ml) | % drug dissolved |
|---|---|---|---|
| 0.083 | 0.172 | 1.04 | 5.2 |
| 0.167 | 0.377 | 6.14 | 30.7 |
| 0.5 | 0.63 | 12.4 | 62 |
| 0.75 | 0.712 | 14.5 | 72 |
| 1 | 0.842 | 17.7 | 88.5 |
| 1.75 | 0.918 | 19.59 | 97.98 |
| 2 | 0.871 | 18.59 | 92 |
| 5 | 0.783 | 16.2 | 81 |
| 10 | 0.692 | 13.98 | 70 |

**A4.2:Dissolution Test for PGS**

| Time (mins) | Abs (nm) | Amount dissolved (mg/100ml) | % drug dissolved |
|---|---|---|---|
| 0.083 | 0.243 | 2.8 | 14 |
| 0.167 | 0.606 | 11.84 | 59 |
| 0.5 | 0.782 | 16.21 | 81 |
| 0.75 | 0.928 | 19.85 | 99.2 |
| 1 | 0.961 | 20.6 | 103 |
| 1.75 | 1.07 | 23.4 | 116 |
| 2 | 1.047 | 22.8 | 114 |
| 5 | 1.005 | 21.76 | 109 |
| 10 | 0.0987 | 21.3 | 98 |

## A4.3: Dissolution Test for MCC

| Time (mins) | Abs (nm) | Amount dissolved (mg/100ml) | % drug dissolved |
|---|---|---|---|
| 0.083 | 0.233 | 2.557 | 1 |
| 0.167 | 0.381 | 6.24 | 31.19 |
| 0.5 | 0.477 | 8.62 | 43 |
| 0.75 | 0.617 | 12.11 | 61 |
| 1 | 0.69 | 13.92 | 70 |
| 1.75 | 0.749 | 15.39 | 77 |
| 2 | 0.692 | 13.98 | 69.8 |
| 5 | 0.501 | 9.22 | 46 |
| 10 | 0.44 | 7.7 | 39 |



## A4.4: Dissolution Test for STL

| Time (mins) | Abs (nm) | Amount dissolved (mg/100ml) | % drug dissolved |
|---|---|---|---|
| 0.083 | 2.56 | 0.197 | 12 |
| 0.167 | 12.29 | 0.623 | 61 |
| 0.5 | 17.19 | 0.821 | 85.92 |
| 0.75 | 21.8 | 1.007 | 109 |
| 1 | 24.59 | 1.119 | 123 |
| 1.75 | 20.4 | 0.952 | 102 |
| 2 | 18.6 | 0.877 | 93 |
| 5 | 15.2 | 0.74 | 76 |
| 10 | 11.04 | 0.574 | 55 |

**Figure A1.1 FTIR of Metronidazole**

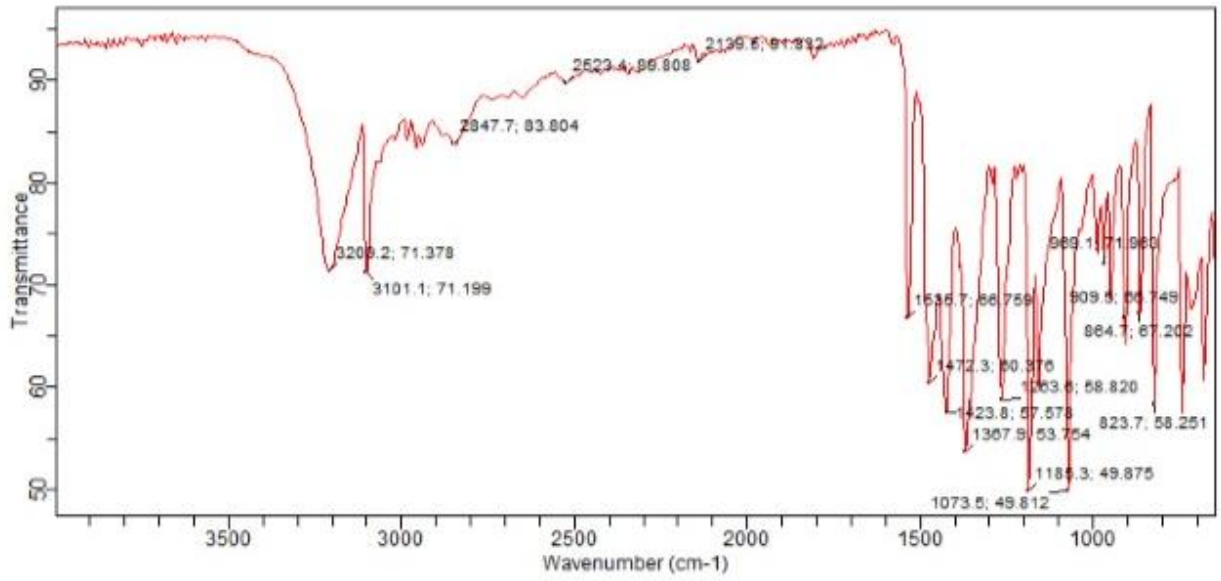


**Figure A1.2 FTIR of PGS +Metronidazole**



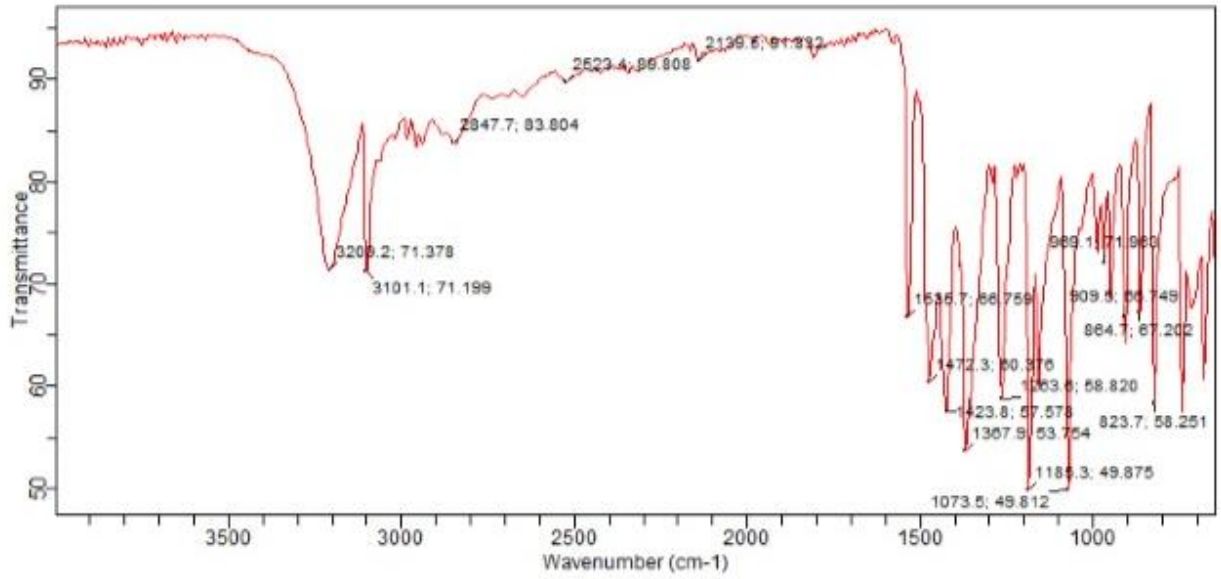


**Figure A1.3 FTIR of AHS6hrs + Metronidazole**

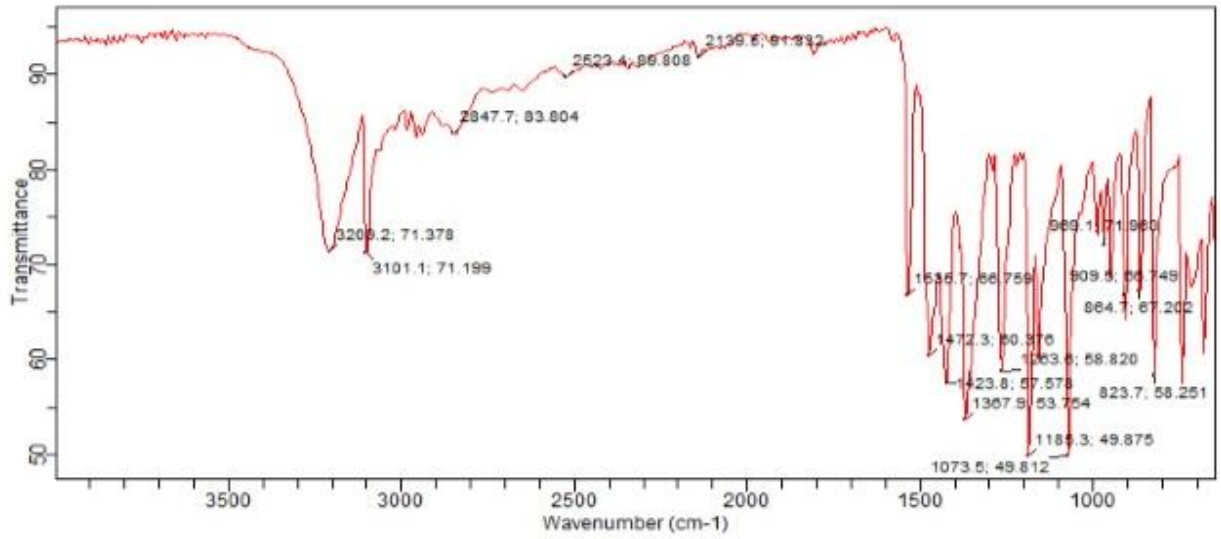


**Fig A1.4:FTIR of AHS12Hrs + Metronidazole**

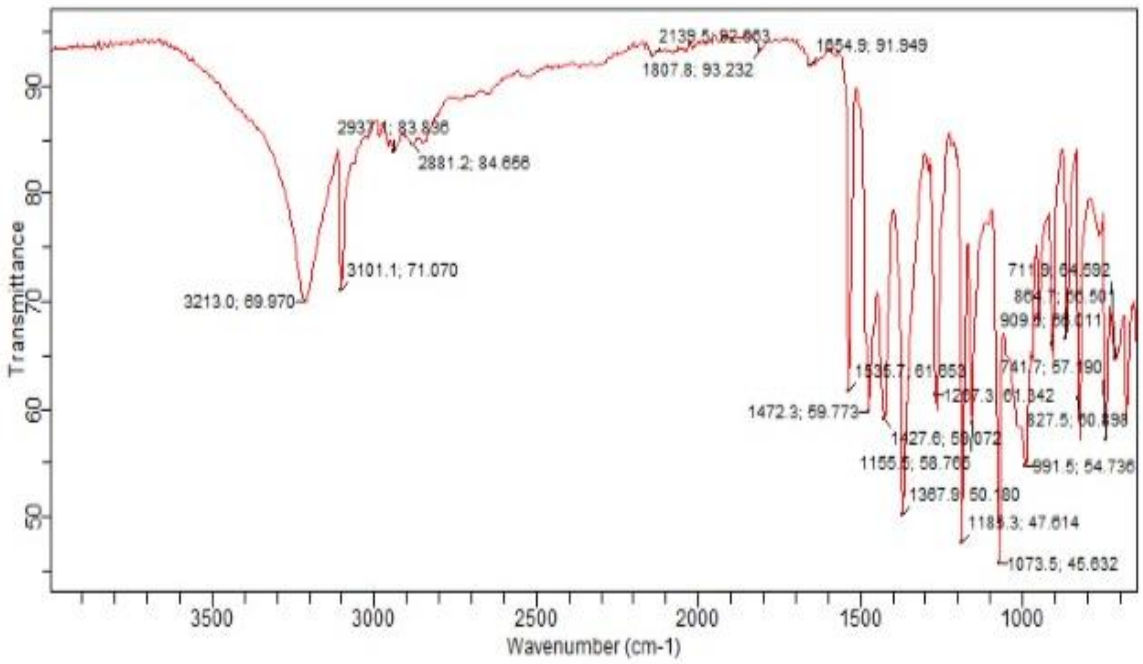


**Fig A1.5:FTIR of AHS18hrs + Metronidazole**

