PREFORMULATION STUDIES OF *CYPERUS ESCULENTUS* STARCH USED AS DISINTEGRANT AND AS BINDER IN THE PRODUCTION OF PARACETAMOL TABLETS

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CERTIFICATION

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DEDICATION

This work is dedicated to the loving memory of my late dad, Mr. Sunday Nwaduruoha Madubuike who supported me greatly in the course of this research though never lived to see the end of it. May his gentle soul rest peacefully in the bossom of the Lord.

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ABSTRACT

Starch is a naturally occurring polymer found in parts of the plants such as leaves, stems, tubers, and fruits. It is a commonly used excipient in pharmaceutical formulations because of its availability, affordability and inertness. *Cyperus esculentus* (tiger nut) is widely cultivated in the country especially in the northern part of Nigeria. Until recently, the use of tiger nut had been limited to food products and few pharmaceutical applications. This research is aimed at characterizing the starch isolated from *Cyperus esculentus* tubers, ascertaining its use as a binder and disintegrant in paracetamol tablet formulations, and to compare it with corn starch BP. *Cyperus esculentus* tubers, paracetamol powder, corn starch, gelatin, talc, magnesium stearate, and sodium benzoate were used for the study. Starch was isolated from *Cyperus esculentus* tubers. Physicochemical tests such as determination of densities, viscosity, pH, ash value, loss on drying, paste clarity, freeze thaw stability, browning and charring temperatures were done on the starch. Wet granulation method of tablet formulation was used to prepare paracetamol granules. The granules produced were characterized and then compressed into tablets. The formulated tablets were evaluated for various tablet properties such as hardness, thickness, friability, weight variation, disintegration time, dissolution rate as quality control measures. The physicochemical properties of starch from *Cyperus esculentus* were found to conform to BP standards for pharmaceutical grade starch. Results obtained from micromeritic studies such as angle of repose of 58.74 ^{o}, compressibility index of 16.0 % and Hausnerôs quotient of 1.19 revealed that *Cyperus esculentus* is a poorly flowing powder. Paracetamol granules produced had good flowability as shown by angle of repose being < 50 ^{o}, Hausnerôs quotient of <1.19 except for two batches that were 1.21 and 1.22. The values of compressibility indices ranged from 6.64 to 20.85 with most of the values falling below 16.0%. Evaluation of tablets showed that all batches passed the uniformity of weight test. The hardness of tablets was significantly affected by the binder concentration used in the formulation. The disintegration times were significantly affected by the concentration, method of incorporation and the type of disintegrant used. Friability values (< 1.0) obtained were within acceptable limits. The dissolution results showed that all batches of tablets released 80 % of the drug in the simulated gastric fluid (SGF) without enzymes, within 30 min. Drug release in the simulated intestinal fluid (SIF) without enzymes was less than 80% in 30 min. It can be concluded that *Cyperus esculentus* starch has acceptable powder properties, and provides excellent disintegrant (as shown by disintegration time of < 15 minutes) and binding properties in paracetamol tablet, without compromising drug release characteristics.

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INTRODUCTION

1.1 BACKGROUND

Excipients are pharmacologically inactive substances included in formulations to serve as a carrier for the active ingredients (1). Excipients can also be seen as compounds or materials which do not possess any health benefit but help in the manufacturing or processing of pharmaceutical formulation (2). They are additives used to convert active pharmaceutical ingredients into suitable dosage forms. Classes of excipients used in tablet formulations include disintegrants, binders, diluents/fillers, lubricants, and glidants.

Excipients can be of either natural or synthetic origin. Those of natural origin are of particular interest to formulation scientists because of their reliability and sustainability. Plant products are therefore attractive alternatives to synthetic products because of biocompatibility, low toxicity, environmental friendliness and low price, compared to synthetic products. Excipients from natural sources are also generally non-polluting renewable sources for the sustainable supply of cheaper pharmaceutical products (3, 4)

In recent years, natural substances, such as starch have evoked tremendous interest due to their diverse pharmaceutical application as diluents, binders, disintegrants and lubricants in tablets. There is, therefore, need to continually source these excipients from plants. This will not only ensure that they are obtained at lower cost, but will ultimately reduce the cost of manufacture when such products are used. They will also provide alternatives to currently available excipients.

1.2 STARCH

Starch is a polysaccharide of glucose. This biopolymeric material is a naturally abundant carbohydrate found chiefly in seeds, leaves, roots, fruits, tubers and

stem piths of plants.(6). It is a natural polymer that is most easily and readily available. It is a white amorphous tasteless powder. Starch contains amylose and amylopectin. Both polysaccharides are based on anhydroglucose units linked by D-(1, 4) glucosidic bonds. The proportion varies somewhat in different starches but the ratio of amylose to amylopectin is usually about 1:4 (5).

Amylose (B-amylose) consists of a linear chain of 250 to 300 residues of 1, 4 linked, Ŭ-glucose arranged in the form of a helix. Amylopectin is also a polymer of Ŭ-glucose residues but the macromolecule is built up of branched chains of the glucose units linked in both the 1,4 and 1,6 positions. Starches can be obtained from corn, potatoes, wheat, cassava, tiger nuts, rice, yam, ginger and other sources. They vary widely in appearance according to their biological origin. Therefore, a thorough investigation of the physicochemical properties is warranted before they are used. Adebayo and Itiola evaluated the properties of starch obtained from *Colocasia esculenta* and *Artocapus cummunis* (7).

Starch has a wide range of uses in our daily life. These include its use as food ingredients and pharmaceutical excipients. Starch is used in a variety of industries including food, textiles, plastics, adhesives, paper, and cosmetics (6).

1.2.1 SOURCES OF STARCH

Sources of starch include the following:

(a) Root tubers: cassava, yam, and sweet potato.

(b) Stem tubers: tiger nut, ginger, and carrot.

(c) Cereals: rice, corn, millet, wheat, guinea corn, and sorghum.

(d) Tree crops: mango, breadfruit, guava, and jackfruit.

(e) Legumes: groundnut, soybeans, and cowpeas.

(g) Herbs/Shrubs: banana, plantain, and amaranthus.

1.2.2 EXTRACTION AND PURIFICATIONS OF STARCH

Starch from any part of the plant needs to be extracted and purified to minimize contamination. Various laboratory methods have been used to isolate starches from their sources. The methodologies differ with respect to the media/solvent to be used for extraction. These involve steeping, defatting, deproteinisation, recovery of starch by centrifugation among others.

1.2.3 PHARMACEUTICAL USES OF STARCH

Starch is one of the most frequently used excipients in pharmaceutical formulations. It is one of the safest excipients and it is included in the GRAS (Generally Regarded as Safe) list of the World Health Organization (2). Starches from various sources have been widely used for various purposes in pharmaceutical formulations (2). In the pharmaceutical industry, starches may be employed as binders, disintegrants, diluents (filler), lubricant, and glidants (6, 8).

They are biodegradable and have a long tradition of use as excipients in drug formulation. It is also used as coating and dusting media for various types of tablet coating, such as sugar and enteric coating (8). Starches are also used for the production of micro-particles for delivery of proteins (9). Starch micro-particles have been used for the delivery of vaccines administered orally and intramuscularly (10).

Starch is the oldest and most commonly used disintegrant (2, 11). A disintegrant is an excipient added to a tablet formulation to cause the tablet to break apart or disintegrate after administration (12). At 5 ï 15 % concentration, starches are applicable as disintegrants in a number of tablet formulations (1, 13). Starch has been chemically modified. Starch derivatives, such as sodium starch glycollate, possess excellent disintegrating property. Pregelatinised starch is also employed

in tablet formulation as a disintegrant in 5% concentration (1). Acid modification of starch enhances its disintegrant action (11).

Starches have been used as excellent binders either as mucilage or in dry powdered form (14). The most common binder used in tablet granulation is starch paste (2). The gelling property of starch is responsible for the binding property. Mainly 2-10 % w/v solution of starch is used as tablet binder (2). Amylose portion of starch is responsible for its gelling as well as binding property (2). In tablet formulations, freshly prepared starch paste is used at a concentration of 5ï 10 %, depending on the starch type as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate (15).

The use of *Dioscorea rotundata* starch as a binder and disintegrant in tablet formulation has been investigated (16). Itiola also investigated the compressional properties of this particular starch. (17). The effect of pigeon pea and plantain starches in the compressional, mechanical and disintegration properties of paracetamol tablets have been investigated. (13).

The role of ginger starch as binder in acetaminophen tablet was studied by Ibezim et al. (14). Pregelatinized starch is also used as a binder (17, 18).

Starch is used as a diluent in pharmaceutical preparations. Diluents are used to increase the bulk of the dosage form. This is done in a situation where the active constituent to be incorporated in the formulation is of less quantity (1). As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations (15). Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix, and to improve powder flow, especially when using dried starches (15). Starch in concentrations of 3ï 10 % w/w can be used as anti-adherent and lubricant in

tablet and capsule filling (15).Starch can be used as nanoparticles. Starch based nanoparticles have been used for the transdermal delivery of the drugs such as flufenamic acid, testosterone and caffeine (2). Encapsulation and release properties of these nanoparticles were studied, showing high encapsulation efficiency for three tested drugs; flufenamic acid, testosterone and caffeine (2).

The skin permeation data for the three drugs suggest that starch nanoparticles have potential for transdermal drug delivery applications.

Starch is also used in topical preparations. It is widely used in dusting powders for its absorbency. It is also used as a protective covering in ointment formulations applied to the skin. Starch mucilage can be applied to the skin as an emollient. It is used as a base for enemas, and has been used in the treatment of iodine poisoning (19). Therapeutically, rice starch-based solutions have been used in the prevention of dehydration due to acute diarrheal diseases (20).

1.3 *Cyperus esculentus* (TIGER NUT)

The plant falls into the following taxonomical classification:

Division : Magnoliophyta

Class : Liliopsida

Order : Cyperalis

Family : Cyperaceae

Genus : Cyperus

Species : esculentus

The plant is a perennial rhizome that originated from South Europe. Tiger nut is really not a nut but a small tuber. It was first discovered some 4000 years ago in ancient Egypt, and is cultivated in China, Spain, and West Africa (21). Tubers grow to heights of 24 to 55 cm tall. The stems are three sided and triangular in

cross-section while the leaves are yellow to green in colour with a distinct ridge. The tuber is between 0.3 - 1.9 cm in diameter and the colour varies between yellow, brown and black (22). Tiger nut tubers are edible with a slightly sweet, nutty flavour. They are commonly seen in the northern part of Nigeria.

The local names are *Aya* (Hausa), *Akiawusa* (Igbo), and Tiger nut (English), *Chufa* (Spanish). It has many descriptions such as Zulu nut, yellow nut grass, ground almond, edible rush nut, earth chest nut, and edible ganglinate. There are yellow and black species of *Cyperus esculentus*. Tiger nut is a perennial herb of both the tropics and temperate regions of the world. It can be found growing naturally as weed but can also be commercially cultivated. It produces rhizomes and small spherical tubers or nuts (23). The stems are three-sided and triangular in cross-section while the leaves are yellow to green in colour with a distinct ridge. The tubers of this plant have high starch content and the starch is comparable to cassava and rice starch in terms of their morphology (6). Starch obtained from tiger nut may serve as a good source of excipient in the pharmaceutical industry.

The nut is very rich in energy content and minerals. Typically, 100 g of tiger nut contains 386 kcal, 7 % protein, 26 % fat, 31 % starch and 21 % glucose. They contain 26 % fiber of which 14 % is non-soluble and 12 % is soluble (24).

The starch of *Cyperus esculentus* can potentially be extracted and purified for industrial uses. For instance, it has been suggested as a potential oil crop for the production of cholesterol (25). Until recently, utilization of tiger nuts has been limited to food products and few pharmaceutical applications such as the use as binder and diluents. Tiger nut was found to assist in reducing the risk of colon cancer, heart attacks, and vascular thrombosis (26). It helps in preventing cancer due to high content of soluble glucose. In Ayuverdic medicine, tiger nuts are used in the treatment of flatulence, diarrhoea, dysentery, debility and indigestion (27).The oil is rich in vitamin E which is an antioxidant that slows

down ageing of body cells. It favours the elasticity of the skin and helps to reduce skin wrinkles (28). It is therefore very useful in the cosmetic industry. It is also believed that they help to activate blood circulation (29), relieve indigestion especially when accompanied with halitosis, benefits nutritionists and those seeking to reduce cholesterol or lose weight.

1.3.1 *Cyperus esculentus* STARCH

Research on extraction and physicochemical properties of tiger nut starch revealed several characteristics, including uniform granular shape, which is round and elliptical (6). Thermal and mechanical properties are similar to common starches. *Cyperus esculentus* starch is a brilliant white, crystalline, odourless, hygroscopic powder with bland taste and smooth texture (6, 23). The starch has a uniform granular size, shape and morphology (6). The granule size has been classified as large (> 25 εm), medium (10-25 εm), small (5-10 εm) and very small (< 5 εm) (6). The starch size is similar to that of rice and cassava (30). Radely indicated that the starch from *Cyperus esculentus* could be used for many starch-based foods, cosmetic products, and fabric stiffening (31). There is a predominance of divalent ions when compared with corn which has more of monovalent ions.

1.4 TABLET DOSAGE FORM

In December 1843, a patent was granted to an Englishman, William Brockendon for a machine that compressed powders to form compacts. This very simple device consisted essentially of a hole (or die) bored through a piece of metal within which the powders were compressed between two cylindrical punches. One was inserted into the base of the die at a fixed depth; the other was inserted at the top of the die and struck with a hammer. The invention was first used to produce compacts of potassium bicarbonate and caught the imagination of a number of pharmaceutical companies. Later, Welcome, in

Britain, was the first company to use the term tablet to describe this compressed dosage form which today accounts for some 70 % of all ethical pharmaceutical preparations produced (32).

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding method (33). The British Pharmacopoeia defined tablets as being circular in shape with either flat or convex faces and prepared by compressing medicaments or mixtures of medicaments, usually with added substances.

1.4.1. TYPES OF TABLETS

(i) **Normal Release Tablets:** These are tablets that are swallowed usually with water. They are meant to disintegrate in the gastrointestinal tract before effective absorption of the drug can take place. They are generally referred to as uncoated tablets.

(ii) **Lozenges or Troches:** These are, by design, intended to dissolve slowly in the mouth. They are to be held in the mouth while they dissolve gradually so that the drug is in contact with the mouth and throat for a prolonged period. This type of tablet can be used for the local effects of antiseptics, astringents and local anaesthetic. Lozenges do not contain disintegrants (34).

(iii) **Sublingual or Buccal Tablets:** They are tablets whose contents are expected to be released in the oral cavity. They are usually small and flat-shaped. They are administered by placing them between the cheek and gum in the mouth. The active ingredient is released and absorbed from the buccal cavity. An example of drug administered by this route is glyceryl nitrate used for the treatment of angina pectoris.

(iv) **Chewable Tablets:** These are designed to be broken down rapidly in the buccal cavity by the action of the teeth. Mannitol is a typical diluent in chewable tablets. It has negative heat of solution, and produces a cooling sensation in the mouth (35).

(v) **Effervescent Tablets:** These tablets are formulated to dissolve instantly with the release of carbon IV oxide (CO_2) on coming in contact with water.

They have become increasingly used because of their rapid release of medicament and reduced chances of gastric irritations. They contain acetic acid or tartaric acid and bicarbonates and are formulated using fusion method.

(vi) **Coated Tablets:** They are tablets that are either coated with sugars to mask obnoxious taste or with polymers to protect them from environmental factors such as light, mechanical damage, and product identification. They enhance or produce modified release of the incorporated drug.

(vii) **Implants and Inserts:** These are tablets or pellets implanted in the body by incision. Hormones used in birth control are often produced as implants which serve as depot from which the hormone is released slowly over a prolonged period. They are usually implanted in the thigh. Inserts include vaginal tablets that are usually compressed into a pear shape and contain excipients which cause rapid release of drugs.

Tablets of Miscellaneous Use

They include dental corks and reagent tablets. Other types of tablets include prolonged release tablets, solution tablets and dispersible tablets.

1.4.2 TABLETTING METHODS

1.4.2.1 WET METHODS

These involve the use of binders and solvents in the formulation of tablets (33). The wet methods include:

Wet granulation: This is the commonest and most popular method of tablet production. It is essentially a process of particle size enlargement involving several steps and the use of binders and solvents. The steps include weighing and mixing, wet massing and screening, drying, dry-screening, lubrication and compression. The solvents usually used are pure water, ethanol, or isopropanol, either alone or in combination.

Spheronization: This is a rapid and flexible process where pharmaceutical products are made into small spheres or spheroids (36). It is a form of wet granulation. Spheronized products are relatively dense, of uniform shape and size and have defined surface characteristics.The flow characteristics of spheres make them suitable for transportation by most systems found in pharmaceutical industry. Spheres provide the lowest surface area to volume ratio. Consequently, pharmaceutical compounds can be coated with a minimum coating material.

Spray drying: Spray drying is a process in which drug entities in solution or suspension are sprayed with or without excipients into a hot stream of air so as to generate dry or highly spherical particles (37, 38). This process continues through series of stages whereby the viscosity of the droplets constantly increases until the entire application medium is evaporated or solid particles are obtained. Spray drying is a unique granulation technique that directly converts liquids into dry granule. The advantages are the speed of forming granules and drying can be a continuous process. Spray drying is suitable for heat and moisture sensitive products. Granules prepared by spray drying technique are

spherical, porous, and uniform in size with fewer sharp edges than those produced by conventional granulation methods.

Fluidized granulation: This is the operation by which fine solids are transformed into a fluid like state through contact with a gas (39). At certain gas velocity, the fluid will support the particles giving them free mobility without entrapment. Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed.
The material processed by fluid bed granulation are fine, free flowing and homogeneous. The system involves the heating of air and then directing it through the material to be processed (39). There are some documented advantages of fluidized granulation. These include production of fines, free flowing and homogenous granules, reduction of dust formation during processing, and improvement of workersô safety. However, it is labour intensive and time consuming. There is difficulty in assurance of its reproducibility (39)

1.4.2.2 DRY METHODS

These are a methods used for drugs which do not compress well after wet granulation or those which are sensitive to moisture (35).

Pre-compression/Dry granulation: In pre-compression, large tablets, known as slugs are produced with a heavy duty machine. Alternatively, they are squeezed between two rollers to produce a sheet of compressed material (roller compaction). Lubricated portion of drug/excipient blend to be tabletted is compressed to obtain slugs which are broken into granules using a mill fitted with appropriate sieve. Aspirin and other drugs that are moisture-sensitive are manufactured using this method.

Direct compression: In direct compression, the powder blend is compressed directly without pre-treatment. The successful application of direct compression

method is dependent on availability of suitable machinery and materials. This method involves pre-mixing, lubrication and compression. Potassium chloride and sodium chloride are good additions for direct compression.

1.4.3 ADVANTAGES OF COMPRESSED TABLETS

1. They enable accurate dosage of medicament to be simply administered
2. They are easy to transport in bulk and carried by the patients.
3. The tablet is a uniform final product with regards to weight. The product is usually more stable than those prepared by a method involving the use of water.
4. The release rate of the drug from the tablet can be designed to meet desired pharmacological requirement.
5. Tablets can be mass produced simply and quickly and the resultant manufacturing cost is therefore very much low when compared with other dosage forms.

1.4.4 COMPONENTS OF TABLETS

Compressed tablets contain active ingredients with or without excipients. The majority of tablets are not composed solely of the drug. Excipients are usually added to achieve desired objectives. Active pharmaceutical ingredients include substances or combination of substances present in a finished pharmaceutical product, intended to furnish pharmacological activity or to, otherwise, have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect on restoring, correcting or modifying physiological functions in human beings (40). It is the component of a tablet that has pharmacological activity. A tablet may have one or more active

ingredients. It is also possible to have zero active ingredients as in placebo or research tablets.

Excipients on the other hand are inactive ingredients used to make up a medication (41).These are substance formulated alongside the active ingredient, and they serve specific purposes in the formulation. Excipients used in pharmaceutical preparations include bulking agents/diluents, binders, disintegrants, lubricants, flavours, sweeteners, and colourants.

1.5 TABLET EXCIPIENTS

1.5.1 BULKING AGENTS/DILUENTS

Diluents, also known as fillers are used to increase the bulk volume of a tablet or capsule (41). This is done in a situation where the active constituent to be incorporated in the formulation is of less quantity (1). In tablet formulation, it is not feasible to make tablets weighing less than 70 mg. Fillers are added in very low strength in drugs that are available in micrograms.

By combining a diluent with the active pharmaceutical ingredients, the final product is given adequate weight and size to assist in production and handling (41).The amount of diluents that appear in the formulation is normally determined by the strength of the drug and the nature and concentration of the other ingredients in the formula.

Bulking agents used in tabletting should be stable over a long period of storage. Diluents should be inert so as not to cause pharmacological activity of their own (41). They should be compactable and of similar particle size as the active ingredient. Diluents should also be non-hygroscopic so that the formulation does not absorb significant amounts of moisture from its surroundings. Bulking agents commonly used in tablet formulations include, lactose, corn starch,

mannitol and microcrystalline cellulose. Sucrose and mannitol are used as diluents for chewable tablets.

1.5.2 BINDERS

Binders are agents employed to impart cohesiveness to the granules (11, 42). They ensure that the tablets remain intact after compression and also improve the flow qualities of granules. Binders impart plasticity and thus increase the inter-particulate bonding strength within the tablet. Binders provide mechanical strength to the tablets. They can be in powder form and liquid form (1). They are mostly polymer materials that possess both cohesive and adhesive properties (14).

Binders function by holding excipients and drug particles together so that after mixing and/or granulation of the resultant mass, a hard granule or compact is obtained on compression. They promote plastic deformation of particles and increase the area of contact for inter-particulate bonding (42). This leads to the formation of more solid bonds in the tablets. Binders form matrix with fillers and drugs embedded in it. On drying, solid binders form glue which holds the particle together. The wet binder is the most important ingredient in the wet granulation process. Most binders are hydrophilic and soluble in water.

Binders are added as dry powders or in the form of solution or dispersion in a suitable solvent usually water or ethanol (14, 17). Uniform distribution and the amount of a binder employed in solution are critical. The choice of a particular binding agent depends on the binding force required to form the granule and its compatibility with other ingredients especially the active drug (14).Examples of binder include starch, gelatin, hydroxypropylmethylcellulose, sodiumcarboxymethylcellulose and polyvinylpyrrolidone.

The development of new excipients for potential use as binding agents in tablet formulation continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose (43). Natural binders such as starches, gums and mucilages, possess binding capacity as well as some other properties such as disintegration, filling or sustained release. Dane et al(2006) evaluated the effects of pigeon pea and plantain starches on the compressional, mechanical and disintegration properties of paracetamol tablets (44). These natural polymers were much safer and economical than polymers such as polyvinylpyrrolidone. Freshly prepared starch paste at a concentration of 5-20% is routinely employed as binder (45).

Starches from rice, potato, maize, wheat, tapioca and gums such as *Ferula gummosa,* boiss, gum olibanum, beilschmiedia seed gum, okra gum, angle marmelod gum, gum pectin ,show good potency as binding agents. Odeku and Itiola (2002) characterized the use of *khaya* gum as binder in paracetamol tablet formulation (46). Adebayo and Itiola (2002) also studied the effects of cocoyam starch binders on fluidity and compressibility of paracetamol granules and the mechanical properties of their tablets (47). Pregelatinized starch also functions as a binder (17).

1.5.2.1 CLASSIFICATION OF BINDERS BASED ON THEIR SOURCE/ORIGIN

(i) Natural polymers: These include starch, pre gelatinized starch, gelatin, acacia, tragacanth and other gums.

(ii) Synthetic polymers: Polyvinylchloride (PVC), hydroxypropylmethylcellulose (HPMC), methylcellulose, ethylcellulose, polyethylene glycol, isopropyl alcohol.

(iii) Sugars: glucose, sucrose, sorbitol

1.5.2.2 CLASSIFICATION OF BINDERS BASED ON METHOD OF APPLICATION

(i) **Solution binders**: These are soluble in solvents such as water and ethanol. They are used in wet granulation process. Examples include gelatin, cellulose derivatives, polyvinylpyrollidone, starch, sucrose and polyethylene glycol.

(ii) **Dry Binders**: These are added to the powder blend, either after a wet granulation step or as part of a direct powder compression formula. Examples include cellulose, methylcellulose, polyvinylpyrollidone and polyethylene glycol.

1.5.2.3 ADVANTAGES OF NATURAL BINDER

1. Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients or additives due to their low toxicity, biodegradability, availability and low cost.

2. They can be used to modify the release of drug, thereby influencing the absorption and subsequent bioavailability of the incorporated drug.

3. They act as vehicles to transport the incorporated drug to the site of absorption. This helps to ensure the stability of the incorporated drug, precision and accuracy of the dosage form.

4. They improve organoleptic properties of the drug where necessary in order to enhance patient adherence (48).

5. They optimize the performance of dosage forms during manufacture as well as when ingested (49).

1.5.2.4 DISADVANTAGES OF NATURAL BINDERS

1. Polymer binders can lead to processing difficulty such as rapid over granulation. Over time, they occasionally lead to tablet hardening and a decrease in dissolution performance (40).

2. When polymer binder are chosen, the addition of strong disintegrants such as super disintegrants is typically required. These are considerably expensive and have a negative effect on product stability as well as film

1.5.2.5 FACTORS THAT AFFECT THE EFFICIENCY OF BINDING AGENTS

(i) **Type of binder**: The type of binder used in a formulation affects the efficiency of the binder because different substances have their different natural and adherence forces.

(ii). **Use level concentration**: It has been shown that the more the concentration of binder, the stronger the tablet produced. This is because more binder confers great stability on the tablet. Therefore the water absorption reduction will be more pronounced (52). Insufficient binder tends to produce poor adhesion, capping and soft tablets. Excessive binder yields a slowly disintegrating and hard tablet. Also the presence of excessive binder in a formulation makes granulation and tabletting extremely difficult.

1.5.3 DISINTEGRANTS

Disintegrants are excipients added to tablet formulations to cause the tablets to break apart after administration (12). Disintegration is viewed as the first stage in the dissolution process, although dissolution does occur simultaneously with

disintegration. (17). Disintegrants break the dosage form into smaller particles when it comes in contact with the liquid. These smaller fragments have greater surface area which increase the dissolution of the drug (1). A good disintegrant must be effective at low concentration to avoid or reduce its influence on tablet properties such as hardness, friability, or compressibility (12) Adebayo et al (2010) carried out a comparative disintegrant activities of breadfruit starch and official corn starch (53). The drug must be released from the tablet matrix as quickly as possible to enhance its rapid dissolution (12).

Various mechanisms of disintegrations have been proposed. Isa et al. (2009) proposed combination of swelling, wicking, and deformation as the mechanisms of disintegrant actions (11). In many cases water uptake alone will cause disintegration, by rupturing the intra-particle cohesive forces that hold the tablet together, resulting in subsequent disintegration (17). If swelling occurs simultaneously with water uptake, the channels for penetration are widened by physical rupture and the penetration rate of water into the dosage form increases (17).

In powder and tablet technology, disintegrants are incorporated to counter the effects of binder and compression force. The stronger the binding agent, and the compression force, the stronger will be the effect of the disintegrant in order to guarantee the release of the active pharmaceutical ingredient in the gastrointestinal tract. Disintegrants in tablet formulations can be incorporated intra-granularly, extra-granularly or by the combination of the two techniques. Adebayo and Itiola (1998) also evaluated the use of breadfruit starches as exo-disintegrants in paracetamol tablet formulation (54).

The conditions best suited for rapid tablet disintegration are sufficient number of disintegrant agglomerates, low compressive pressure and the presence of

water. The concentration of disintegrant used is also very crucial. If it is below the optimum concentration, then there will be insufficient channels for capillary action. But if it is above the optimum concentration, then it will be difficult to compress the tablet.

1.5.3.1 EXAMPLES OF COMMON DISINTEGRANT

(a) Starch

Starch is the oldest and first most commonly used disintegrant (11). Examples of starch used as disintegrants are corn starch, potato starch, sodium starch glycollate, cross-linked sodiumcarboxymethylcellulose. Acid modification of starch enhances its disintegrant action (11). Starch is used as disintegrant in the concentration range of 5 to 20% of the tablet weight.

Starch was the first disintegrating agent widely used in tablet manufacturing (55). Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation. Iwuagwu and Onyekweli (2002) carried out a preliminary investigation into the use of *Pleurotus tuber-regium* powder as a tablet disintegrant (56). They prepared tablets with less than ten percent of the disintegrants and discovered that tablets with pleurotus starch disintegrated faster than that of maize starch. The ability of the pleurotus powder to swell by over three times its volume in the presence of water may explain its disintegrant properties. However, native starches have certain limitations and have been replaced by certain modified starches with specialized characteristics.

The mechanism of action of starch as disintegrant is wicking and restoration of deformed starch particles on contact with aqueous fluid. In doing so, there is a release of certain amount of stress which is

responsible for disruption of hydrogen bonding formed during compression (15).

(b) Pregelatinized Starch

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grains. It is a directly compressible disintegrant and its optimum concentration is 5-10 % (15, 55 and 57).

(c) Modified Starch

To have a high swelling rate and fast disintegration, starch is modified by carboxymethylation followed by cross-linking. Modified starch is therefore also known as cross-linked starch (57). An example of modified starch is sodium starch glycollate. Other carboxymethyl starches are also marketed as Explotab® and Primojel®.

The mechanism of action of modified starches as disintegrant involves rapid and extensive swelling with minimal gelling. Their optimum concentrations are 4-6 %. If the concentrations go beyond this range, then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentrations because of their great swelling capacity (57).

(d) Cellulose and its derivatives

Sodium carboxymethylcellulose (NaCMC and Carmellose sodium have highly hydrophilic structure and are soluble in water. But when they are modified by internal cross linking, the result is cross-linked cellulose, i.e. cross-carmellose sodium. This is nearly water insoluble due to internal

cross linking. It rapidly swells to 4-8 times its original volume when it comes in contact with water (57).

(e) Microcrystalline cellulose (MCC)

MCC exhibits very good disintegrating properties because it is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC. It also serves as an excellent binder and has a tendency to develop static charges in the presence of excessive moisture content. Therefore, sometimes, it causes separation in granulation. This can be partially overcome by drying the cellulose to remove the moisture (57).

(f) Alginates

Alginates are hydrophilic colloidal substances which have high sorption capacity. Chemically, they are salts of alginic acid. Alginic acid is insoluble in water and slightly acidic in reaction. Hence, it should be used with only acidic or neutral materials.

Unlike starch and MCC, alginates do not retard flow and can be successfully used with ascorbic acid, multivitamin formulations and acid salts of organic bases (57).

(g) Ion-exchange resin

Ion exchange resin (e.g. AmberliteIPR-88®) has higher water uptake capacity than other disintegrating agents such as starch and sodium CMC. It has the tendency to adsorb certain drugs (57).

(h) Miscellaneous

The miscellaneous category includes disintegrants such as surfactants, gas producing disintegrants and hydrous aluminium silicate. Gas producing disintegrating agents are used in soluble tablets, dispersible tablets and effervescent tablets.PolyplasdoneXL® and Polyplasdone®XL10 act by wicking, swelling and possibly some deformation recovery. PolyplasdoneXL® does not reduce tablet hardness, but provides rapid disintegration and improved dissolution. PolyplasdoneXL® as disintegrating agent has small particle size distributions that impart a smooth mouth feel and rapid dissolution.

(i) Superdisintegrants

Superdisintegrants are the substances which facilitate faster disintegration with smaller quantity than the conventional disintegrants (58). They are effective in low concentrations and have greater disintegrating efficiency. They are more effective intra granularly (57). Superdisintegrants provide quick disintegration due to the combined effects of swelling and water absorption (58). The swelling of the superdisintegrant causes the wetted surface of the carrier to increase, thus promoting the wettability and dispersibility of the system. This ultimately enhances disintegration and dissolution (58). Superdisintegrants are, however, hygroscopic. They are not used with moisture sensitive drugs (57).

1.5.3.2 MECHANISMS OF ACTION OF TABLET DISINTEGRANT

Presently, there is yet no proper theory to explain the mechanism of disintegration action. But it is obvious that no single mechanism can sufficiently explain disintegration action. Several factors, such as wetting

ability, which depends on contact angle, hydrophilicity and appropriate porosity, are involved. However, the mechanisms are classified into six groups as follows:

(i) **Swelling:** This is the most accepted mechanism of disintegration action. Most disintegrants can swell, and there are several works demonstrating that swelling efficiency promotes rapid water uptake into the tablet.

The conventional disintegrants, such as pregelatinised starch, have small degrees of swelling enough to cause the tablets to disintegrate when incorporated in adequate quantities to form a hydrophilic network.(59) In swelling mechanism, particles swell and break up the matrix from within. Swelling sets up localized stress which spreads throughout the matrix. Examples of such disintegrants are alginates, pregelatinised starch, and polyvinylpyrollidone.

(ii) **Deformation:** An excipient in a tablet during formulation is deformed under the pressure of compression that forms the tablet. Starch grains, for instance, are generally thought to be ôelasticô in nature, meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed.

With the compression force involved in tabletting, these grains are believed to be ôenergy richô and the energy is released upon exposure to water. Lowenthal illustrated maize starch grain deformation using the light microscope (60). The result obviously showed that the deformed granules returned to their original shapes when exposed to moisture. During the process, a strain is created inside the tablet which eventually caused shattering of the tablet. In deformation, particles swell to pre-compression size and break up the matrix.

(iii) **Disintegrating particle-particle repulsion theory:** According to this theory, as water is drawn into the pores, particles repel each other because of the resulting electrical force (61, 62). This explains why non-swellable materials can promote disintegration and are sometimes superior to swellable materials, in terms of disintegrant efficiency. Researchers have shown that the repulsion is secondary to wicking (61).

(iv) **Capillary action and porosity (wicking):** Disintegrants are hydrophilic agents with low free surface energy. Water penetration into the tablet pores exerts forces between the particles compressed within the tablet causing expansion. This expansion is due to the fact that the water replaces air adsorbed on the particles, which weakens the intermolecular bonds and breaks the tablets into fine particles (61). Disintegrants (with low cohesion and compressibility) enhance these forces and allow the water to penetrate quickly. This rapid penetration of the water rapidly expands the tablet and ruptures the inter-particulate bonds causing the tablets to break apart. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary. This helps in disintegration by creating a hydrophilic network around the drug particles.

(v) **Release of gas:** Carbon dioxide is released within tablets on wetting due to the interaction between bicarbonates or carbonates with citric acid or tartaric acid (61). The tablets disintegrate due to generation of pressure within the tablets. This effervescent mixture is used when the pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablets. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is

either added immediately prior to compression or can be added in two separate fractions of formulation.

(vi) **Enzymatic reaction:** Enzymes present in the body also act as disintegrants (62). The enzymes destroy the binding action of binders and help in disintegration (63). Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration (62).

(vii) **Heat of wetting:** When disintegrants with exothermic properties get wetted, localized stress is generated due to capillary air expansion which helps in disintegration of tablets (64). This mechanism, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrants (64, 65).

1.5.3.3 CHARACTERISTICS OF AN IDEAL DISINTEGRANT

1. Poor solubility
2. Poor gel formation
3. Good hydration capacity
4. Good moulding and flow properties
5. No tendency to form complex with the drugs.

1.5.3.4 FACTORS THAT AFFECT DISINTEGRANT EFFICIENCY

(1) **Type of dinsintegrant:** This is because different disintegrants have different physicochemical properties which are responsible for their behaviours and, in turn, their functions when used.

(2) **Concentration of disintegrant:** The more the concentration of the disintegrant, the lower the disintegration time of the formulation.

(3) **Effect of fillers:** The solubility and compression characteristics of fillers affect both the rate and mechanism of disintegration of the tablet. If soluble fillers are used, they may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents. As they are water soluble, the tablets are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebili and Cartilier (66) proved that tablets made with spray dried lactose (water soluble filler) disintegrated more slowly due to the amorphous character of the lactose and has no solid planes on which the disintegrating forces can be exerted, as compared with the tablets made with crystalline lactose monohydrate.

(4) **Effect of binder:** As the binding capacity of the binder increases, the disintegrating time of tablet increases and this counteracts rapid disintegration. The concentration of the binder can also affect the disintegration time of tablets (67).

(5) **Effect of lubricants:** Most lubricants are hydrophobic. They are used in smaller quantities than other ingredients in the tablet formulation (67). When the mixture is formed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits wetting and consequently tablet disintegration. Lubricants have a strong negative effect on water uptake when the tablet contains no disintegrant or a high concentration of slightly swelling disintegrant. On the contrary, the disintegration time is hardly affected if some strongly swelling disintegrants are present in the tablet (67). One exception however is

sodium starch glycolate whose effect remains unaffected in the presence of hydrophobic lubricants.

(6) **Effect of surfactants:** Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because hydrophobic active ingredients in the tablet prolongs the disintegration time. The disintegration time of granules of water-soluble drugs is not improved by the addition of a nonionic surfactant during granulation. The desired effect of a surfactant appears when granules are made of slightly soluble drugs. The speed of water penetration is increased by the addition of a surfactant. Sodium lauryl sulphate increases absorption of water by starch but has a variable effect on water penetration in tablets (68).

Other Factors affecting disintegration include;

1. Disintegrating medium used.
2. Temperature.
3. Operator experience.
4. Nature of the drug (particle size or molecular weight).

1.5.3.5 METHODS OF INCORPORATION OF DISINTEGRANTS

There are three basic methods of incorporating disintegrants into tablet formulations. These are:

(a) Intra-granular,

(b) Extra-granular

(c) Intra-granular ï extra-granular.

In intra-granular incorporation, the disintegrant is mixed with other excipients before the incorporation of the binder solution. Extra-granular incorporation involves incorporating the disintegrant into the granules prior to the addition of lubricants. Intra-granular-extra granular incorporation involves mixing half or a portion of the disintegrant with the other excipients before the addition of the binder solution and adding the remainder to the granules before compression. Intragranular-extragranular incorporation appears to be the best method. The extra-granularly added portion causes immediate disruption of the tablet into the previously compressed granules while the portion added intra-granularly causes further erosion of the granules to the original powder particles.(34)

1.5.4 LUBRICANTS

Lubricants are agents added in small quantities to tablet or capsule formulations to improve certain processing characteristics (41). Lubricants prevent ingredients from clumping together and sticking to the tablet punches or capsule filling machine (41). They are used to reduce the friction between the tablets and die cavity when the tablet is being ejected from the die (1). Lack of lubricant can lead to problems such as capping, scratches on the sides of the tablet, fragmentation of the tablet andothers.

There are four lubrication mechanisms. They include hydrodynamic lubrication, elastohydrodynamic lubrication, mixed lubrication, and boundary lubrication (69). In the pharmaceutical industry, boundary lubrication is the most common mechanism functioning in unit operations (69). There are two major types of lubricants used in pharmaceutical processes. They are the hydrophobic and the hydrophilic lubricants (41). Most hydrophobic lubricants have both anti-adherent and glidant properties. Consequently, they are used more frequently in the pharmaceutical industry than the hydrophilic lubricants (41).

For a lubricant to function properly, the time of addition, the concentration in which it is to be added and the combination are the important parameters (1).The time of mixing is important as over mixing may lead to reduction in tablet dissolution and prolongation of disintegration (1).

1.5.5 GLIDANTS

Glidants are inert excipients that are added to tablet formulations to reduce the interparticulate friction and improve the flow properties of granules from the hopper into the feed mechanism and ultimately into the die cavity(70).They aid in particle rearrangement within the die during the early stages of compression (71).

Glidants are required at the surface of feed particles. They should be in fine state of division and appropriately incorporated in the mixture (71). If their concentrations are taken beyond a certain limit, a drag action may come into operation. This brings down the rate of flow (71). There are hydrophilic and hydrophobic glidants (70).

Hydrophobic glidants include talc, silicon dioxide, calcium phosphate and metallic stearates while the hydrophilic glidants are exemplified by corn starch BP, yam starch, pregelatinized starch, and cassava starch (70). Other examples of lubricants include stearic acid, magnesium stearate , glyceryl behenate, glyceryl palmito stearate, polyethylene glycol, polyoxyethylene stearate, lauryl sulphate salt (1).

1.5.6 FLAVOURS AND SWEETENERS

Flavours are incorporated into the formulation to give a pleasant taste to the formulation (1).Flavouring agents and sweeteners are incorporated in tablet formulation to enhance patient acceptance and achieve palatability. Flavouring agents are mostly restricted to the formulations which are intended to be released in the mouth or chewable tablets (1). They are usually added along

with the granules (3). Flavours may be natural (fruit extract) or artificial (1). Flavours such as mint, cheery, and anise can be used to modify the taste of bitter products (41). Peach, apricot, and liquorice are used in salty products.

Sweeteners are agents employed in liquid formulations designed for oral administration specifically to increase the palatability of the therapeutic agent (72). They are compounds that interact with taste buds to evoke a characteristic response (73). Sweeteners have the ability to impart sweet taste by masking the taste of the material in which they are added (73).

Sweet taste perception is believed to involve multiple receptor types and transduction mechanisms (73). Competitive inhibition of the sweetenerôs receptors is one proposed mechanism. Other mechanisms include interference with channels and second messenger in the taste buds (73). Non-specific interaction with the taste buds is also believed to be one of the mechanisms through which sweeteners act on the taste buds (73). Sweeteners should have low calorific value and possess the ability to mask taste at low concentrations. The ideal sweetener should be free from harmful side effects and be suitable for long term use. They should remain stable at a wide range of temperatures and pH. Ideal sweeteners should have a quick onset of action. They should be non-hygroscopic, water soluble and possess high dissolution rates.

Sweeteners are broadly divided into two, the natural and artificial (synthetic) sweeteners. The natural sweeteners include xylose, ribose, glucose, mannitol, mannose, galactose, sucrose, sorbitol, xylitol, glycerin, and fructose (72, 73). The artificial sweeteners are exemplified by sodium cyclamate, aspartame, sodium saacharin, and ammonium glycyrrhizinate (72,73). Vanilla is used to reduce the sweetening effects of products (41). Other flavouring agents include peppermint oil and orange oil.

1.5.7 COLOURANTS

Colourants are additives that are used in tablet formulation for aesthetic appearance or as identification guide. They are added to improve the appearance of a formulation (41) and to increase the patient compliance or for identification of the formulation (1). Usually colourants are added in the form of insoluble powder or as liquid in the granulation step (1). Colour consistency is important as it allows easy identification of a medication. Some commonly used colourants are erythrosine and tartrazine.

1.6 PREFORMULATION STUDIES

Preformulation is a branch of pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of a pharmaceutical substance. The goal of preformulation studies is to choose the correct form of the substance, evaluate its physical properties and generate a thorough understanding of the materialôs stability under various conditions, leading to the optimal drug delivery system. The preformulation study focuses on the physicochemical parameters that could affect the development of an efficacious dosage form. These properties may ultimately provide a rationale for formulation design. It will also help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing productôs time to the market. It gives the information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form. The overall objective of preformulation testing is to generate information useful in developing the desired stable and bioavailable dosage forms.

The use of preformulation parameters maximizes the chances of formulating an acceptable, safe, efficacious and stable product. Preformulation encompasses the following tests:

(i) Bulk Characterization

Crystallinity, polymorphism and hygroscopicity of powders (flow, compaction, density, particle size and surface area)

Microscopy (morphology, particle characteristics).

Molecular spectroscopy (FT-IR).

(ii) Solubility Analysis

Solubility.

pH solubility profile.

Common ion effect.

Thermal effect on solubility.

Solubilization.

Dissolution.

(iii) Stability Analysis

Stability to heat, light, acid, base, oxidizer.

Solution stability, solid-state stability.

Excipient compatibility.

1.6.1 PREFORMULATION PARAMETERS TO BE CONSIDERED IN TABLET FORMULATION

The commonly investigated preformulation parameters include ,but not limited to, angle of repose, bulk density, tapped density, Carrôs compressibility, Hausnerôs ratio, particle size and shape (morphology), true density and melting point.

1. **Angle of Repose:** This is the maximum angle to the horizontal at which substances such as powders remain stable without sliding. At the angle of repose, the material on the slope face is on the verge of sliding. The angle of repose can range from 0^0 to 90^0. Angle of repose is related to the density, surface area and shape of the particles and the coefficient of

friction of the material. However, a 2011 study shows that the angle of repose is also gravity-dependent (74).

2. **Bulk Density:** This takes into account the macroscopic inter-particle spaces. It is defined as powder mass divided by its bulk volume without any tapping. Powder bulk density depends primarily on particle size distribution, particle shape and the tendency of particles to adhere to each other. Some particles may pack loosely leading to fluffy and light powder while others may contain smaller particles that sift between larger particles to fill the void leading to dense and heavy powder. Bulk density is often used to calculate the size for blender granulator.

3. **Tapped density:** This is measured after the powder is subjected to mechanical tapping. It is the density of material itself exclusive of void or interparticulate pores larger than molecular or atomic dimension in the crystal lattice. On the other hand, the true density can be predicted from the crystal lattice and is often determined experimentally using a pycnometer.

4. **Carr's Compressibility index:** This is derived from the values of bulk density and tapped density. A free flowing powder should have a low compressibility index because, the inter particulate forces are not as significant as in a poorly flowing powder, which implies that the value of the bulk density is close to that of the tapped density. As a general rule of thumb, compressibility index higher than 30 % indicates poor powder flow.

5. **Hausner's quotient:** This is derived from the values of bulk density and tapped density.

$$Hausner's\ Quotient = \frac{Tap\ density}{Bulk\ density} \quad \text{é é é é é é é é é é é é é ..(1)}$$

6. **Particle size and shape:** These have far reaching impact on the bioavailability, processibility, physical stability and chemical stability of solid dosage form. For instance, for a low dose, direct compression formulation, where the drug content uniformity is of particular concern, the particle size of the substance has to be small enough to meet the US Pharmacopoeial requirement for content uniformity. Zhang and John (75) have shown that low dose blend containing a larger particle size (18.5 εm) failed to meet USP requirement, whereas the blend containing smaller particle size (6.5 εm) passed the test. The morphology of a solid may also affect the properties. Many pharmaceutical active ingredients crystallize in needle shaped crystals that are difficult to filter and exhibit poor flow properties. Milling of long needle-like crystals can enhance flow properties. On the other hand, the flow of small particles (less than 10 εm) through an orifice is restricted because the cohesive forces between the particles are of the same magnitude as the gravitational force. This tends to create large tablet weight variations during compression.

7 **Particle surface area**: The rate at which a solid dissolves is proportional to its surface area exposed to the dissolution medium. Therefore, particle size reduction which leads to increased surface area has long been used to enhance the dissolution and bioavailability of a poorly soluble drug. In addition, the flow properties and compatibility of pharmaceutical powders may also be impacted by surface area of the solid. The primary factors impacting compactibility are low compact bonds formed, and the surface area over which the binders are active.

8. **pH:** The effect of pH on drug stability is important in the development of both oral and parental dosage forms. Many drugs are stable within the pH range of 4 to 8. Acidic and alkaline pH influence the rate of decomposition of most drugs. As little as one pH unit change can cause a change of ten fold in rate constant.

9. **Melting point:** This helps to determine the processing condition of the substance under test. It is the temperature at which a solid substance turns to the liquid phase. It can be measured by three techniques:

(i) Capillary melting

(ii) Hot stage microscopy

(iii) Differential scanning calorimetry or thermal analysis.

10. **Chemical stability profile:** These studies include both solution and solid state experiments under conditions typical for handling, formulation, storage and administration of a drug candidate, as well as stability in the presence of other excipients. For instance, the method of sterilization of a potential product will be largely dependent on the temperature stability of the drug. A drug having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by other means such as filtration.

Chemical stability profiles are determined through:

- Solid state stability
- Elevated temperature studies
- Stability under high humidity conditions
- Photolytic stability
- Stability to oxidation
- Compatibility studies (stability in the presence of other excipients)
- Solution phase stability

1.6.2 FACTORS TO BE CONSIDERED BEFORE A FORMAL PREFORMULATION PROGRAMME

1. The amount of test substance available.
2. The physicochemical properties of the substance already known.

3. Therapeutic category and anticipated dose of compound, in the case of a drug substance.
4. The nature of information a formulation should have or would like to have.

1.7 OBJECTIVES OF THE STUDY

1. To extract the starch contained in *Cyperus esculentus* nut, and determine its physicochemical properties.
2. To evaluate the use of *Cyperus esculentus* starch as a binder in paracetamol tablet formulation.
3. To evaluate its use as a disintegrant in paracetamol tablet formulation.
4. To compare both the binding and disintegrant properties of starch from *Cyperus esculentus* with that of maize starch.
5. To establish the usefulness or otherwise of *Cyperus esculentus* starch as a tablet excipient.

CHAPTER TWO

EXPERIMENTAL

2.1 MATERIALS

N ï Hexane (BDH, England) was used to extract oil from milled tigernuts. Sodium metabisulphite (Jay Dinesh chemicals, India) was used in the steeping process to avoid oxidation and subsequent colour change of the starch being extracted. Distilled water was used as the extracting solvent for the starch as well as for the preparation of buffer solutions. Liquid paraffin (J .C Enterprise, Mumbai, India) was used as a non-dissolving solvent in the determination of particle density. Paracetamol powder (RPS, France) was employed as the drug and active ingredient in the formulation. Sodium benzoate (BDH, England) was used as a preservative in the paracetamol tablet formulation while magnesium stearate (Hopkin and Williams, U.K) was the lubricant. Iodine (ISE Chemicals,

Japan) solution was used to test for the presence of starch in the extracted substance. Corn starch (BDH, England) was used as the control.

Cyperus esculentus tubers (purchased from Nsukka Central Market) was employed as the test substance. Talc (BDH, England) was used as a glidant. Sodium chloride (Focus Technology co. Ltd, China) and concentrated hydrochloric acid(Riedel- dehaen, E C Label C.O.O, Germany) were used in the preparation of simulated gastric juice. Monosodium dihydrogen phosphate dehydrates (Sigma-Aldrich, UK), sodium hydroxide (Merck, Germany) and disodium monohydrogen phosphate anhydrous (Sigma- Aldrich, UK) were used to prepare simulated intestinal fluid. Peptone, monopotassium phosphate (Sigma- Aldrich, UK), sodium chloride and disodium phosphate (Sigma-Aldrich, UK) were utilized for the preparation of peptone buffer solution. Casein peptone (Sigma- Aldrich, UK), soya bean peptone (Sigma- Aldrich, UK), sodium chloride and agar (Marine Chemicals, India) were used to prepare soya bean casein digest agar medium. Peptone, agar and glucose (Balaji Nutraceuticals, India) were used to prepare Saboraud Dextrose Agar medium whereas a pre-mixed powder of lactose, pancreatic digest of gelatin and beef extract (BD Diagonostic, UK) was used to prepare lactose broth medium. Amylose fraction of starch used as standard (Obtained from soil science laboratory, University of Nigeria, Nsukka)

2.2 METHODS

2.2.1 Isolation of starch from tubers of C*yperus esculentus*

A quantity of *Cyperus esculentus* tubers (6.92 kg) was sorted to remove stones and other unwanted particles. They were washed, dehauled by peeling with knife and milled without water in an attrition mill. The crushed fibers were passed through a Soxhlet extractor, using n-hexane as the defatting solvent at a temperature of 67.0± 3.0^0C.

Starch was extracted from the pulp of C*yperus esculentus* tubers by the modified method of Umerie et al (76). The defatted pulp was steeped in 4 l of sodium metabisulphite ($Na_2S_2O_5$) solution (0.08 %) at 30^0C for 48hours, but the steep water was changed at 24 hours. The pulp was re-suspended in 5 l of $Na_2S_2O_5$ solutions, stirred and allowed to stand for 10 h. The starch milk obtained was stirred again and passed through a muslin cloth and the suspension was allowed to stand for 24 h. The supernatant was decanted off and the starch sediment collected was re-suspended in 1.2 l of distilled water and allowed to settle for 8 h. The water was again decanted off and the starch cake was re-suspended in 1l of distilled water for further purification. After about 8 h, the water was decanted off. The wet starch cake was dried in air overnight and subsequently in a hot air Oven (Mernel Oven, England) at a temperature of 45^0C for 5 h.

2.2.2 CHARACTERIZATION OF C*YPERUS ESCULENTUS* STARCH

i. **Jelly formation**: A smooth mixture of the starch slurry was prepared by adding 2 ml of distilled water to 1 g of the starch. The mixture was stirred into 5 ml boiling water and was allowed to boil gently for 2 min and then cooled (77).

ii) **Iodine Test**:

(a) Starch mucilage from the jelly formed was made and one drop of iodine test solution was added and the color change observed.

(b) A quantity of the starch mucilage equivalent to 0.2 % w/v was made by adding 15 ml of water to 0.03 g of starch at a temperature above 85^0C for 30 min on a water bath. It was allowed to cool and then two drops of 0.1N iodine solution were dropped into the starch mucilage and the colour change was observed.

(iii) **Texture:** A quantity of two grams of the starch was weighed using an analytical balance (Ohaus Adventurer, England) placed between two fingers and pressed to determine the texture.

(iv) **Dissolvability of starch**: A quantity of starch (0.1 g) was added to 100 ml of water at room temperature. Also, another one hundred milligram portion of starch was weighed and put in 100 ml of 95 % alcohol. The two mixtures were observed to know the extent of dissolution of the starch in the mixtures

(v) **Acidity test:** A quantity of starch (10.0 g) was weighed and added to 100 ml of ethanol which was previously neutralized using phenolphthalein solution as indicator. The mixture was shaken for 1 h, filtered and 50 ml of the filtrate titrated with 0.1 N NaOH solution, the quantity of NaOH used was recorded(78).

The titration was done in triplicate and the mean value calculated . The volume of 0.1N NaOH that neutralized the starch solution is the acidity.

The same procedures were carried out on corn starch BP

2.2.3 PREPARATION OF SIMULATED GASTRIC FLUID (SGF)

The SGF without pepsin was prepared by dissolving 2.0 g of sodium chloride (NaCl) in 7 ml of concentrated hydrochloric acid (HCl) and adding enough distilled water to bring the final volume to 1000 ml. The pH was adjusted to 1.2 using a pH meter (pHep US).

2.2.4 PREPARATION OF SIMULATED INTESTINAL FLUID (SIF)

The SIF without pancreatin was prepared by adding 3.1 g of monosodium dihydrogen phosphate dehydrate in 10.0 g of disodium monohydrogen phosphate anhydrous and adding sufficient distilled water to bring the final

volume to 1000 ml. The pH was adjusted to 7.4 using a pH meter by adding sodium hydroxide solution in drops.

2.2.5 PREPARATION OF PEPTONE BUFFER

A quantity of peptone (1.0 g) and 3.689 g of monopotassium phosphate were mixed geometrically in a beaker. Then, 4.30 g of sodium chloride was added to the mixture followed by 18.23 g of disodium phosphate. After mixing thoroughly, sufficient distilled water was added to bring the final volume to 1000 ml. The solution was autoclaved for 15 min at 121^{o}C. The pH of the buffer solution was adjusted to 7.0.

2.2.6 PREPARATION OF SOYA BEAN CASEIN DIGEST AGAR MEDIUM

Five grams each of sodium chloride and soya bean peptone were mixed in a beaker containing 100 ml of distilled water. Fifteen grams of casein peptone was added to the mixture followed by the addition of eighteen gram of agar. Distilled water was added to bring the final volume to 1000 ml. The medium was autoclaved for 15 minutes at 121^{o}C. The pH was adjusted to 7.1.

2.2.7 PREPARATION OF SABORAUD DEXTROSE AGAR MEDIUM.

Ten grams of peptone (derived from meat and casein) was mixed geometrically with fifteen grams of agar after which forty grams of glucose was added and mixed thoroughly. Distilled water was added to bring the final volume to 1000 ml. The preparation was autoclaved at 121^{o}C for 15 min. The pH was determined.

2.2.8 PREPARATION OF LACTOSE BROTH MEDIUM.

A pre-mixed powder of lactose 5.0 g, pancreatic digest of gelatin, 5.0 g and beef extract was put in a beaker and the volume made up to 1 l with distilled water.

2.2.9 EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF *CYPERUS ESCULENTUS* STARCH

2.2.9.1 DETERMINATION OF DENSITY

(i) Bulk Density

Thirty grams of *Cyperus esculentus* starch was measured into a calibrated measuring cylinder (100 ml) and the bulk volume determined. The bulk density was calculated as the ratio of the mass of the starch to the volume of the starch in the cylinder.

(ii) Tapped density

Thirty grams of starch was weighed into a 100 ml calibrated measuring cylinder and tapped 500 times (The height of cylinder to the base being about 5 cm). The volume occupied was recorded as the tapped (consolidated) volume. The tapped density is the ratio of mass of starch to the volume occupied.

iii) True density

This was done using 50 ml pycnometer. The empty pycnometer was weighed and its weight recorded as W1. Thereafter, 10 ml of liquid paraffin was measured into the pycnometer which was weighed to obtain W2. Then, 2.0 g of starch sample was introduced into the pycnometer containing 10.0 ml of liquid paraffin and the weight was taken to be W3.

The true density was computed by the relation;

$$True\ Density = \frac{W2 - W3}{50\ (W2 - W1 + W3)}$$ ---------- (2)

Where W1= Weight of empty pycnometer

W2= weight of liquid paraffin + pycnometer

W3=weight of pycnometer + starch suspension in liquid paraffin.

The tests were done on corn starch BP

2.2.9.2 DETERMINATION OF VISCOSITY

Two percent of aqueous starch suspension was made and heated in a water bath at about 85 ^{0}C to form a paste. The viscometer (Haake rotovisco) spindle was set at a rotational speed of 30 revolutions per minute for 60 seconds after which the viscosity reading was taken from the meter.

2.2.9.3 SWELLING STUDIES

(i) Wettability and Hydration capacity

One thousand milligrams of *Cyperus esculentus* starch powder was weighed in an electronic balance into a calibrated 10 ml capacity centrifuge cell. It was dispersed in 4 ml of water with the aid of a glass rod. The volume was immediately made up to 10 ml mark with distilled water. The mixture was shaken for 5 min and immediately centrifuged for 15 min at 100 revolutions per min (rpm). The volume of the solid sediment and that of water layer were observed from the cell and recorded. The wettability of the starch was determined by the following equation;

$$Wc = \frac{Sf}{St}\ X\ 100$$ ---------- (3)

where Wc = Wettability

Sf= final volume of sediment

St= Initial volume of sediment

Secondly, the process was repeated but this time, the dispersion liquid was allowed to stand for 2 h after which it was centrifuged for 15 min at 1000 rpm. The dispersion was separated and the volume of solid sediment and water layer were observed and recorded. The hydration capacity was also determined as the difference in the initial and final volumes of water separated expressed as a percentage

(ii) Swelling power

Two hundred milligrams of *Cyperus esculentus* starch was weighed and put into a beaker. It was dispersed in water at 85 ^{0}C by stirring for 30 min with intermittent shaking at 5 min intervals. After 30 min period, the mixture was centrifuged at a speed of 2000 rpm for 15 min. The supernatant was collected and evaporated at 105 ^{0}C for 2 h and weighed afterwards. The solubility was calculated. Also the swelling power was calculated according to the formula

$$Solubility\ (S)\% = {}^{A}/_{W} \times 100$$

and ---------- (4)

$$Sp = \frac{Ws}{Wi(100 - S)}\ X\ 100$$ ---------- (5)

where Ws = weight of starch sediment (g)

W (Wi) = weight of sample (g)

A= Weight of dried filtrate

Sp= Swelling power

The experiment was repeated with water at temperatures of 55 ^{0}C, 65 ^{0}C, 75 ^{0}C and 95 ^{0}C and was also carried out on corn starch BP.

(iii) Rate of Swelling

The swelling characteristics were investigated in water, pH 7.0, simulated gastric fluid (SGF) without pepsin, pH 1.2, and simulated intestinal fluid (SIF) without pancreatin, pH 7.4. The *Cyperus esculentus* (5.6 g) starch was placed in 10 ml measuring cylinder up to 2 cm level in each case and tapped 20 times. The level L, at zero time was taken. Water, SGF or SIF as the case maybe was added to the mass to 10 ml level. The rise in volume of the starch at ten minute intervals was recorded over a period 1 h and later left to stand at room temperature for 24 h and the new volume was recorded. The test was done in triplicate and the average taken. The rate of swelling was expressed ml/ sec and recorded.

(iv) Effects of Electrolytes on Rate of Swelling

Five millilitres of different concentrations of sodium chloride (NaCl) and magnesium chloride ($MgCl_2$) (2.0 , 0.1 , 0.5 and 1.0 N) respectively was carefully added to the starch contained in a 10 ml measuring cylinder and the electrolyte was allowed to get absorbed by the starch. The change in the volume of starch was recorded at 10 minute intervals for 1 h. It was later allowed to stand for 24 h after which the changes in volume of starch were noted and the rate of swelling calculated.

2.2.9.4 MICROMERITICS

(i) Determination of Flow Rate

Thirty grams of the *Cyperus esculentus* starch was weighed into a mounted funnel having orifice diameter of 1 cm with the shutter closed and supported with a retort clamp. The funnel was clamped at 7 cm (height of fall) from the

platform to the tip of the funnel. A stop watch was used to measure the duration of flow of starch from the funnel. The flow rate was obtained by the expression of mass of powder divided by the time of flow in seconds. i.e.

Flow Rate= Mass of powder

time of flow ---------- (6)

The experiment was also done for corn starch BP.

(ii) Static Angle of Repose

An open-ended cylinder was placed on the platform of a rubber cork of base diameter 4.0 cm and the starch (20 g) was carefully introduced to fill the cylinder. By raising the cone up, the powder flowed out and formed a heap on top of the rubber cork base. The height of the heap formed was measured with the aid of graph cathetometer attached. The distance between the rubber base and the apex of the heap formed, represented the height of the heap (h). The radius of the cork base (r) was 2 cm. The process was repeated two times and the average value taken.

The angle of repose, ˜Ω was calculated by the relation

$$\text{Tan}\,\theta = \frac{h}{r}$$

Angle of repose, $\theta = \frac{h}{r}\tan^{-1}$ ---------- (7)

(iii) Carr's index and Hausner's Quotient

Compressibility index being one of the indices of flowability was derived using the value of tapped and bulk densities according to the relation.

$$Carr's\ index = \frac{Tapped\ density \quad bulk\ density}{Tapped\ density}$$ ----------

(8)

$$Hausner's\ Quotient = \frac{Tap\ density}{Bulk\ density}$$ ---------- (9)

2.2.9.5 LOSS ON DRYING

Two grams each of the starch samples were placed in crucibles of known weight. The crucibles and content were placed in a hot air oven, which were heated at a temperature of 102^{o}C. The starch was, thus dried in the oven for at least 18 h. They was then placed in a desiccator, and allowed to cool at room temperature. The crucible and its content were reweighed, and the percentage loss in weight was calculated as;

$$LoD = \frac{W-Wf}{W}\ X\ 100$$ ---------- (10)

where W= initial weight of sample

Wf= weight of sample after drying

2.2.9.6 Freeze Thaw Stability Test

One gram of starch sample was dispersed in 100 ml of water, frozen for 18 h, allowed to thaw for 6 h at room temperature. It was centrifuged at 3,000 rpm for 15 min. The percentage of water separated after each freeze thaw cycle was determined by measuring the volume of water separated after the centrifugation process and expressing as percentage of the total volume of water added.

2.2.9.7 PASTE CLARITY

One gram of C*yperus esculentus* starch was dispersed in 25 ml of distilled water to get 4 % concentration from which concentrations of 0.5, 1.0, 1.5, 2.0 and 2.5 % were made. The amount of light transmitted was determined using a spectrophotometer (Jeanway 6305. UK) at a wavelength of 283 nm. The transmittance readings were recorded for each of the starch concentrations

2.2.9.8 BROWNING AND CHARRING TEMPERATURES

One gram of *Cyperus esculentus* starch powder was weighed out and some quantities put into a capillary tube that was sealed at one end. It was heated at a rate of 60 ^{0}C per minute for 5 min in a melting point apparatus (SuPII, Biocide) to a temperature of 300 ^{o} C. The temperature at which the starch turned to brown colour was noted as the browning temperature and the temperature at which it was charred was recorded as the charring temperature. The test was done in triplicate and the result taken as the average of the 3 readings in each case. It was also done for corn starch BP.

2.2.9.9 GELATINIZATION TEMPERATURE

A quantity of *Cyperus esculentus* starch (1.2g*)* was weighed and dispersed in 5 ml of distilled water inside a test tube. The test tube was placed in a water bath set at 50 ^{o} C which was then increased gradually by 4 ^{o} C per minute. The slurry was observed visually at each temperature.

The point at which there was a transformation from starch slurry to starch mucilage was observed and the gelatinization temperature estimated. The test was done in triplicate and the mean value taken. Corn starch BP was similarly analyzed.

2.2.9.10 ASH VALUE

Twenty five gram of starch sample was ignited in the presence of oxygen in a crucible using hot plate (Jenway 1000) at a temperature of 200 ^{0}C until it was charred (at 4 min). The charred starch was transferred to a furnace (Vecstar furnace, Crust field, UK model F3) and burned at 600 ^{0}C for 8 h. It was allowed to cool, and the residue was weighed .The test was done in triplicate and the ash value (As) was calculated as the percentage of starch sample lost using the formula; (79).

$$As = \frac{W-Wo}{W} X\,100 \text{ ---------- (11)}$$

Where Wo is the initial weight of starch sample

W is the weight of starch sample after cooling

The test was also carried out on corn starch BP.

2.2.9.11 HYDROGEN ION CONCENTRATION (pH)

Two grams of *Cyperus esculentus* starch powder was accurately weighed in an electronic balance, dispersed in 100 ml of distilled water with glass rod for 5 min and allowed to stand for 10 min. The pH of the supernatant liquid was determined three times using a pH meter (E.Kent, England). The average pH was taken.

2.2.9.12 FOAM CAPACITY

Two gram quantity of the starch contained in a 100 ml measuring cylinder was homogenized in 100 ml of distilled water using a vortex mixer for 5 min. It was allowed to stand for 30 s after which the volume was recorded. The foam capacity was expressed as the percentage increase in volume. Mean of three replicated test is reported. This test was carried out on corn starch BP.

2.2.9.13 EMULSION CAPACITY

Two gram quantity of the starch was dispersed in 25 ml of distilled water using a vortex mixer (Scientific Industries Vortex Geni 2) for 30 s. After complete dispersion, 25 ml of vegetable oil (groundnut oil) was added gradually and the mixing continued for another 30 s. The suspension was centrifuged at 1,600 rpm for 5 min. The volume of oil separated from the sample was determined. The emulsion capacity is the amount of oil emulsified and held per gram of the sample. The test was done in triplicate and the average reading taken. The experiment was similarly conducted on corn starch BP.

2.2.9.14 MOISTURE CONTENT

Five grams of *Cyperus esculentus* starch was accurately weighed in an analytical balance and was evenly spread on a clean watch glass of 86 cm diameter which was previously weighed. The set up was placed in an oven and maintained at 60 ^{0}C. Occasionally, the set up was brought out and reweighed after cooling in desiccators until constant weight was achieved. The experiment was repeated using corn starch BP.

2.2.9.15 MORPHOLOGY AND SURFACE AREA

The shape, mean diameter and size distribution of *Cyperus esculentus* starch granules was measured using a light microscope (Olympus model UPFL, UK). One gram of *Cyperus esculentus* starch was dispersed in 5 ml of water. The suspension was stirred at room temperature for 30 s after which it was viewed under the light microscope to check the area of the slide covered by the starch granule.

2.2.10 PHYTOCHEMICAL STUDIES

Five hundred milligrams of the starch sample was dispersed in 10 ml of water to form starch slurry and the following tests were carried out.

(a) **Test for alkaloids:** 1 ml of Dragendorffôs (potassium bismuth iodide solution) reagent was added to 1 ml of starch slurry and observed for orange red precipitate

b) **Test for carbohydrates:** 1 ml of Ŭ-naphthol solution was added to a 2 ml portion of the starch slurry and few drops of concentrated sulphuric acid (H_2SO_4) was slowly added down the side of the sloping test tube. The tube was observed for purple or reddish violet colour at the junction of the two liquids

c) **Test for flavonoids:** A 0.1 ml quantity of Amyl alcohol, sodium acetate and ferric chloride solutions were added to 1 ml portion of the starch slurry and observed for a yellow color solution which disappears on addition of an acid.

e) **Test for saponins**: 20 ml of distilled water was added to 1 ml portion of starch slurry, and shaken for 15 min lengthwise and then observed for the formation of a layer of foam.

f) **Test for tannins:** 0.5 ml of ferric chloride solution was added to I ml portion of the starch slurry and observed for the formation of dark blue or greenish black coloured product.

g) **Test for phenolic compounds:** 0.5 ml of strong potassium dichromate solution was added to 1 ml of the starch slurry. It was observed for a yellow colour precipitate.

h) **Test for proteins and amino acids:** 1 ml of 40 %sodium hydroxide solution (NaOH), and 2 drops of 1 % copper sulphate solution ($CuS0_4$) were added to 1 ml portion of the starch slurry which produced a blue colour. 1 ml of the starch slurry was added to the mixture and then observed for the formation of pink or purple violet colour.

2.2.11 ELEMENTAL ANALYSIS OF THE STARCHES

One gram of each of the starches was heated in a furnace to ash by the dry combustion method. The ashed starch sample was digested in 10 ml of 50 % HCl and made up to 100 ml with distilled water. The digested sample was analysed in atomic absorption spectrometer (GBC Scientific equipment, Savant AA, Australia) equipped with lamps of various metals. Corn starch BP was also analyzed using the same procedure.

2.2.12 THERMAL ANALYSIS

Thermal characteristics of starch sample were studied by using differential scanning calorimeter (PerkinElmer,USA) equipped with a thermal analysis station. Each of the starch samples (3.5 mg), dry weight was loaded into an aluminum pan and 0.00245 ml of distilled water was added with the help of Hammitton micro syringe to achieve a starch-water suspension containing 70 % water. These pans were hermetically sealed, equilibrated at room temperature for 1 h and heated at 20 to 120 ^{o}C at a heating rate of 10 ^{o}C/min. The melting enthalpy and the temperature axis were calibrated with indium. Each test was carried out with an empty pan as a reference and the onset temperature of gelatinization (To), the peak temperature (Tp), the gelatinization temperature at conclusion (Tc), and melting enthalpy (DH) were recorded.

The range of gelatinization temperature (R) was computed as (Tc-To) and the peak height index (PHI) was calculated as the ratio DH/Tp-To

2.2.13 AMYLOSE /AMYLOPECTIN RATIO IN *Cyperus esculentus* STARCH

For amylose content, 10 mg of *Cyperus esculentus* starch sample was weighed into 100 ml beaker and 10 ml of 0.5 N potassium hydroxide solution was added. The mixture was stirred with a glass rod until fully dispersed. The dispersed sample was transferred into a 50 ml volumetric flask and diluted to the mark with distilled water. Five millitres of the mixture was pipetted in a 50 ml volumetric task, 5 ml of 0.1 N hydrochloric acid (HCl) and 0.5 ml of 0.1 N iodine were added and the mixture diluted to 50 ml with distilled water. The absorbance the resulting solution was taken at the wavelength of 625 nm. The result was compared with a prepared standard amylase sample.

For total starch, 0.5 g of the *Cyperus esculentus* starch was weighed and heated at at temperature of 67 ^{o}C ± 2 ^{o}C in 50 ml of distilled water for 30 min. One millilitre of the sample suspension was pipetted into a beaker and 9 ml of Anthrone reagent was added after which the absorbance was measured at 620 nm. The absorbance was compared with that of a standard *Cyperus esculentus* starch sample.

Amylopectin: This was determined by taking the difference in the absorbance values of amylose and total starch.

Similar test was done for corn starch BP.

2.2.14 MICROBIOLOGICAL ASSAY:

(a) Microbial Limit Test:

Preparation of medium

For bacteria: 15 ml of liquefied casein soya bean digest agar medium at a temperature of 40 ^{0}C was poured into a Petri dish of about 10 ml capacity (80).

For fungi: 15 ml of liquefied saboraud dextrose agar (SDA) medium at a temperature of 40 ^{0}C was poured (81). The total aerobic count in the substance was examined by plate count method.

One gram of *Cyperus esculentus* starch was dispersed in 10 ml of pre-sterilized sodium chloride peptone buffer solution and the pH was adjusted to 7.0 (step 1) Five test tubes were taken and 9 ml of sodium chloride peptone buffer solution was transferred into each of the test tubes and sterilized by autoclaving at 121 ^{0}C for 15 min (step 2). The sample (from step 1) was diluted serially from 10^{-1} to10^{-5} with distilled water. Using test tubes (from step 2), casein soya bean digest agar and saboraud dextrose agar (SDA) were spreaded with 100 εL of the serial solutions 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4} to 10^{-5} respectively. Casein soya bean digest agar plates were incubated at 35 ^{0}C for 2 days and SDA plates were incubated at 25 ^{0}C for 5 days.On the fifth day, the plates were examined for microbial contamination. The number of colony forming units was counted using a colony counter. Control plates were also prepared. The tests were done in triplicate and the average values taken.

(b) Coliform test:

One gram of *Cyperus esculentus* starch sample was added to lactose broth medium, made up to 10 ml and incubated for 24 h at 30 ^{0}C. The tube was shaken slightly and a portion of the fluid was taken using an inoculating loop. It was streaked on McConkey agar medium and incubated for 24 h at 30 ^{0}C. The plate was then examined for brick red colouration.

2.2.15 DEXTROSE EQUIVALENCE OF *Cyperus esculentus* Starch

One hundred milligrams of starch sample was weighed into a boiling tube and allowed to boil for 3 h in the presence of 5 ml of 2.5 N HCl to achieve complete hydrolysis. The hydrolysate was cooled to room temperature and neutralized with solid sodium carbonate (Na_2CO_3) until the effervescence ceased. It was made up to 100 ml volume with distilled water and centrifuged at 2000 rpm for 15 min. The supernatant was collected and 0.5 and 1 ml aliquot of it respectively were taken for analysis using ultraviolet spectrophotometer at wavelength of 340 nm. The dextrose content was analyzed by comparing with a standard solution of glucose. A calibration curve was obtained with the standard glucose by dissolving 8 mg of glucose in 200 ml of distilled water (0.004 mg/ml) and withdrawing 5 ml aliquot of the stock solution for analysis.

2.2.16 PHYSICAL COMPATIBILITY STUDIES

Drug-excipient compatibility test was undertaken to determine the interaction of paracetamol with various excipients. Three batches of drug-excipient mixtures were tested as A, B and C according to the formula in Table 1. The A, B and C admixtures were stored for 4 weeks at 40 ^{o}C/ 75 %RH and at 50 ^{0}C/ 75 %RH. They were checked every week for any change in physical appearance.

2.2.17 FORMULATION OF PARACETAMOL TABLETS

2.2.17. 1 Granulation Procedures

(A) Endo disintegrants

Fifty grams of paracetamol, 0.5 g, 1.0g, 2.5 g, and 5.0 g of *Cyperus* starch (Tiger nut starch) as the case may be, was weighed in a porcelain mortar. The powders were wet massed with binder solution formed by mixing 4.0 g of corn starch, 0.8 g of gelatin and 0.05 g of sodium benzoate made in a paste by heating at 100 ^{o} C with about 10 ml of water for 2 min to form an adhesive mass

The wet-massed powder blend was screened through a sieve of 1.7 mm mesh screen. The screened wet granules were spread as a thin layer on a tray and dried in an oven (tray drier) at a controlled temperature between 48 and 52^{o} C for 30 min. The dried granules were screened through sieve 1.0 mm mesh and bottled.

(B) Exo disintegrant

Fifty grams of paracetamol was weighed in a porcelain mortar. The powders was wet massed with binder solution formed by mixing 4.0 g of corn starch, 0.8 g of gelatin and 0.05 g of sodium benzoate made in a paste with about 10 ml of water to form an adhesive mass.The wet-massed powder blend was screened through a sieve of 1.7 mm mesh screen. The screened wet granules were spread as a thin layer on a tray and dried in an oven (tray drier) at a controlled temperature between 48 and 52^{o} C for 30 min. dried granules were screened through sieve 1.0 mm mesh and bottled.

Table 1 Drug excipient-admixtures

Materials	**A**	**B**	**C**
Paracetamol (g)	50.00	50.00	50.00
Corn starch (g)	4.00	ð	ð
Cyperus esculentus (g)	ð	ð	4.00
Gelatin (g)	0.80	0.80	0.80
Sodium benzoate (g)	0.05	0.05	0.05
Talc (g)	0.80	0.80	0.80
Magnesium stearate (g)	1.20	1.20	1.20

Table 2. Formula for Paracetamol tablets using *Cyperus esculentus* starch as a disintegrant.

Substance	Concentration of the starch disintegrant				
	1%	2%	5%	10%	Control
Paracetamol (g)	50.00	50.00	50.00	50.00	50.00
Corn starch (g)	4.00	4.00	4.00	4.00	4.00
Tiger nut starch (g)	0.50	1.00	2.50	5.00	----
Gelatin (g)	0.80	0.80	0.80	0.80	0.80
Sodium benzoate (g)	0.05	0.05	0.05	0.05	0.05
Mag. stearate (g)	1.20	1.20	1.20	1.20	1.20
Talc (g)	0.80	0.80	0.80	0.80	0.80
Water (ml)	10.00	10.00	10.00	10.00	10.00
Corn starch (g)	-----	----	-----	-----	2.50

(B) Exo disintegrant

Fifty grams of paracetamol was weighed in a porcelain mortar. The powders was wet massed with binder solution formed by mixing 4.0 g of corn starch, 0.8 g of gelatin and 0.05 g of sodium benzoate made in a paste with about 10 ml of water to form an adhesive mass.

The wet-massed powder blend was screened through a sieve of 1.7 mm mesh screen. The screened wet granules were spread as a thin layer on a tray and dried in an oven (tray drier) at a controlled temperature between 48 and 52^{o} C for 30 min. dried granules were screened through sieve 1.0 mm mesh and bottled.

(C) Endo-Exo disintegrant

Fifty grams of paracetamol, 0.25, 0.5, 1.25, or 2.5 g of *Cyperus esculentus* starch in each case were weighed and mixed by geometric dilution in a porcelain mortar. The mixed powders were wet massed with binder solution formed by mixing 4.0 g of corn starch, 0.8 g of gelatin and 0.05 g of sodium benzoate made as a paste with about 10 ml of water to form an adhesive mass.

The wet-massed powder blend was screened through a sieve of 1.7 mm mesh screen. The screened wet granules were spread in a thin layer on tray and dried in an oven (tray drier) at a controlled temperature between 48 and 52^0 C for 30 min. The dried granules were screened through sieve 1.0 mm mesh and bottled. Control samples were prepared using 5 % corn starch as exo, endo and exo-endo disintegrants.

(D) Starch Used as Binders

Fifty gram of paracetamol powder, 4.0 g of corn starch were weighed and mixed by geometric dilution in a porcelain mortar. The mixed power were wet-massed with binder solutions (2.5, 5.0, 7.5 or 10.0 % tiger nut starch as the case may be) mixed with 0.05 g of sodium benzoate to form an adhesive mass. The wet massed powder blend was screened through a sieve of 1.7 mm mesh screen. The screened wet granules were spread as a thin layer on tray and dried in an oven (tray drier) at a controlled temperature between 48 and 52 ^{0}C. The dried granules were screened through sieve 1.0 mm mesh to separate them into coarse and fine granules. Control samples were prepared using 5 % corn starch as binder.

2.2.17.2 MICROMERITIC PROPERTIES OF PARACETAMOL GRANULES

The following properties of the granules were evaluated; granule flow rate, tapped and bulk densities of granules, Hausnerôs quotient and compressibility

index, angle of repose and loss on drying (LOD). The methods used were similar to those used for the starch sample.

Granule size distribution: The granules were analyzed for size distribution using sieve analysis method (82). The granules were all passed through sieves of sizes 1.0 mm and 0.7 mm. The different weights were taken and percentage size distribution calculated.

Determination of moisture content of granules: This was determined using a moisture analyzer (Satorious, Germany). 1g of paracetamol granules was weighed and spread out on the pan. The samples were dried at 105 ^{o} C for 10 min. The weight difference due to loss of moisture was computed and expressed as the percentage moisture content (83).

Determination of percentage fines of granule batches: The percentage fines was determined by the sieve method. The fine granules were passed through sieve of aperture 0.7 um. The weights of the fines were taken and the percentage calculated with respected to the weight of the whole granule batch.

Table 3.Formulation of Paracetamol using starch as binder.

Substance	**Concentration of the starch binder**				
	2.5%	5%	7.5%	10%	Control
Paracetamol (g)	50.00	50.00	50.00	50.00	50.00
Corn starch (g)	4.00	4.00	4.00	4.00	4.00

Tiger nut starch (g)	1.25	2.50	3.75	5.00	----
Sodium benzoate (g)	0.05	0.05	0.05	0.05	0.05
Gelatin	0.80	0.80	0.80	0.80	0.80
Mag. stearate (g)	1.20	1.20	1.20	1.20	1.20
Talc (g)	0.80	0.80	0.80	0.80	0.80
Water (ml)	10.00	10.00	10.00	10.00	10.00
Corn starch	-----	----	-----	-----	2.50

2.2.17.3. BLENDING WITH LUBRICANT AND GLIDANT

(A) Endo disintegrants

Eight hundred milligram of talc and 1.2 g of magnesium stearate were weighed and incorporated into the fine granules. The mixing was done in a powder bottle by rolling the bottle in a figure 8 manner for 5 min after which it was mixed with coarse granules. The admixture was blended for about 2 min.

(B) Exo disintegrants

Eight hundred milligram of talc and 1.2 g of magnesium stearate, 0.5, 1.0, 2.5, or 5.0 g of *Cyperus esculentus* starch as the case may be were weighed and incorporated into the fine granules contained in a powder bottle.

The mixing was done by rolling the bottle in a figure 8 manner for 5 min after which it was mixed with coarse granules. The ad mixture was blended for about 2 min.

(C) Endo-exo disintegrants

Eight hundred milligram of talc and 1.2 g of magnesium stearate, 0.25, 0.50, 1.25, or 2.50 g of *Cyperus esculentus* starch as the case may be were weighed and incorporated into the fine granules. The mixing was done in a powder bottle by rolling the bottle in a figure 8 manner for 5 min after which it was mixed with the coarse granules. The admixture was blended for about 2 min.

(D) Starch used as binders: Eight hundred milligram of talc and 1.2 g of magnesium stearate were weighed and incorporated into the fine granules. The mixing was done in a powder bottle by rolling the bottle in a figure 8 manner for 5 min after which it was mixed with coarse granules. The admixture was blended for about 2 min.

2.2.17.4 COMPRESSION OF PARACETAMOL GRANULES INTO TABLETS

Compression of granules into tablet was done in a single punch tabletting machine (Manesty F3, UK) fitted with 9.00 mm punch and dies. The tablets were compressed automatically and the targeted tablet weights were between 266.75 and 289.25 mg. 200 tablets ± 9 tablets were produced for each batch.

2.2.18 EVALUATION OF PARACETAMOL TABLET PROPERTIES

2.2.18.1 APPEARANCE:

The appearance of paracetamol tablets produced was evaluated visually.

2.2.18.2 DIMENSIONS:

The diameter and thickness were measured using a Venier calipers.

2.2.18.3 WEIGHT VARIATION

Twenty tablets from each batch of the tablet formulation were picked at random and weighed three times individually using an electronic weighing balance (OHAUS Adventurer, England). The tablets were also weighed individually and their weights recorded. The mean weight, standard deviation and coefficient of weight variation were calculated.

2.2.18.4 RESISTANCE TO ABRASION

Twenty tablets were randomly selected from each batch of the tablets, de-dusted carefully and lightly until any surface powder was removed. The twenty tablets were weighed accurately with the mettler balance and the initial weight, W_o was recorded. They were placed inside the Erweka Friabilator and rotated for 4 minutes at a speed of 25 rpm. The tablets were removed from the Friabilator, de-dusted and reweighed. The final weight, W was recorded. The friability F, for each batch was calculated. The test was done in triplicate and the mean percent friability calculated using the following formula.

Friability $F = \frac{1-W}{Wo} X\ 100$ ---------- (12)

2.2.18.5 CRUSHING STRENGTH AND TENSILE STRENGTH

The crushing strength was determined using Monsanto hardness tester. The diametrical hardness was tested for. A tablet was held between the fixed and moving jaw of the hardness tester. The load gradually increased until the tablet just fractured. The value of the load at this point gives a measure of the tablet hardness. The hardness of six tablets from each batch, picked at random was determined from which the average was obtained. The tensile strength was also derived from these hardness values. The tensile strength of paracetamol tablet batches produced was calculated according to the formula (84)

$$T = \frac{2F}{\pi Dt} \quad \text{---------- (13)}$$

Where T = tensile strength (Nm^{-2})

F = Force required to cause fracture (N)

D = tablet diameter (m)

t = tablet thickness (m)

Note: 1kgF = 10N

2.2.18.6 *IN VITRO* DISINTEGRATION TIME

The disintegration times of the tablets produced were determined in a 700 ml of distilled water at 37 ^{0}C ± 5 ^{0}C using Manesty disintegration test unit (). Six tablets from each batch, picked at random were placed into each tube of the disintegration time tester. The discs were placed on the tablets in each tube. The units were switched on simultaneously with a stop watch. The times taken for the tablets to break down into fragments and completely pass through the wire mesh or to leave behind a palpable fluffy mass were recorded as the disintegration time. Determinations for each batch were made in quadruplicate and the mean values taken.

2.2.18.*7 IN VITRO* DISSOLUTION RATE/ DRUG RELEASE PROFILE

The in vitro dissolution rate studies were performed in a dissolution test apparatus () operated at 50 rpm. The dissolution medium was 900 ml of SGF or SIF pH, 1.2 and 7.4 respectively at 37 ^{0}C ± 0.5 ^{0}C. At 10 min intervals, 10 ml sample was withdrawn and immediately replaced with 10 ml sample of fresh medium maintained at the same temperature. The withdrawn samples were diluted appropriately and the amount of drug analyzed spectrophotometrically at 243 nm for SGF and 272 nm for SIF. Cumulative percentage drug release was determined as a function of time and drug release at ten minutes interval. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time, t (measured using Trapezoidal rule) and expressed as a percentage of the area of the trapezium described by 100% dissolution in the same time (85).

$$AUC_T = \frac{1}{2}(a+b)h \text{ ---------- } (14)$$

Where AUC_T = Area under the dissolution curve at time t

a = time t, 10 minutes before the time under consideration

b = time t, 10 minutes after the time under consideration

h = concentration of the dissolution medium

Dissolution Efficiency $DE_x = \frac{AUC \text{ at time } x}{AUCo} \; x \; 100$ ------(15)

Where AUC_O = Area under curve over the entire course of release.

2.2.18.8 CALIBRATION CURVE OF PARACETAMOL

A stock solution of 0.147 mg/ml of paracetamol was prepared by dissolving 250 mg of the drug in 1700 mls of 0.1 N NaOH. Various dilutions of the stock were made to obtain 0.00147, 0.00294, 0.00441, 0.00585, 0.00735, and 0.00882 mg/ml with 0.1 N NaOH. The absorbance of the various dilutions was taken at wavelength of 243 nm using a UV-VIS spectrophotometer. A plot of absorbance (A) against concentration (mg/ml) of the drug was made from which the calibration curve was determined from the slope of the graph.

2.2.18.9 DENSITY OF TABLETS

The average weights, diameter and heights of four tablets picked at random were taken. The bulk density of the tablets were determined by applying the equation

$$Bd = \frac{4W}{\pi d^2 h}\ gcm^{-3} \quad \text{---------- (16)}$$

Where h = thickness of tablets (cm^3)

w = weight of tablets (g)

d = diameter of tablets (cm)

Bd = Bulk density of tablets

Tablet particle density

The particle density was determined by fluid displacement method. A 25 ml capacity Pycnometer (density bottle) was filled with liquid paraffin at room temperature. The weight of the filled Pycnometer was taken. Also, the weight of empty Pycnometer was taken. The weight of the Pycnometer, with the liquid paraffin and Paracetamol tablets dropped inside was taken in each case.

The particle density was determined by applying the equation of Ohwourworhua et al (86).

$$Q1 = \frac{N}{\{(a+w)-b\}SG} \quad \text{---------- (17)}$$

Where; ϱ_1 = tablet particle density in g/cm^3

W = tablet weight in g

SG = Liquid paraffin specific gravity = 0.802

a = pycnometer + liquid paraffin weight in g

b = pycnometer + liquid paraffin + tablet weight in g

The packing fraction of the tablets were calculated by the equation (87).

$$Packing\ fraction = \frac{Bulk\ density\ of\ tablets}{Particles\ density\ of\ tablets} \text{-----} \quad (18)$$

The porosity of tablets was determined by applying the equation (88).

$$Tablet\ porosity = 1 - packing\ fraction$$

$$= 1 - \frac{Bulk\ density}{Particle\ density} \text{----------} \quad (19)$$

2.2.18.10 CRUSHING STRENGTH, FRIABILITY, DISINTEGRATION TIME RATIO

This was calculated by finding the ratio of crushing strength to the friability and also relating it to the corresponding disintegration time ratio (89).

2.3 STATISTICAL ANALYSIS

The whole data were collated and analyzed using SPSS Version 21. All the values are expressed as mean ± SD. Statistically significant differences means were assessed by Studentôs T-test ($P<0.001$) and ANOVA.

CHAPTER THREE

RESULTS AND DISCUSSION

3.1 IDENTIFICATION OF *CYPERUS ESCULENTUS* STARCH

Table 4. Results of identification tests of *Cyperus esculentus* and Corn starch BP

	Starches	
Properties	*Cyperus esculentus*	Corn starch BP
Colour	White	White
Odour	Odourless	Odourless
Taste	Tasteless	Tasteless
Texture	Fine and creaks when placed in between fingers	Fine and creaks when placed in between fingers
Gel formation	Positive	Positive
Iodine Test	Positive	Positive
Solubility	Insoluble in cold water and in 95 % alcohol	Insoluble in cold water and in 95% Alcohol

Table 4 shows some of the properties of *Cyperus esculentus* starch and corn starch BP that help in their identification. The results reveal that *Cyperus esculentus* starch conforms well to BP standard for pharmaceutical grade starch. It has strong affinity for moisture as a result of abundance of OH (hydroxyl) groups in the molecule. *Cyperus esculentus* starch is insoluble in water owing to the strong intramolecular hydrogen bonds holding the starch polymer together.

The white coloured *Cyperus esculentus* starch turned blue black in the presence of iodine. This blue black colouration of *Cyperus esculentus* starch with 0.1N iodine solution is due to the fact that the iodine complexes with coiling *Cyperus esculentus* starch molecule to form helical conformations called clarathes, thereby producing the colour ranging from deep blue to light red depending on the length of the coiled chain(90).

3.2 PERCENTAGE YIELD OF STARCH

The starch extracted was weighed and the percentage yield calculated as follows;

Weight of starch =0.93 Kg

Weight of *Cyperus esculentus* tubers =6.92kg

Percentage yield, $Y = \frac{0.93}{6.92} X\,100$ = 13.4 %

The percentage yield obtained from extracting starch from *Cyperus esculentus* tubers was 13.4 %. The yield was good. The availability, high yield, simplicity of extraction and low cost of *Cyperus esculentus* tubers indicate that it can be a potential source of pharmaceutical raw material.

3.3 SOME PHYSICOCHEMICAL PROPERTIES OF *CYPERUS ESCULENTUS* STARCH

Table 5: Physicochemical properties of *Cyperus esculentus* and Corn starch BP

Properties	*Cyperus esculentus*	Corn starch
Acidity	1.93	1.76
Bulk density (gcm^{-3})	0.59	0.59
Tapped density (gcm^{-3})	0.72	0.76
True density (gcm^{-3})	1.011	1.42
Flow rate (gs^{-1})	0.298	0.403
Angle of repose (^{0})	58.74	36.08
Compressibility index (%)	16.00	22.37
Hausnerôs quotient (%)	1.19	1.29
Porosity (%)	16.00	16.50
Dynamic Viscosity of 2 % w/v mucilage at 25 ^{O}C (mPa.S)	13.00	12.60
Wettability (%)	1.25	1.31
Hydration capacity	10.3	1.71
Amylose: Amylopectin ratio	1 : 7	1: 4
Browning temperature (^{O}C)	240	226
Charring temperature (^{O}C)	257	262
Ash value (Dry basis) (%)	4.8	4.2
pH	5.2	6.5
Foam capacity (%)	5.67	5.0
Emulsion capacity (ml/g)	2.3	5.2
Gelatinization temperature (^{O}C)	64 ï 67	68-70
% of Simple sugar	8	6.8

Particle size (εm)	8.5 ï 11	8.6-13
Moisture content (%)	2.72	11.42
Loss on drying (%)	4.10	2.35

The physicochemical parameters of starch were presented in table 5. *Cyperus esculentus* starch possesses excellent physicochemical properties as shown in Table 5. Acidity value of *Cyperus esculentus* starch was 1.93 ml. The BP specification for acidity value is that not more than 2 ml of NaOH should neutralize a pharmaceutical grade starch (77). Both *Cyperus esculentus* and corn starch passed the test. The value of hydration capacity of 10.3 % is relatively high. The implication of this is that *Cyperus esculentus* starch can absorb water 10.3times its own weight (91). This makes it a good candidate for use as a disintegrant.The percentage of amylopectin is relatively high. Studies have shown that amylose fraction of a starch sample is responsible for disintegration. While the amylopectin expands, the amylose gives osmotic pressure (92). This also makes it suitable for use both as binder and as disintegrant.

Although starch rarely contains volatiles other than water, loss on drying (LOD) is a good technique to determine the volatile components present in the sample. The 4.1 % LOD for *Cyperus esculentus* starch is within the limits set by the USP and is attributed to the presence of moisture. Ash value of 4.8% also shows that it has fewer impurities. This low value is good because of its health implications. A pH of 5.2 is within USP range (93) of 4.5 ï 7. This implies that when *Cyperus esculentus* starch is used in formulation, it will not likely react with pH sensitive active ingredients and other excipients in the formulation.

The particle size range of 8 ï 11 εm is also within range. It has been shown that the spherical shape of starch increases the porosity of tablets thus promoting capillary action (94). This in turns enhances disintegration of the tablets and ultimately bioavailability. The moisture content of 2.7% is adequate and within specified limit as recommended by British Pharmacopoeia, 2011 (95). This

ensures that the osmotic pressure present in the starch is such that it prohibits growth. Thus C*yperus esculentus* starch can be stored indefinitely if kept dry. The value of gelatinization temperature is also low. This is of economic importance because it will be adequate for food or products requiring moderate temperature process. The browning and charring temperatures are high. This is in agreement with the works of Builders, Emeje and Kunle (96). However, the values of foam and emulsion capacities (5.67 % and 2.3 ml/g) are low. Therefore, it cannot be used as an emulsifier (97).This agrees with the work of Omojola and Akinwunmi (98).The results of micrometric studies show that *Cyperus esculentus* starch is a poorly flowing powder and has low density (99). Most starches start gelling at a temperature of 60 ^{o}C. The findings for Cyperus esculentus starch agrees with that of Attama, Nnamani, Mbonu and Adikwu (100).

Cyperus esculentus starch granules exhibits elliptical to spherical shape with a relatively smooth surface as shown in Fig 1. Size distribution of a potential excipient has been shown to affect various formulation characteristics such as flowability, compactibility, water binding capacity, and drug release (1). Although no precise categorization of granule size is documented in the literature, starch granules have been arbitrarily classified as large (>25εm), medium (10-25εm), small (5-10εm), and very small (Ò5εm) (1). *Cyperus esculentus* starch predominantly consists of small-to-medium-sized granules (percent volume basis) with a mean particle size of 9.5 εm.

Result of freeze thaw stability test is shown in Table 6. It can be seen that *Cyperus esculentus* starch paste released large amount of water. This may be attributed to the low amylose content as well as possible aggregation and amylose crystallization occurring during the first storage hours at different storage conditions (6). This suggests that *Cyperus esculentus* starch gel will be

stable at extremes of temperatures and even when subjected to mechanical stress involved in processing and transportation.

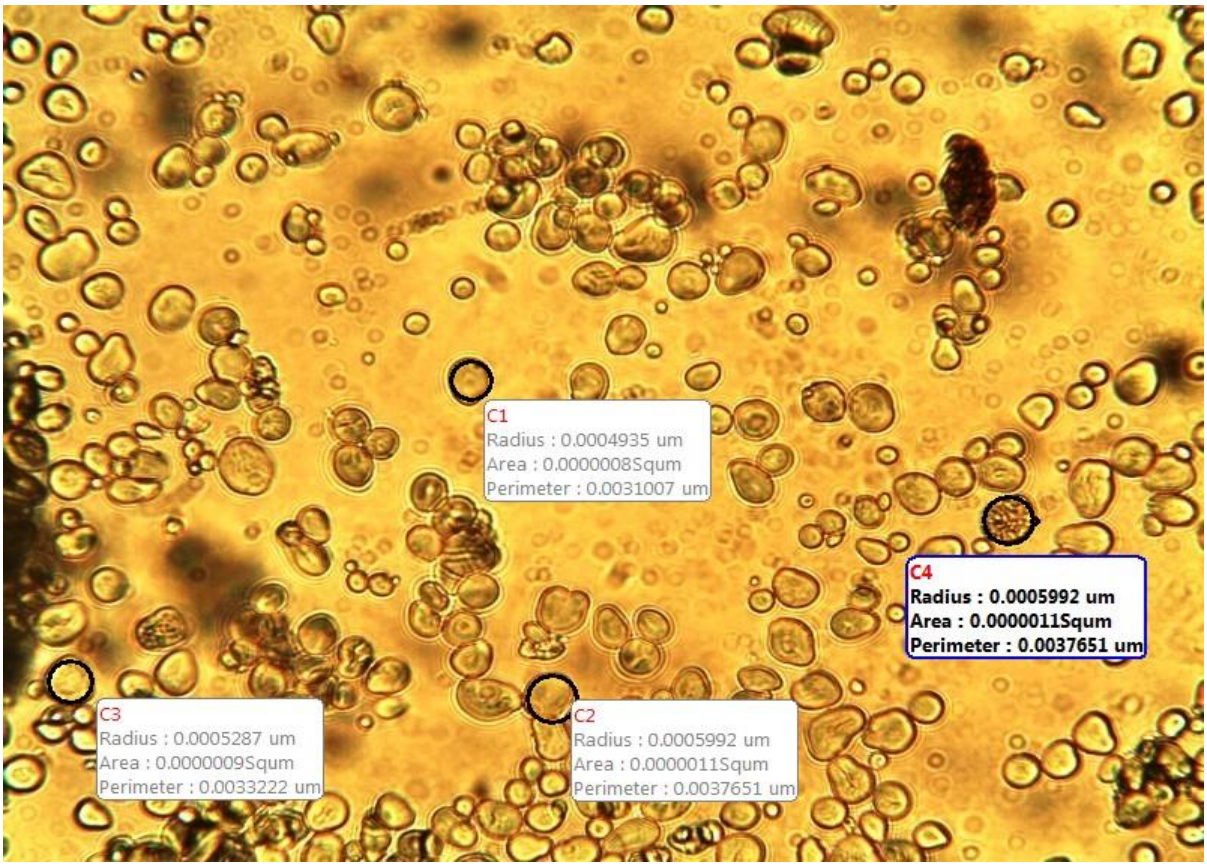


Fig 1: Photomicrograph of *Cyperus esculentus* starch granules (x 40 Magnification)

3.4 FREEZE THAW STABILITY

Table 6: Percentage of water separated after six freeze thaw cycles

No of Cycles	% water separated
1	82.20
2	85.50
3	88.89
4	88.89
5	88.89
6	88.90

3.5 CLARITY

Table 7: Percentage of light transmitted through different concentrations of *Cyperus esculentus* starch paste.

Concentration (%)	Transmittance (%)
0.50	4.00

1.00	2.00
1.50	2.00
2.00	1.00
2.50	1.00

The paste clarity results are shown in Table 7. The transmittance values are low. This may affect the aesthetic appearance of the final product when this starch is used.

Table 8 revealed that phytochemicals are absent in *Cyperus esculentus* starch. Therefore, the possibility of interaction with any phytochemical and an active ingredient when used is not there. This may be the reason why *Cyperus esculentus* starch like any other starch is regarded as generally safe and non toxic.

Table 9 shows some of the metallic elements present in *Cyperus esculentus* and corn starch BP. Native starches are known to contain varying amounts of monovalent and divalent cations inherited from the parent material. Incinerating the starch sample and analyzing the residue (known as ash) can be used to estimate the metal ions present in the sample (1). *Cyperus esculentus* starch samples show a predominance of divalent cations as compared with maize starch, which has been shown to primarily contain monovalent cations such as sodium and potassium (101).The B.P gives limit test for a number of possible contaminants in pharmaceutical raw materials which may be introduced into the finished product during processing. Such tests include those for lead, arsenic, calcium, iron, aluminum, potassium, halogens and a host of others.

Although the pharmacopoeial requirements are not categorical on the exact tolerable level of any possible contaminant, it should be presumed that unusual impurities are not tolerated. Atomic absorption spectrophotometric results of

Cyperus esculentus starch as shown in Table 9 revealed that heavy metals such as lead (Pb) and mercury (Hg) were absent. The presence of heavy metals in formulated products is highly undesirable as they form stable covalent or co-ordinate complexes with body proteins which may act as catalysts (due to their variable valency states) to induce auto-oxidative reactions. The pharmacopoeia has therefore placed stringent limits on the amount of lead and other heavy metals that may be present in pharmaceutical products.

3.6 PHYTOCHEMICAL CONSTITUENTS

Table 8: Phytochemical constituents in Cyperus esculentus starch

Alkaloids	Absent
Carbohydrate	Present
Reducing sugars	Absent
Flavonoids	Absent
Saponins	Absent
Tannins	Absent
Phenolic compound	Absent
Protein	Absent

3.7 ELEMENTAL COMPOSITION

Table 9: Elemental composition of I g weight of *Cyperus esculentus* and corn starch BP.

Starch Elements	**Value (ppm)**	
	Cyperus esculentus	**Corn starch BP**

Copper	0.000	0.000
Zinc (Zn)	0.700	0.000
Magnesium (Mg)	11.00	0.003
Calcium (Ca)	1.070	0.006
Potassium (K)	0.000	0.014
Iron (Fe)	0.790	0.000
Manganese (Mn)	0.030	0.000
Sodium (Na)	0.000	0.007
Lead (Pb)	0.000	0.000
Aluminum (Al)	0.000	0.000

3.8 THERMAL PROPERTIES

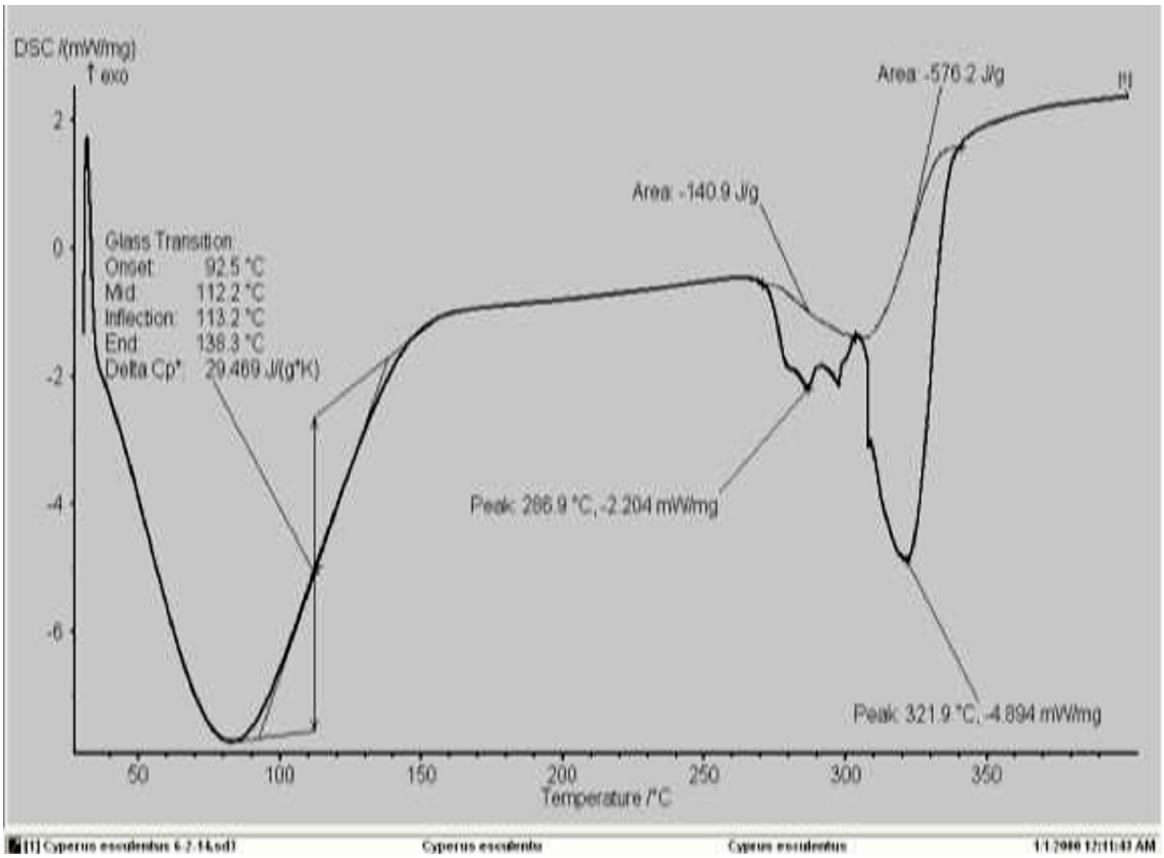


Fig 2; DSC Thermogram of *Cyperus esculentus* starch

From fig 2, it can be seen that the onset temperature of glass transition was 92.5 ^{0}C. The peak temperature was 286.9 ^{0}C. The glass transition temperature at conclusion was 138.3 ^{0}C. The melting enthalpy (æH gel) was 140.9 J/g. This value of æH gel reflects melting of amylopectin crystallites (102). It is the energy required to break hydrogen bonds of amylopectin. The range of glass transition temperature (R) is 185 ï 276.6 ^{o} C. This suggests the presence of crystallites of varying stability within the crystalline domain of the granule (103). The peak height index (PHI) which is a measure of uniformity in glass transition is 0.720 J/g/^{0}C

3.9 MICROBIAL LOAD

The total amount of bacteria in the *Cyperus esculentus* was found to be 7.75CFU/g. That of fungi was 5.31 CFU/g. There was absence of lactose fermenters (coliforms). The total microbial load is an important parameter which determines the suitability of a substance for use as excipient in pharmaceutical formulation. According to many pharmacopoeias, for synthetic and semi-synthetic substances, the total aerobic count should not be more than 100 colony forming unit (CFU) per gram and the total fungal count including yeast and mould should not exceed 50CFu/g. If the excipient is of natural origin, the total aerobic count should not be more than 1000CFu/g and the total fungi should not exceed 1000CFu/g. If these microbes were not controlled, they could lead to a change in viscosity and pH of the product. This occurs because

bacterial growth splits the starch molecules causing lower viscosity and the acid produced lowers the pH (104). This can cause production and finished product quality problem.

3.10 DEXTROSE EQUIVALENCE

The percentage of simple sugar which is also the average degree of polymerization is 8%. This means that *Cyperus esculentus* starch cannot be easily hydrolyzed. It will be stable in the presence of amylase enzymes.

3.11: EFFECT OF TEMPERATURE ON SOLUBILITY

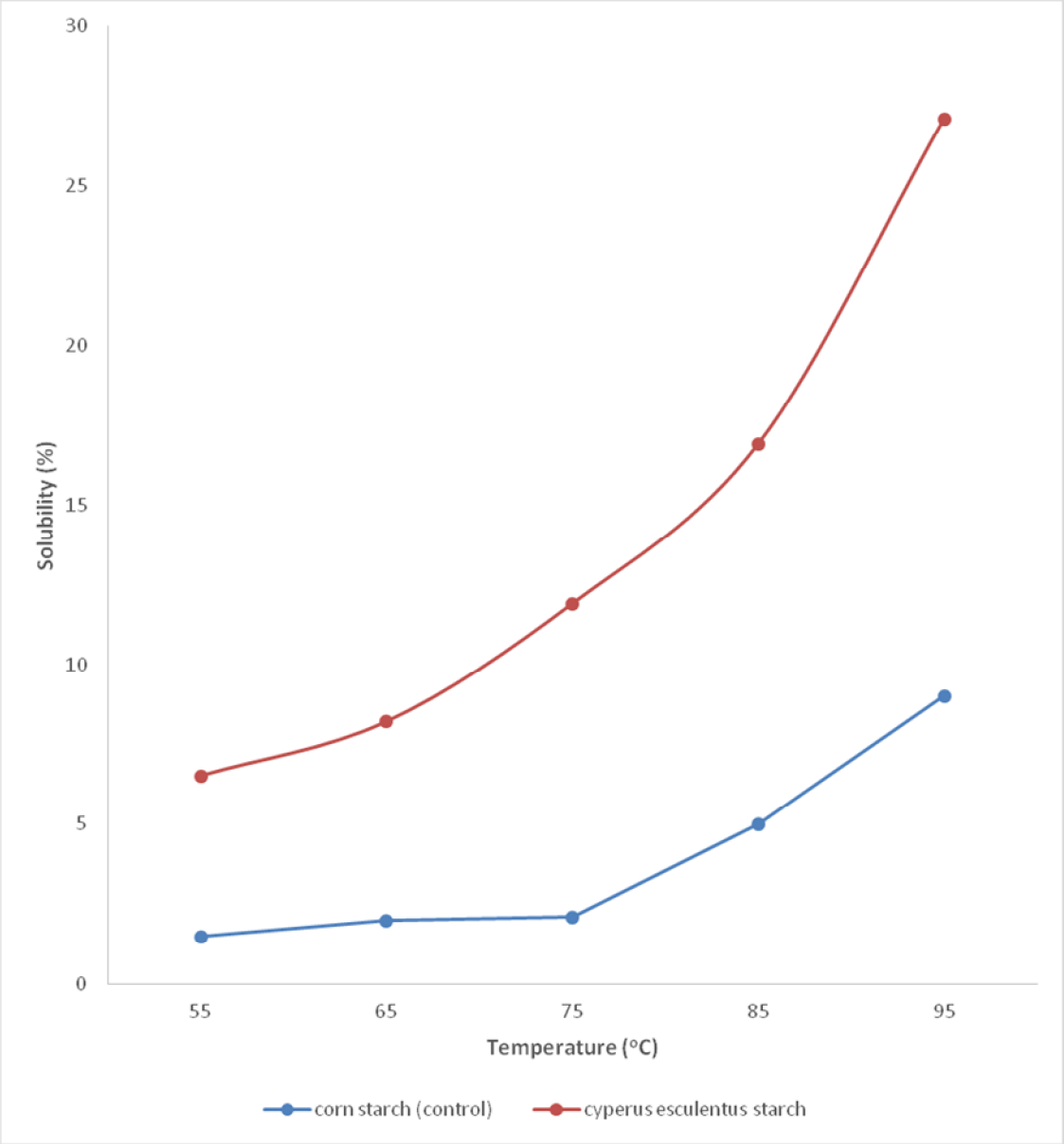


Fig 3: Effect of temperature on solubility of *Cyperus esculentus* starch in water

3.12: Effect of temperature on swelling power

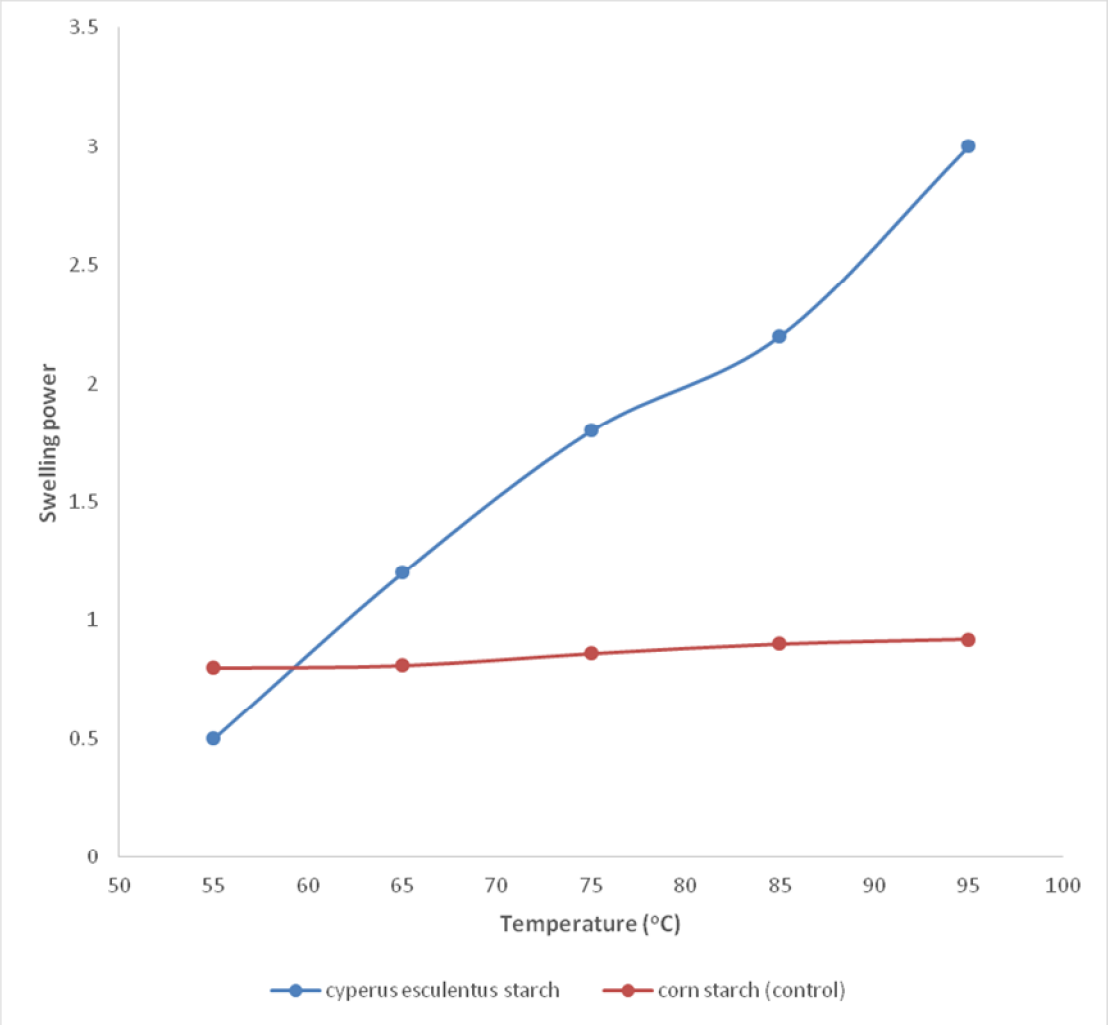


Fig 4: Effect of temperature on swelling power of *Cyperus esculentus* starch in water

Figs 3 and 4 show the effects of temperature on solubility and swelling power of both *Cyperus esculentus* starch and corn dispersions. It can be seen that both

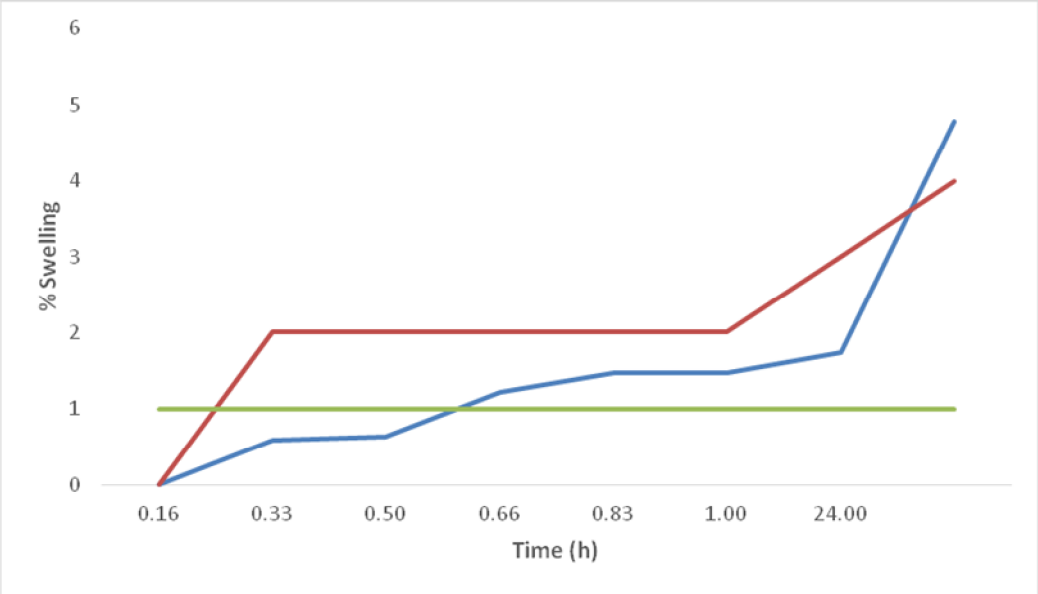
solubility and swelling power obviously increased as the temperature increased. Solubility and swelling power depends on temperature. This may be because as temperature increases, inter-molecular bonds are broken and the molecules tend to tear apart. The swelling power of starch has been reported to depend on water binding capacity of starch molecules brought about by hydrogen bonding. The result shows that the highest solubility occurred at 95 ^{o} C. The result is in agreement with that obtained by Kong, Bao and Corke (105).

3.13 EFFECT OF pH ON PERCENT SWELLING.

Fig. 5 shows of the effect of pH on percent swelling of *Cyperus esculentus* starch. SGF, SIF and distilled water represented acidic, alkaline and neutral media.It can be seen that there was gradual increase in swelling of starch with time in distilled water and SIF. This may be attributed to the amylose and amylopectin contents of *Cyperus esculentus* starch. This is an indication that the starch will make a good binder.

Swelling is an index of the ability of individual powdered substance to take up a particular fluid. It can be described in terms of rate of maximum fluid uptake at equilibrium. Starch swelling is claimed to be dependent upon amylose and amylopectin content. As amylopectin expands, the amylose releases osmotic pressure. No swelling occurred in the SGF medium.

Swelling can be looked at as the initial phase of dissolution (106). What happens is that as liquid is absorbed by the semi solid substance, the void spaces are filled. This increases the pressure within the solid. This pressure will tend to pull the molecules apart and they begin to swell. Further increase in pressure will lead to erosion or dissolution as the case may be. Sometimes substances take up liquids without measurable increase in volume, and this is called imbibition.



Distilled water

SIF

SGF

Fig 5; Effect of pH on percent swelling of *Cyperus esculentus* starch

3.14 EFFECT OF ELECTROLYTES (NaCl AND $MgCl_2$) ON PERCENT SWELLING

3.14.1 MONOVALENT ELECTROLYTE

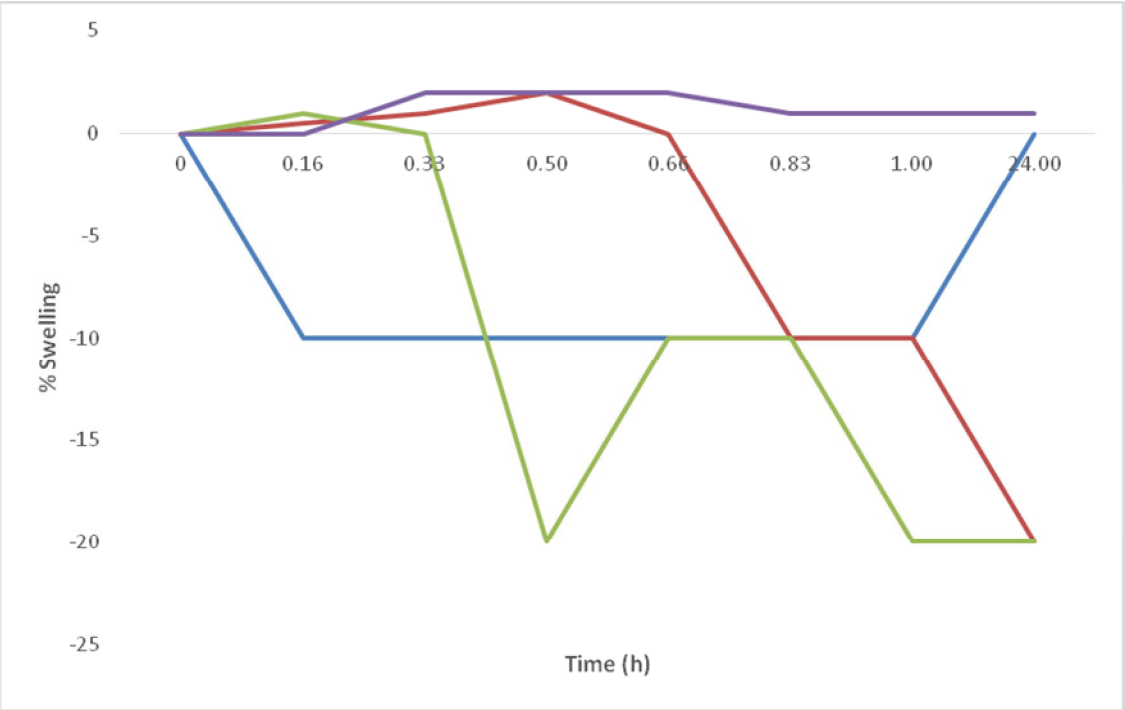


Fig 6; Effects of monovalent electrolyte on extent of swelling of Cyperus esculen

3.14.2 DIVALENT ELECTROLYTE

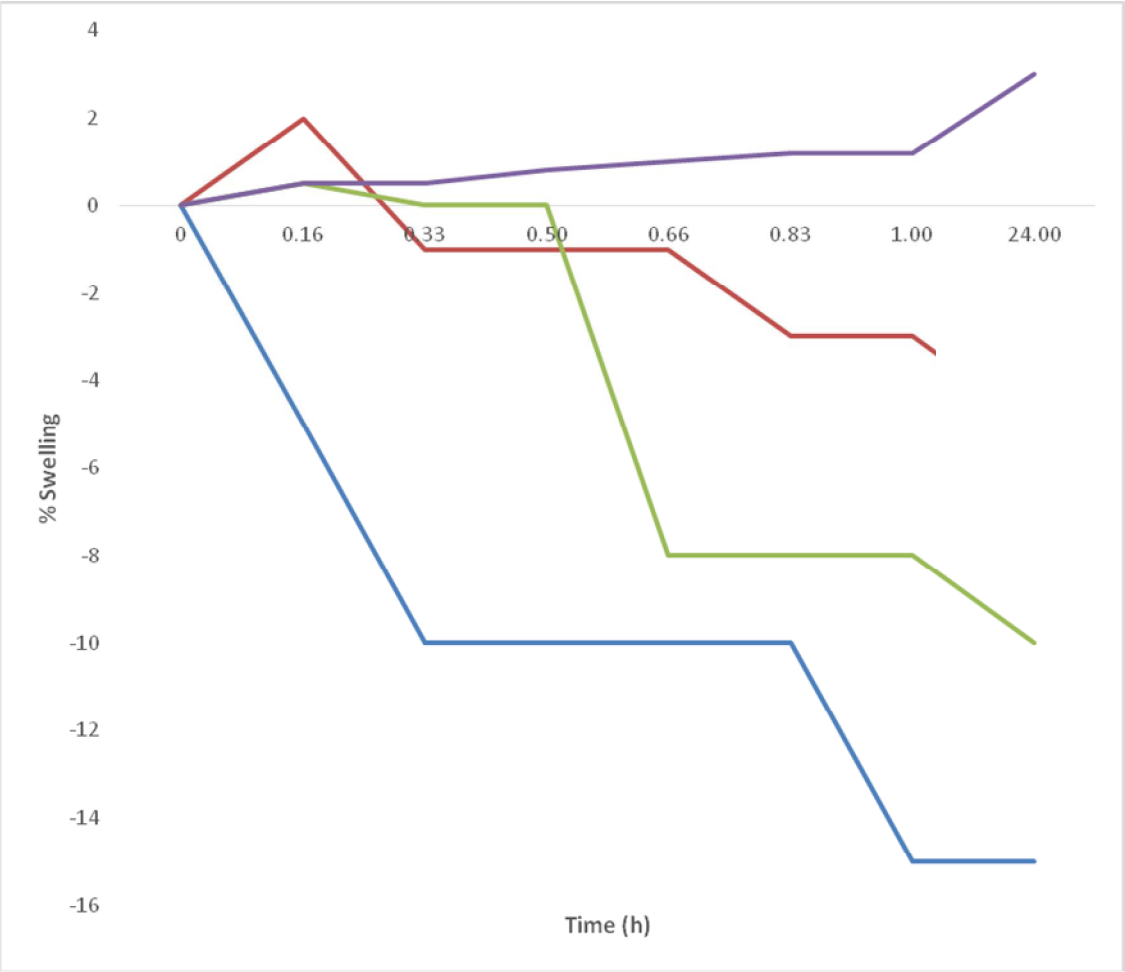


Fig 7; Effect of divalent electrolyte on degree of swelling of Cyperus esculentus starch

Figs 6 and 7 show the effect of monovalent and divalent electrolytes (NaCl and $MgCl_2$ respectively) and their concentrations on the swelling properties of *Cyperus esculentus* starch.

The graphs show the dependency of swelling on the ionic strength of *Cyperus esculentus* starch. The decrease in the extent of swelling observed upon the addition of electrolytes was presumably due to the effect of the electrolytes on the polymer. The addition of large amounts of highly soluble salts to a polymer often leads to changes in some of its physicochemical properties. The effect of an additive depends very much on the influence it has on the structure of the polymer or its ability to compete with solvent molecule. Various investigations have shown that the presence of electrolytes in solution decreases the swelling of polymers. Ionic strength, which is a measure of the integrity of the electrical field in solution, provides a basis for evaluating electrostatic interactions between ions (107). It has been shown that the effect of an electrolyte on polymer depends on the intensity of electrical field in the solution (108). Generally, increase in concentration of the electrolytes caused decrease in the fluid uptake, a finding which has already been reported for other polymers (109). The increase in ionic strength of the solution decreases the osmotic pressure inside the charged molecule and its swelling is thus reduced.

3.15 CHARACTERISTICS OF GRANULES PRODUCED.

Table 10 shows the properties of granule batches produced. It can be seen that densification of paracetamol powder improved the flow. These results revealed a good flowing granule as indicated by the results in table 10. The values of compressibility index ranged from 6.64 to 20.85 with most of the values falling below 16.00%. Low compressibility index (<16) indicates that it is a free

flowing granule while compressibility index of 16 ï 20 is indicative of fair flow properties (110).

The values of Hausnerôs quotient for the granule batches were below 1.19 except for granule TX2 and TEX1.On the other hand, the value of angle of repose for the granule batches ranged from 36.27 to 41.45. Hausnerôs quotient below 1.19 shows a good flow property while angle of repose below 50^0 indicate good flow (99).

The value of moisture content of the granules produced ranges from 2.11% to 3.00%. Granules should have about 2% moisture so that it will enhance intermolecular bonding and also resist microbial growth. The moisture content should therefore be controlled. If the moisture content is high, it can lead to tablet sticking to the punches, die cavities and granule poor flow. On the other hand, low moisture content of granule can lead to tablet capping, tablet roughness and granule brittleness (110).

The percentage of fine granules was less than 15 except for granules of batch CE3 which was 16.15. Fine granules are important in that they fill the void spaces in tablets ensuring hardness of tablets. A good granule batch should have less fine particles which may indicate that there would be more unfilled voids during the process of compression (111). This may lead to hard and friable tablets. On the other hand, if they are in excess, it can lead to excessive hardness. Also small particles cause laminations and capping and create a dusty operation. It increases dissolution and decreases disintegration time (112). High percentages of fine particles will require large quantities of lubricants. In fact fine dusty particles are the source of most tablet defects.

Table 10 Characteristics of granules produced.

Batch*	Av. Flow rate g/s	Av. Bulk Density g/cm3	Tapped density g/cm3	True density g/cm3	Hausner's quotient	Compress-ibility Index (%)	Angle of repose (degrees)	% Fines	Moisture content (%)	Loss on drying (%)
CE3	7.79	0.417	0.478	0.704	1.1410	12.39	40.58	16.15	2.80	3.95
TE1	8.64	0.421	0.486	0.711	1.1540	10.04	39.52	12.20	2.52	4.30
TE2	8.62	0.413	0.481	0.697	1.1650	14.14	39.77	15.60	2.95	2.10
TE3	8.49	0.421	0.467	0.711	1.1090	9.85	40.57	14.65	2.61	3.85
TE4	9.09	0.393	0.459	0.664	1.1530	13.29	38.92	13.64	2.93	4.40
CX3	8.54	0.413	0.479	0.696	1.1590	13.77	41.45	10.90	2.41	3.86
TX1	8.52	0.413	0.471	0.697	1.1400	12.31	39.64	12.20	2.31	3.54
TX2	8.59	0.387	0.489	0.654	1.2640	20.85	39.69	15.05	2.21	4.00
TX3	8.57	0.417	0.473	0.705	1.1340	11.83	40.77	9.90	2.11	4.10
TX4	8.67	0.378	0.462	0.639	1.2220	18.18	39.95	19.90	2.85	6.50
CEX3	8.13	0.422	0.452	0.713	1.0710	6.64	40.72	11.88	2.61	3.66
TEX1	8.55	0.350	0.433	0.592	1.2230	18.24	41.39	20.69	2.85	4.45
TEX2	8.96	0.370	0.438	0.625	1.1840	15.53	40.30	15.82	2.73	4.31
TEX3	8.06	0.413	0.449	0.696	1.0870	8.02	41.23	15.01	2.66	4.21
TEX4	9.12	0.390	0.450	0.659	1.2190	18.00	36.27	10.70	2.61	3.60
BC3	10.87	0.441	0.490	0.706	1.1110	10.00	39.81	11.78	2.99	3.05
BT1	9.06	0.418	0.466	0.657	1.1150	10.30	36.67	48.38	2.28	4.81
BT2	9.90	0.389	0.442	0.759	1.1360	11.90	39.38	15.39	2.50	4.21

BT3	10.00	0.449	0.490	0.758	1.0910	8.37	38.79	15.96	2.80	2.00
BT4	10.10	0.430	0.486	0.726	1.1300	11.52	37.48	14.67	3.00	3.24

*Description of symbols are shown in the glossary

Granule size distribution.

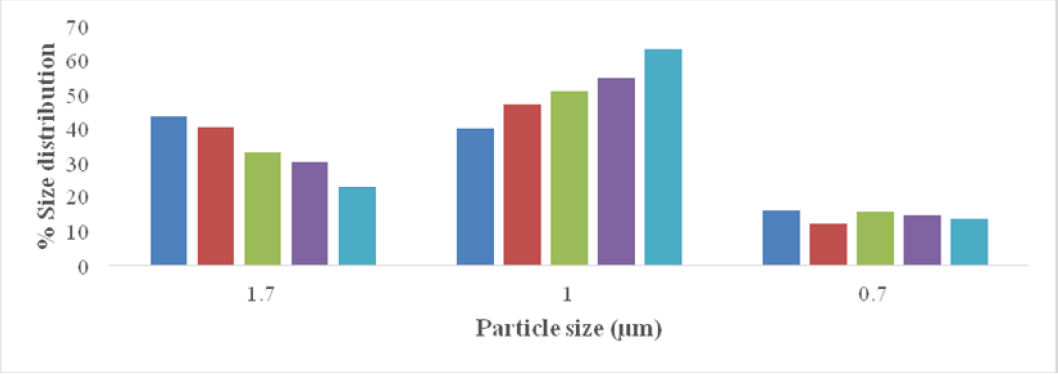


Fig 8; Percentage size distribution of paracetamol granules with starch disintegrant incorporated intra-granularly.

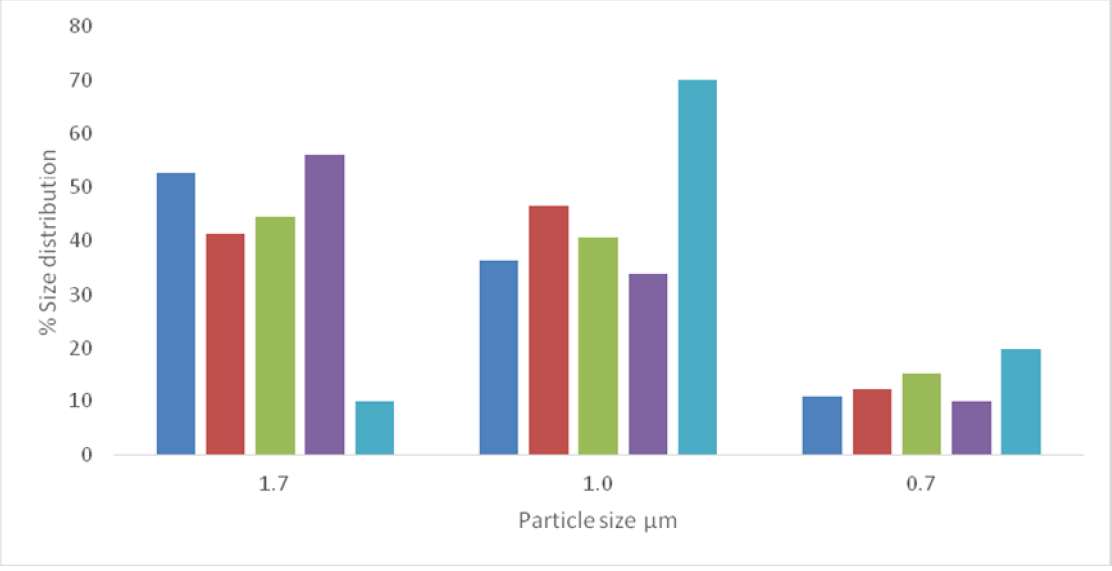


Fig 9; Percentage size distribution of paracetamol granules with starch disintegrants incorporated extra-gr .

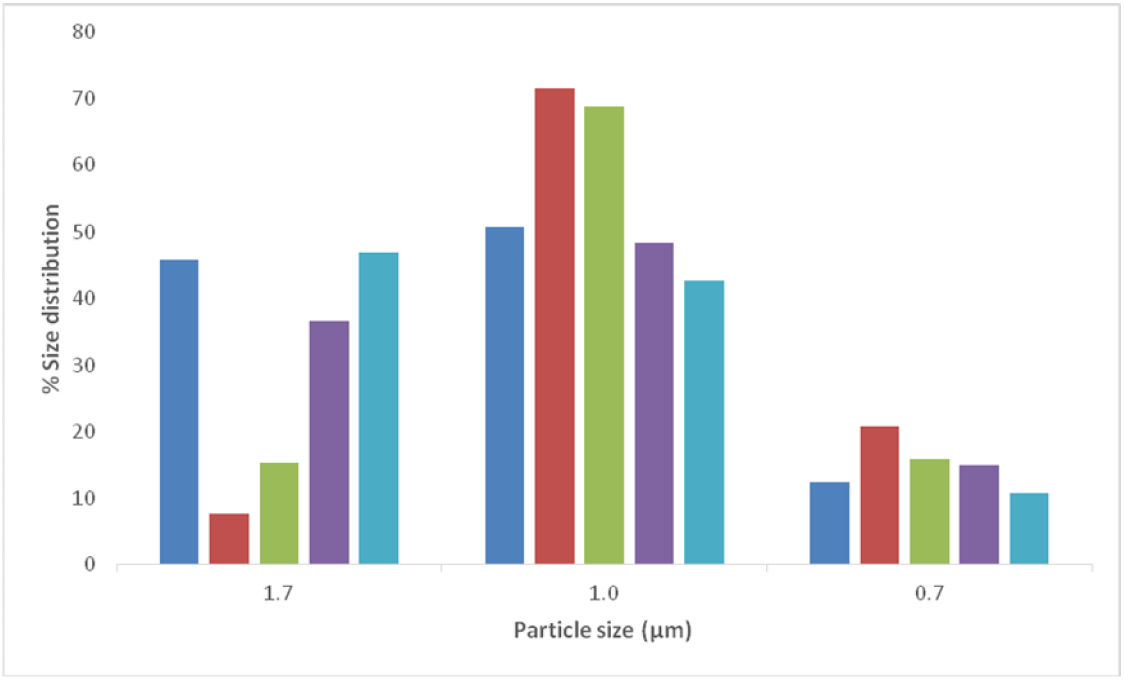


Fig 10; Percentage size distribution of paracetamol granules with starch disintegrants incorporated intra-extra-granularly

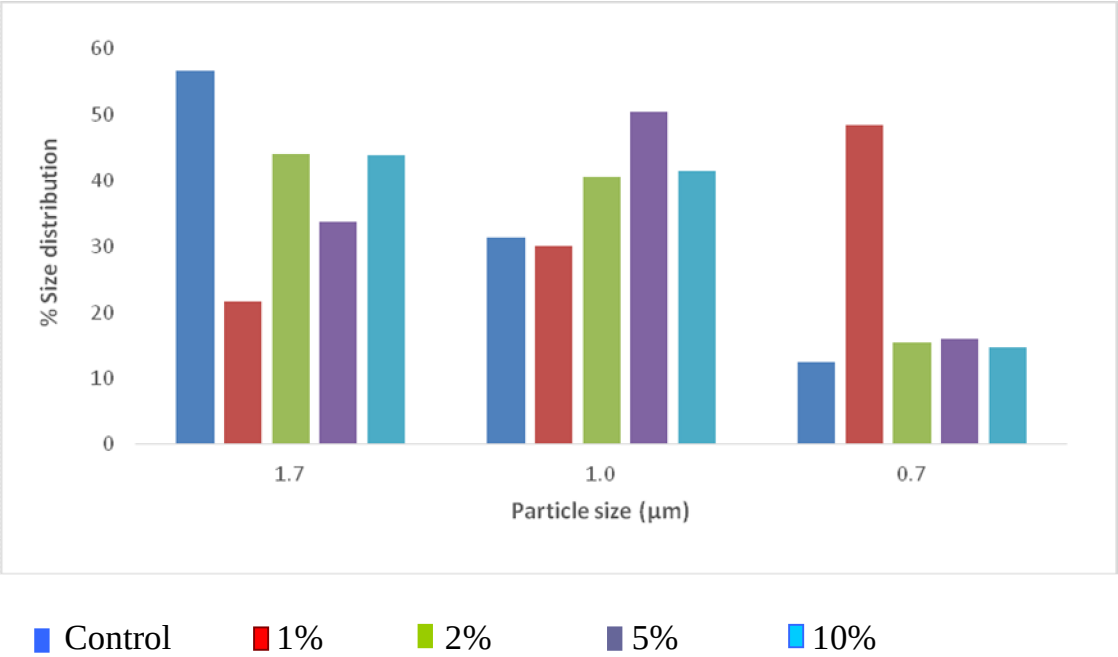


Fig. 11: Percentage size distribution of paracetamol granules with starch as binder

Figs. 8 - 11 show the percentage size distribution of paracetamol granule batches. The granule sizes for all the batches were appropriately distributed. Fine particles are important as they will fill up the spaces within the coarse granules in order to maintain good hardness. All the three sizes of granules were well represented in each of the batches. Establishing an appropriate size distribution will improve tablet quality and will reduce overall cost in the long run. Particle size distribution needs to be controlled to avoid sticking or picking as the case may be because large granules tend to lock in moisture which can cause sticking (113).

3.16 APPEARANCE OF PRODUCED TABLETS

Paracetamol tablets of mean weight 250 ±0.1 mg, white in colour, with smooth texture and 9.00 mm diameter, with a biconvex shape were produced.

3.17 DRUG-EXPICIENT COMPATIBILITY STUDIES

Selected batches of tablets which were screened for compatibility studies using differential scanning calorimeter gave the following results.

Figs 12 - 14 represent the DSC thermogram of samples for compatibility studies. This was done to understand the nature of drug in the formulated tablets. Thermograms obtained for pure drug and *Cyperus esculentus* formulation of the drug showed endothermic peak equivalent to its melting point at 312.9ęC whereas thermograms of the paracetamol formulation with *Cyperus esculentus* starch did not show any significant shift in the endothermic peak. There was no disappearance nor broadening of the melting exotherm.

This DSC scan carried out was also used to determine the physical stability of the drug. The samples were found to be physically stable as shown in the scan.

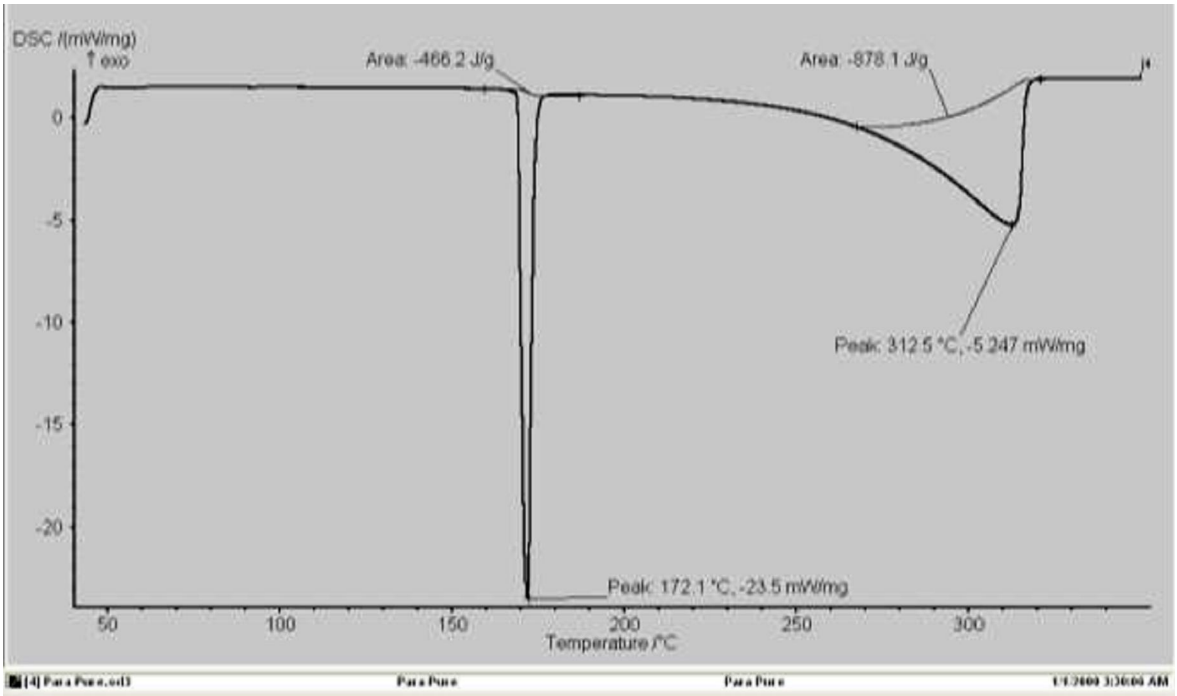


FIG 12; DSC thermogram of pure paracetamol

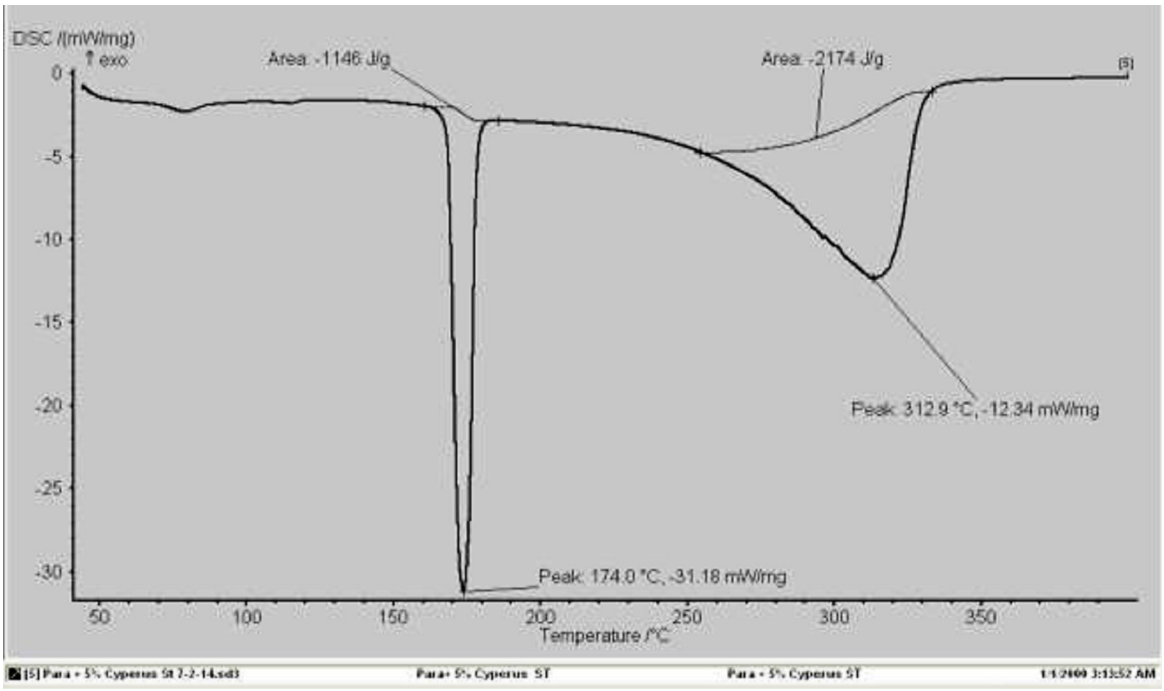


Fig 13; DSC thermogram of paracetamol with 5% *Cyperus esculentus* starch a disintegrant

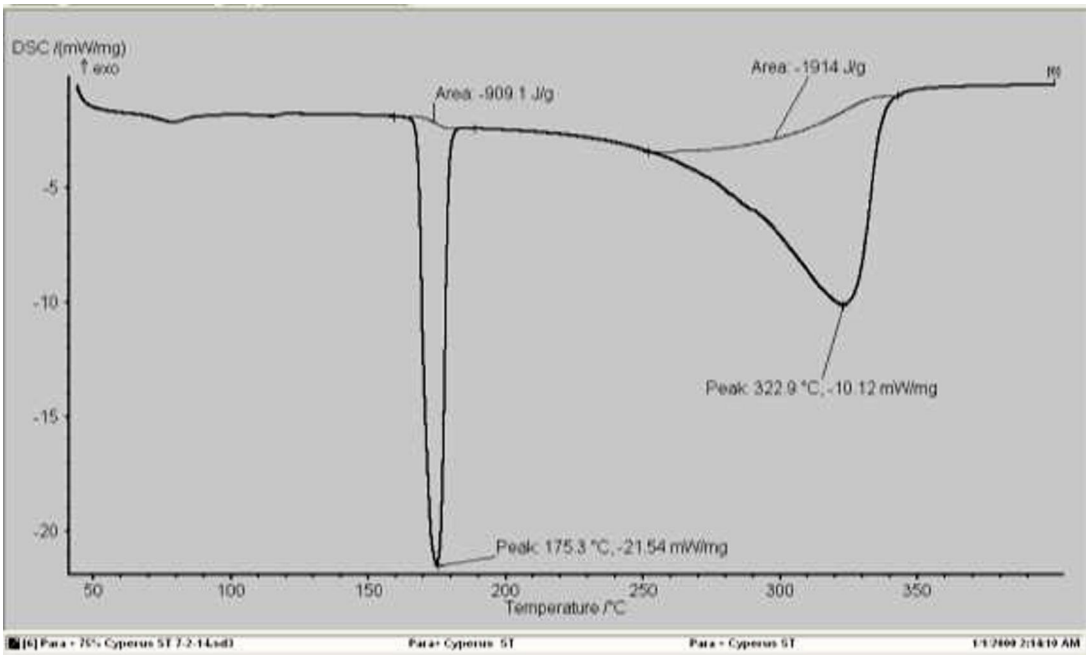


Fig 14; DSC thermogram of paracetamol tablets with 7.5% *Cyperus esculentus* starch as binder.

3.18 PROPERTIES OF TABLETS

3.18.1 WEIGHT UNIFORMITY

Table 11 shows the mean weight, standard deviation and percentage deviation of the tablets

Tablet batch*	Mean weight (mg)	Standard deviation	Percentage deviation (%)
CE3	286.10	4.03	0.00
TE1	285.05	6.04	-3.91
TE2	286.30	4.17	-3.97
TE3	292.00	4.10	0.00

TE4	301.50	7.05	0.00
CX3	300.50	6.04	4.72
TX1	290.00	5.62	0.00
TX2	291.00	5.73	1.27
TX3	299.00	5.52	-6.66
TX4	310.00	4.66	0.00
CEX3	299.00	6.41	0.00
TEX1	285.45	11.85	4.1
TEX2	289.50	5.10	-9.16
TEX3	290.70	4.80	3.84
TEX4	307.70	4.79	3.67
BC2	292.00	4.10	0.00
BT1	280.10	4.36	-8.08
BT2	291.50	5.87	0.00
BT3	296.70	4.80	3.84
BT4	308.30	5.80	-6.60

*Description of symbols are shown in the glossary

Table 11 is a table showing the average weight percentage deviation and standard derivation of paracetamol tablets produced. The mean weight of the tablet produced ranged from 285.4 mg to 310.0 mg. Percentage deviation is a statistical tool used to control variability in weight of tablets during manufacturing. This is important because it helps to guide against over dosage or under dose as the case may be. There are therefore acceptable values of percentage deviation upon which the tablet weights are acceptable. For tablets weighing 250mg and above, the value of percentage deviation should not be more that 5 % (29). All the tablet batches passed weight variation test.

Table 12 shows the crushing strength, friability and disintegration time ratio of the tablets.The values of crushing strength ranged from21 to 100 newton with most of the batches falling within the range of 40 to 70 newton. The disintegration times of the tablets were within 15 min except for tablet batch BT4. The friability values ranged from 0.12 to 1.94 %. Crushing strength provides measure for tablet strength while friability provides a measure for tablet weakness (11). There is no official requirement for crushing strength and friability in the British Pharmacopoeia (77) probably because, in the case of crushing strength, the desired crushing strength is largely dependent on the intended use of the tablet (115).

Crushing strength of 4-7 kgF is usually acceptable for normal release tablet such as paracetamol while friability of <1.0 is acceptable (34). From the results in Table 12, all tablet batches passed both tests. The implication is that the tablets can withstand mechanical stress of handling, packaging and transportation. Bioavailability of this drug is also guaranteed.

95 % of the tablets passed disintegration time test as they disintegrated in less than 15 min. The disintegration time of corn starch is lower than that of Cyperus esculentus starch when used at the same concentration (5%). The difference is however statistically not significant (p>0.01).

3.18.2 CRUSHING STRENGTH, FRIABILITY, *IN VITRO* DISINTEGRATION TIME (CS/FR/DT) RATIOS

Table 12; Crushing strenght, friability and disintegration time ratio of the tablets

Tablet batch *	Average crushing strength (N)	Friability (%)	Disintegration time (min)	CS/Fr (N/%)	CS/Fr/DT ratio (N/% min)
CE3	90.00	0.19	2.20	273.68	124.40
TE1	60.00	0.28	2.72	214.29	78.78

TE2	70.00	0.12	3.23	583.33	180.60
TE3	62.00	0.16	2.70	387.50	143.52
TE4	82.00	2.25	3.12	36.44	11.68
CX3	69.00	0.35	5.10	197.14	38.66
TX1	65.00	0.29	7.17	224.14	31.28
TX2	57.00	0.33	1.92	172.73	89.96
TX3	69.00	0.35	5.10	197.14	38.66
TX4	59.00	1.94	1.58	30.41	19.25
CEX3	90.00	0.12	3.65	762.71	208.96
TEX1	68.00	0.14	2.10	485.71	231.29
TEX2	56.00	0.33	5.10	169.70	32.76
TEX3	63.00	0.21	5.80	300.00	51.72
TEX4	100.00	0.17	4.20	588.24	138.08
BC2	57.00	0.28	3.08	203.57	65.20
BT1	21.00	0.75	1.32	28.00	21.20
BT2	63.00	0.28	10.00	225.00	22.50
BT3	50.00	0.18	5.21	27.78	58.32
BT4	92.00	0.15	32.00	613.33	19.17

*Description of symbols are shown in the glossary

Tablets containing starches incorporated extra-granularly exhibited rapid disintegration in the current study. This is in agreement with similar works by Itiola, Adebayo, and Adedokun (89,116). Capillary action due to poor structure of the tablet as well as swelling is generally accepted as the main mode of action of such disintegrant as starch and cellulose derivatives (117). As can also be seen in Table 12, as disintegrant concentrations increased, crushing strength also increased. This relationship could be due to the fact that as more starch disintegrant is added, more particles are available for close contact, thus

enhancing inter-particulate bonding forces. This is important in formulation studies and suggests that low concentration of disintegrant may be sufficient to achieve desired effect in particular tablet formulation.

The values of disintegration time increased as the density of tablets increased. This may be due to the reduction in porosity (that is capillary microstructure) of the tablets as the particle density increased. According to Bi, Yonezawa and Sunada (118), a decrease in porosity leads to formation of more solid bridges, thus making annihilation of inter-particulate bonds more difficult. This reduction in porosity may lead to slow water penetration into the tablets and consequently swelling would be reduced. This ultimately will increase disintegration time.

Crushing strength friability, disintegration time ratio (Cs/Fr/DT) has been suggested as a better index for assessing tablet performance as regards disintegrant activity especially when compared with the crushing strength friability ratio (Cs/Fr). This is because, in addition to measuring tablet strength (crushing strength) and weakness (friability), it simultaneously assesses the net effect of these parameters in disintegration time (119). Generally, the higher the value of crushing strenght/ friability/ Disintegration time, the better the combined effect of binding and disintegrant activity in a tablet.

3.18.3 DRUG CONTENTS

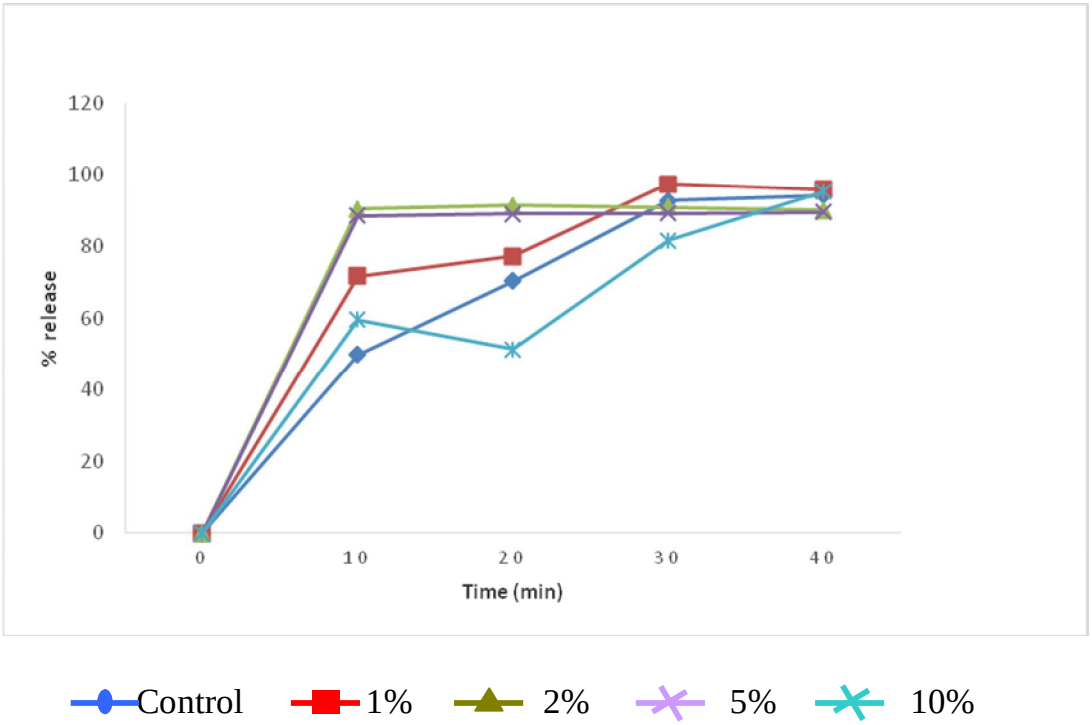


Fig 15; Drug release profile of paracetamol tablet in SGF with disintegrant incorporated intra-extragranularly

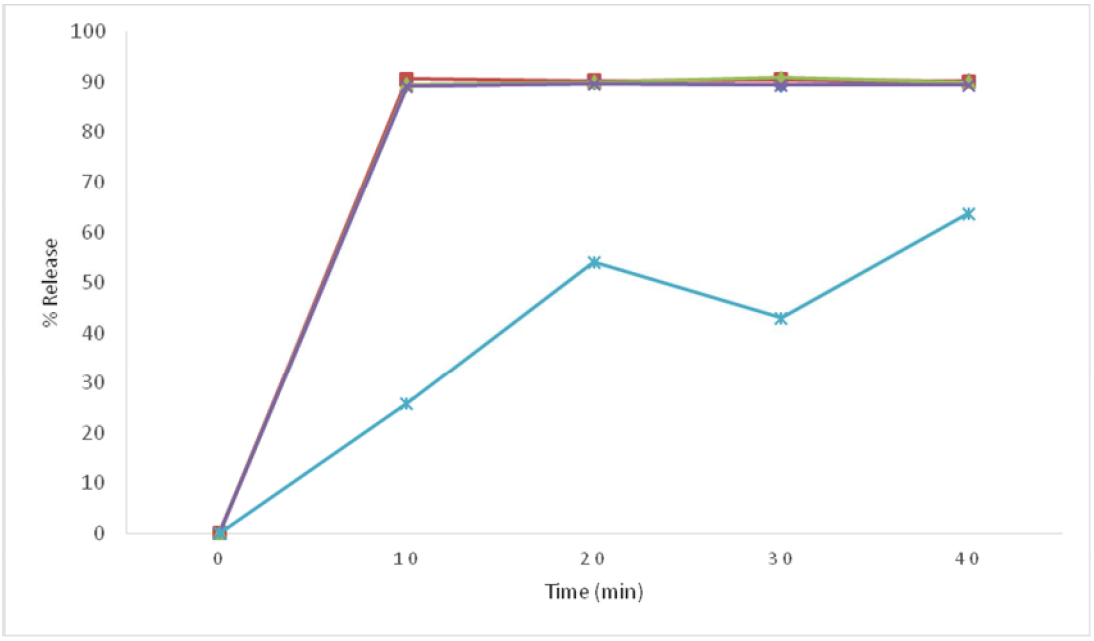
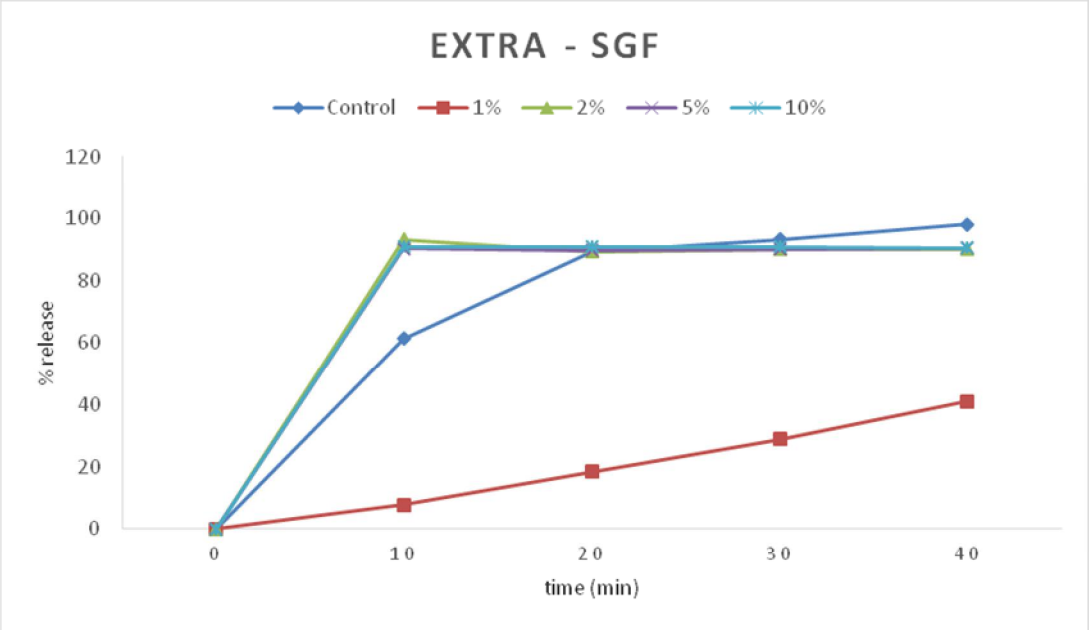
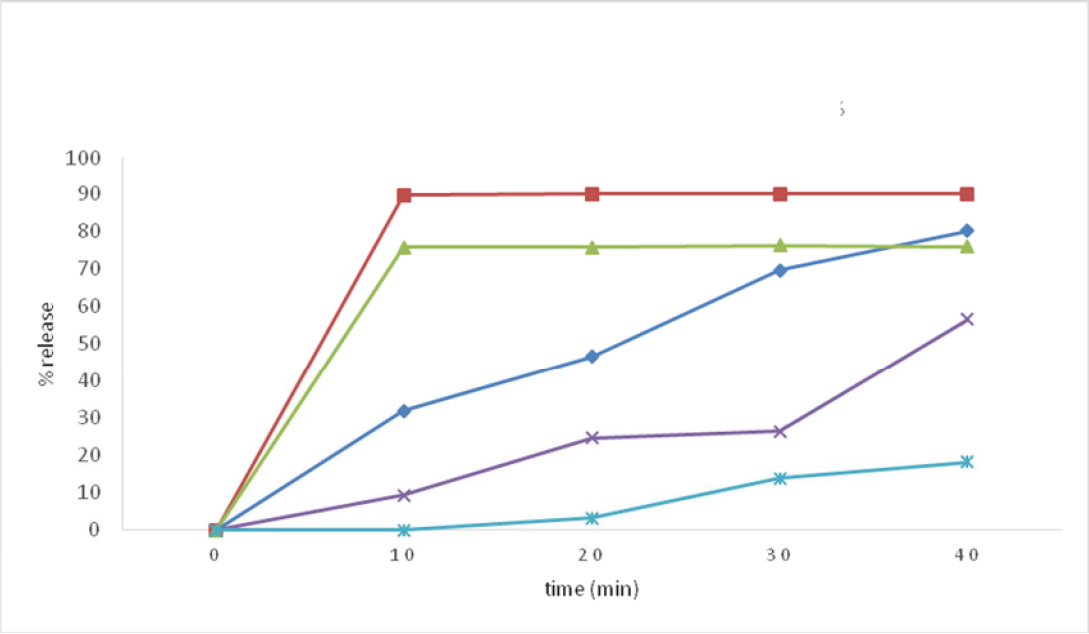


Fig 16; Drug release profile of paracetamol Tablet in SGF with disintegrant incorporated intragranularly



Control 1% 2% 5% 10%

Fig 17; Drug release profile of paracetamol tablet in SGFwith disintegrant incorporated extagranularly



Control 1% 2% 5% 10%

Fig 18; Drug release profile of paracetamol tablets in SGF with starch as binder

Drug release profile of paracetamol tablets in SGF with starch as binder

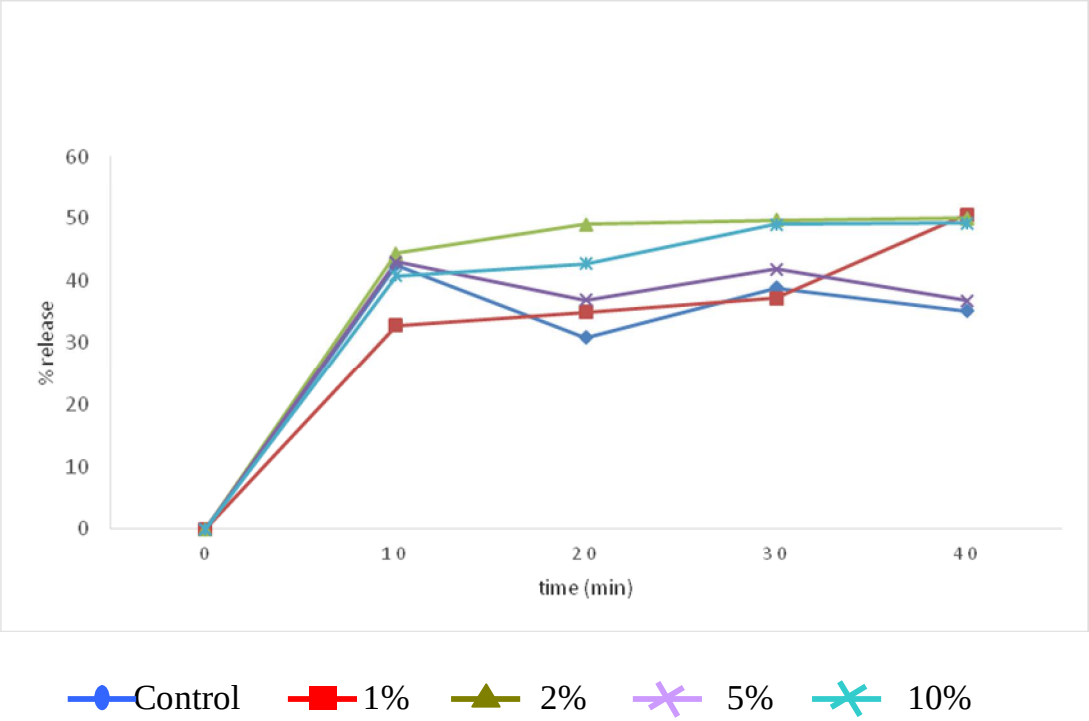


Fig 19; Drug release profile of paracetamol tablet in SIF with disintegrant incorporated intra-extragranularly

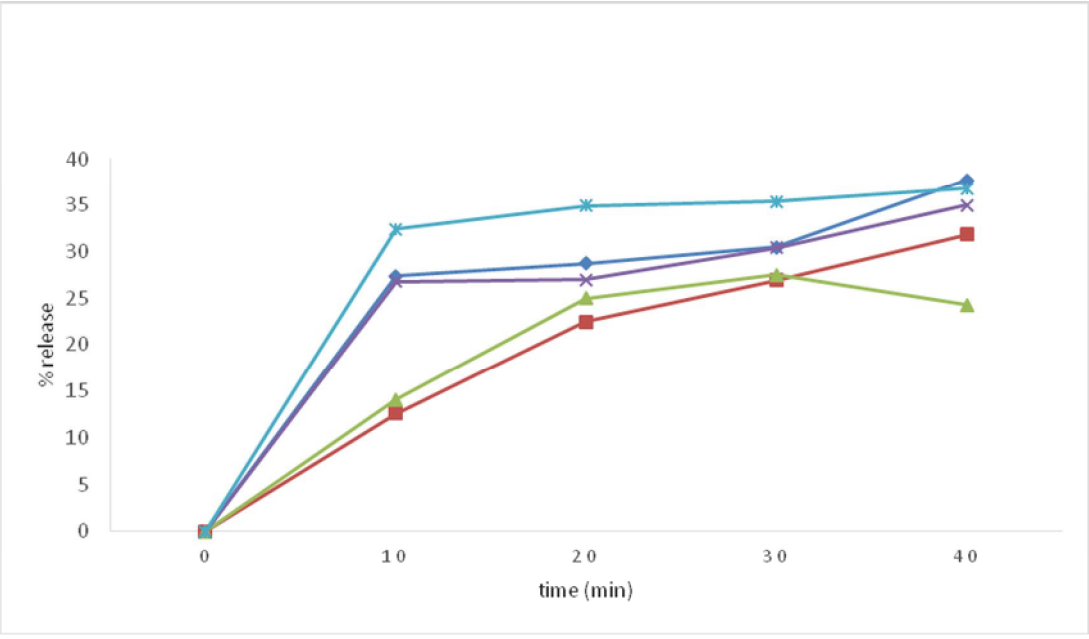


Fig 20; Drug release profile of paracetamol tablets in SIF with disintegrant incorporated intra granularly

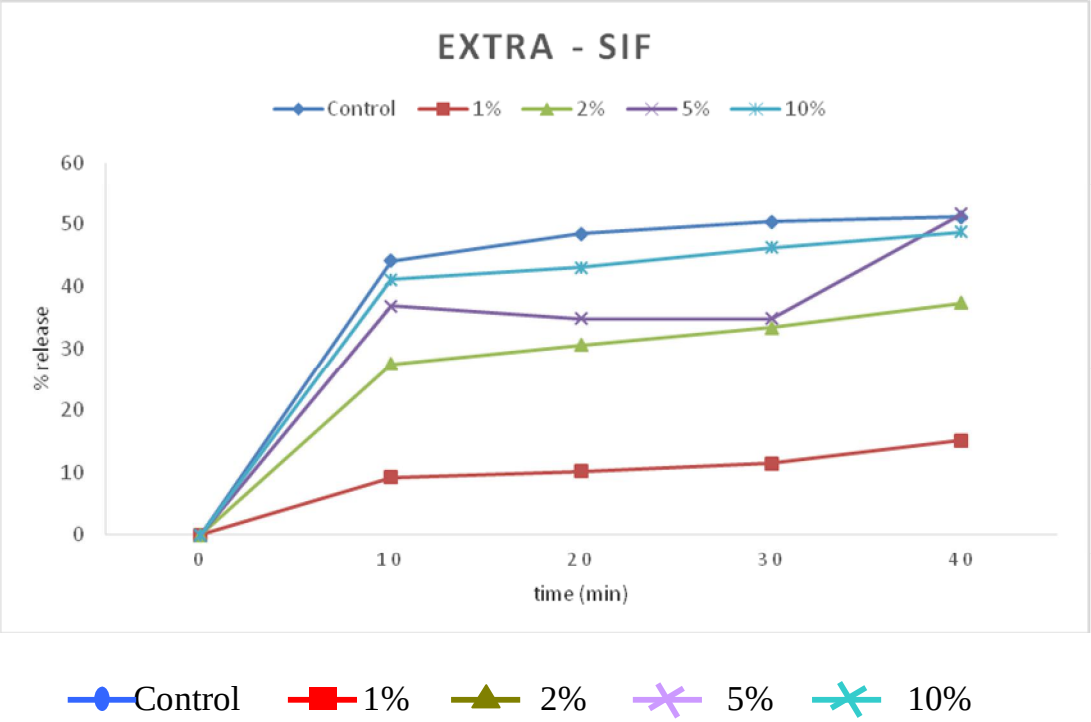


Fig 21; Drug release profile of paracetamol tablets in SIF with disintegrant incorporated extra granularly.

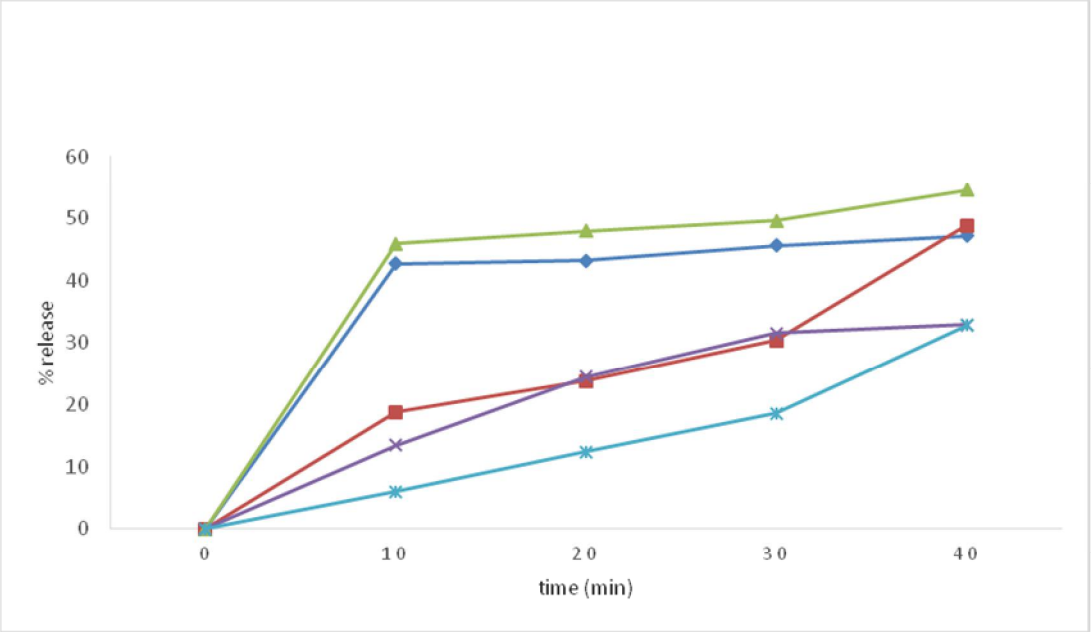


Fig. 22: Drug release profile of paracetamol tablets in SIF with starch as binder.

Figs 15 - 22 show the *in vitro* dissolution profiles of paracetamol tablet in two dissolution media (SGF and SIF). It can be seen that for all the batches, bioequivalent of paracetamol was within range. The results also revealed that as the concentration of the disintegrant increases, the dissolution rate increases. In all the batches, more paracetamol was released from tablets in SGF without enzyme than in SIF without enzyme.

Table 13 shows the area under the dissolution curve and the dissolution efficiency (DE). The DE was used to determine the performance of the drug under different test conditions. From the result, there was satisfactory dissolution profile for all three methods of incorporation of disintegrants. However, endo-exo disintegrants exhibited enhanced dissolution probably due to increased porosity. It was observed that porosity increased with increase in concentration of disintegrant. When these tablets come in contact with water, the pore spaces are filled with the water molecules which exert pressure on the tablets. This could potentially lead to improvement in bioavailability of the paracetamol tablets. It has been shown that the rate of oral absorption of a drug is usually controlled by its dissolution rate in the gastro intestinal tract (120). Bioequivalent studies as shown in Appendix xxv were within the range 85-125%.

Table 14 shows the hardness and tensile strength of the paracetamol tablet batches produced. All tablet batches passed hardness test (4-6kgF) except for batches CEX3 and BT4. It is observed that an increase in binder concentration led to a corresponding increase in the hardness of the tablets. This had direct effect on the tensile strength of the tablets.

The tablets have sufficient hardness to withstand mechanical stress during manufacturing and the stress of handling (during packaging) and that of transportation.

3.18.4 DRUG RELEASE DATA

Table 13: Total area under dissolution curve (auc_t), at 30 mins (auc_{30}), and the dissolution efficiency (de) of tablets.

	SGF			SIF		
Tablet batch*	**AUC_{30}** (mg/ ml min)	**AUC_T** (mg/ ml min)	**Dex**	**AUC_{30}** (mg/ ml min)	**AUC_T** (mg/ ml min)	**DE**
CE_3	559.02	1788.64	31.13	1909.56	6629.29	28.80
TE_1	5660.77	1807.31	31.32	1681.87	5473.82	30.73
TE_2	5683.92	18058.88	31.47	1720.46	4970.58	34.961
TE_3	5599.02	1719.17	31.25	1901.84	6321.32	30.09
TE_4	2689.13	10621.31	25.32	2214.45	7154.92	30.95
CX_3	5826.71	18532.79	31.44	3156.11	1001.54	31.52
TX_1	1809.22	6189.33	29.23	720.91	2548.50	28.29
TX_2	5626.03	18021.06	31.22	12087.09	6843.86	30.49
TX_3	5626.03	18045.76	31.18	2175.85	8470.93	25.69
TX_4	5676.20	18143.78	31.28	2893.68	9289.09	31.15
CEX_3	5795.84	17307.09	33.49	2426.70	7205.09	33.68
TEX_1	6093.00	18268.82	33.35	2326.36	8487.14	27.41
TEX_2	5683.92	18124.43	31.36	3109.79	9886.50	31.45
TEX_3	5579.72	17855/11	31.25	2615.81	7762.37	33.69
TEX_4	5101.17	16101.46	31.68	3067.34	9484.37	32.34
BC_2	4807.87	15277.12	31.47	3129.09	10235.38	30.57

BT_1	3377.93	18006.39	31.27	1901.84	7305.43	26.03
BT_2	4773.14	15225.41	31.35	3105.93	10246.96	30.31
BT_3	1654.85	7663.57	21.59	1975.17	5947.74	33.21
BT_4	871.42	2387.87	33.67	1168.59	4590.05	25.46

*Description of symbols are shown in the glossary

3.18.5 TENSILE STRENGTH

Table 14 shows the hardness, thickness, diameter and tensile strength of tablets produced

Tablet Batch*	Hardness (N)	Thickness (m)	Diameter (m)	Tensile strength $2F/\pi DT$ (Nm^{-2})
CE3	52.00	0.0081	0.0090	4.54×10^5
TE1	60.00	0.0077	0.0090	5.53×10^5
TE2	74.00	0.0081	0.0090	6.46×10^5
TE3	62.00	0.0078	0.0090	5.61×10^5
TE4	82.00	0.0082	0.0090	7.06×10^5
CX3	69.00	0.0081	0.0090	6.03×10^5
TX1	65.00	0.0071	0.0090	6.46×10^5
TX2	57.00	0.0081	0.0090	4.98×10^5
TX3	62.00	0.0083	0.0090	5.29×10^5
TX4	60.00	0.0084	0.0090	5.06×10^5
CEX3	90.00	0.0081	0.0090	7.86×10^5
TEX1	68.00	0.0076	0.0090	5.79×10^5
TEX2	56.00	0.0080	0.0090	4.96×10^5
TEX3	63.00	0.0082	0.0090	5.45×10^5

TEX2	10.00	0.0085	0.0090	8.33×10^5
BC3	57.00	0.0078	0.0090	5.45×10^5
BT1	21.00	0.0075	0.0090	1.98×10^5
BT2	63.00	0.0079	0.0090	5.65×10^5
BT3	50.00	0.0078	0.0090	4.55×10^5
BT4	92.00	0.0081	0.0090	8.03×10^5

*Description of symbols are shown in the glossary

3.18.6 DENSITY, PACKIING FRACTION, AND POROSITY

Table 15: Density, Packing fraction, and Porosity of the Paracetamol Tablets

Tablet Batch*	**Tablet mean weight (g)**	**Tablet diameter d^2 (cm^2)**	**Tablet thickness h (cm)**	**Bulk density $BD=4w/\pi d^2h$ (gcm^{-3})**	**Particle density of tablet (gcm^{-2})**	**Packing fraction PF=BD/PD**	**Tablet porosity 1-PF**
CE3	0.284	0.81	0.81	0.55	1.73	0.32	0.68
TE1	0.286	0.81	0.77	0.58	1.73	0.34	0.66
TE2	0.286	0.81	0.81	0.55	1.82	0.31	0.69
TE3	0.283	0.81	0.78	0.57	1.65	0.35	0.65
TE4	0.302	0.81	0.82	0.58	1.78	0.33	0.67
CX3	0.302	0.81	0.81	0.59	1.96	0.30	0.70
TX1	0.291	0.81	0.71	0.64	1.57	0.42	0.58
TX2	0.288	0.81	0.81	0.56	1.91	0.29	0.71
TX3	0.300	0.81	0.83	0.57	2,08	0.27	0.73
TX4	0.310	0.81	0.84	0.58	2.04	0.28	0.73
CEX3	0.298	0.81	0.81	0.58	1.79	0.33	0.67
TEX1	0.286	0.81	0.76	0.59	1.73	0.34	0.66
TEX2	0.289	0.81	0.80	0.57	1.90	0.30	0.70

TEX3	0.298	0.81	0.82	0.57	1.97	0.29	0.71
TEX4	0.308	0.81	0.85	0.57	1.76	0.33	0.68
BC2	0.299	0.81	0.78	0.60	1.56	0.39	0.61
BT1	0.287	0.81	0.75	0.55	1.91	0.29	0.71
BT2	0.289	0.81	0.79	0.59	1.72	0.34	0.66
BT3	0.292	0.81	0.79	0.58	1.64	0.35	0.65
BT4	0.279	0.81	0.76	0.58	1.45	0.40	0.60

*Description of symbols are shown in the glossary

Table 15 shows the density, packing fraction and porosity of the paracetamol tablets.

It was observed that an increase in the binder concentration increased the bulk density of granules which in turn increased the crushing strength of the tablets. This could be due to decrease in porosity and subsequent increase in the number of contact points leading to an increase in the degree of bonding between the particles (121).

There is therefore a reduction in the absorption of water which is more pronounced. There is a significant difference ($p<0.001$) in the porosity of tablets containing *Cyperus esculentus* binder at concentrations of 2.5 and 5% when compared with 5% corn starch. It is also significant ($p<0.01$) at *Cyperus esculentus* binder concentration of 7.5 % as shown in appendix II. It is generally believed that porous granules dissolve faster than dense granules since pores allow water to penetrate granules more easily.

CHAPTER FOUR

CONCLUSION, SUMMARY AND RECOMMENDATION

4.1 CONCLUSION

The research project is on preformulation studies of *Cyperus esculentus* starch in the production of paracetamol tablets. It is aimed at determining the physicochemical, binding, and disintegrant properties of *Cyperus esculentus* starch. The study is also aimed at establishing the usefulness or otherwise of *Cyperus esculentus* starch as a tablet excipient. It involved isolation of starch from *Cyperus esculentus* tubers. Physicochemical tests were conducted on the starch. Paracetamol tablets were produced by wet granulation method. The formulated tablets were subjected to quality control tests. Statistical analysis was carried out using SPSS Version 21. All values are expressed as mean ± SD and statistically significant differences between means assessed by Student T-test ($p< 0.01$) and ANOVA.

The results of the study showed that *Cyperus esculentus* starch possesses excellent physicochemical properties that qualify it as a pharmaceutical grade starch. The controlled particle size and morphology imply usefulness in a variety of carrier-based formulations. *Cyperus esculentus* starch has also shown good properties as disintegrant. The disintegrant activity of starch was determined by their nature, forms, mode of incorporation and use concentration. The disintegration times were significantly ($p<0.01$) affected by these. The binding efficacy of *Cyperus esculentus* is more than that of corn starch. The hardness of the tablets was significantly ($p<0.01$) influenced by the concentration of the binder used in the formulation. This fact is further corroborated by the inherent swelling ability wherein it showed resistance to swelling. Physicochemical parameters such as swelling capacity, water

solubility as well as hydration capacity exhibited more direct effect on disintegrant activity of the starch.

The widespread availability, high yield, and simplicity of the extraction serve as impetus for its commercial exploitation. *Cyperus esculentus* starch has good properties and provides excellent disintegrant and binding properties in paracetamol tablet formulations without compromising drug release characteristics. Therefore, to satisfy the ever increasing demand for highly specific and functional excipients, *Cyperus esculentus* starch may provide a viable alternative

4.2 SUMMARY AND RECOMMENDATION

The results of the evaluation carried out in this work showed that C*yperus esculentus* starch offers a fertile ground for further research. This is because, some of the properties of C*yperus esculentus* starch such as the ash value and hydration capacity require further research to maximize their potential usefulness.

The possible application of *Cyperus esculentus* starch in other pharmaceutical formulations should be evaluated. Such evaluations may include its use as dusting powder, muco-adhesive agents, and glidants. This will help to expand the usefulness of *Cyperus esculentus* starch in pharmaceutical formulations. The functionality of the starch can be improved upon by modification. Paste clarity, and the flow properties can be enhanced by the modification of the *Cyperus esculentus* starch.

GLOSSARY

BATCH CODES

1. CE_3: 5 % endo disintegrant (cornstarch)
2. TE_1 : 1 % endo disintegrant (tiger nut starch)
3. TE_2 : 2 % endo disintegrant (tiger nut starch)
4. TE3 : 5 %endo disintegrant (tiger nut starch)
5. TE_4 : 10 % endo disintegrant (tiger nut starch)
6. CX_3 : 5 % exo disintegrant (corn starch)
7. TX_1 : 1 % exo disintegrant (tiger nut starch)
8. TX_2 : 2 % exo disintegrant (tiger nut starch)
9. TX_3 : 5 % exo disintegrant (tiger nut starch)
10. TX_4 : 10 % exo disintegrant (tiger nut starch)
11. CEX_3 : 5 % endo ï exo disintegrant (corn starch)
12. TEX_1 : 1 % endo-exo disintegrant (tiger nut starch)
13. TEX_2 : 2 % endo- exo disintegrant (tiger nut starch)
14. TEX_3 : 5 % endo-exo disintegrant (tiger nut starch)
15. TEX_4 : 10 % endo-exo disintegrant (tiger nut starch)
16. BC_2 : 5 % starch as binder (cornstarch)
17. BT_1 : 2.5 % starch as binder (tiger nut starch)
18. BT_2 : 5 % starch as binder (tiger nut starch)
19. BT_3 : 7.5 % starch as binder (tiger nut starch)
20. BT_4 : 10 % starch as binder (tiger nut starch).

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APPENDICES

APPENDIX: I

Tablet porosity – Tiger nut

	Tablet Porosity		
Group	Intras	Extra	Intra-Extra
Control	0.68±0.06	0.70±0.06	0.67±0.06
Tiger nut 1%	0.65 ± 0.10^{NS}	0.58±0.06***	0.71±0.10***
Tiger nut 2%	0.69 ± 0.06^{NS}	0.73±0.06***	0.70±0.06**
Tiger nut 5%	0.66 ± 0.10^{NS}	0.72±0.10*	0.68 ± 0.06^{NS}
Tiger nut 10%	0.67 ± 0.06^{NS}	0.71 ± 0.10^{NS}	0.66 ± 0.10^{NS}

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX II

Tablet porosity ï Binder

Group	**Tablet Porosity**
Control	0.61±0.12
Binder 2.5%	0.71±0.10***
Binder 5%	0.66±0.06***
Binder 7.5%	0.65±0.06**
Binder 10%	0.60 ± 0.06^{NS}

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX III

Dissolution studies- SGF

Intra-extra dissolution studies

% Release in SGF

Group	10 min	20 min	30 min	40 min
Control	49.8±0.06	70.3±0.05	92.7±0.11	94.2±0.02
Tiger nut 1%	71.6±0.07***	77.2±0.11***	97.4±0.13*	95.8 ± 0.02^{NS}
Tiger nut 2%	90.3±0.23***	91.4±0.11***	90.9 ± 0.17^{NS}	90.0±0.10*
Tiger nut 5%	88.4±0.20***	88.9±0.10***	89.2 ± 0.17^{NS}	89.5±0.02*
Tiger nut 10%	59.6±0.30***	51.3±0.16***	81.6±0.13***	95.2 ± 0.13^{NS}

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX IV

Intra dissolution studies

% Release in SGF

Group	10 min	20 min	30 min	40 min
Control	89.3±0.06	89.8±0.13	89.5±0.14	90.3±0.26
Tiger nut 1%	90.6±0.13***	90.3±0.03***	90.5±0.12***	90.2 ± 0.07^{NS}
Tiger nut 2%	89.6±0.16***	90.0±0.13***	90.9±0.01***	90.0±0.22***
Tiger nut 5%	89.2 ± 0.03^{NS}	89.7 ± 0.11^{NS}	89.5 ± 0.03^{NS}	89.5±0.16***
Tiger nut 10%	25.9±0.04***	54.0±0.10***	43.0±0.16***	63.7±0.12***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX V

Extra dissolution studies

% Release in SGF

Group	10 min	20 min	30 min	40 min
Control	61.4±0.06	89.2±0.15	93.2±0.16	98.1±0.13
Tiger nut 1%	7.8±0.10***	18.3±0.11***	28.9±0.17***	41.0±0.07***
Tiger nut 2%	93.2±0.20***	89.3 ± 0.13^{NS}	90.0±0.24***	90.0±0.05***
Tiger nut 5%	90.2±0.20***	89.7±0.13***	90.0±0.05***	90.5±0.02***
Tiger nut 10%	90.9±0.31***	90.8±0.24***	90.8±0.01***	90.5±0.01***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX VI

Binder dissolution studies

% Release in SGF

Group	10 min	20 min	30 min	40 min
Control	32.0±0.03	46.7±0.07	69.8±0.24	80.2±0.17
Binder 2.5%	89.7±0.07***	90.0±0.23***	90.0±0.13***	90.0±0.11***
Binder 5%	75.9±0.09***	75.9±0.09***	76.3±0.19***	76.0±0.19***
Binder 7.5%	9.3±0.08***	24.7±0.07***	26.4±0.20***	56.7±0.06***
Binder 10%	0.0±0.0***	3.3±0.01***	13.9±0.05***	18.3±0.25***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX VII

Dissolution studies- SIF

Intra-extra dissolution studies

% Release in SIF

Group	10 min	20 min	30 min	40 min
Control	42.5±0.06	30.9±0.31	38.8±0.03	35.2±0.23
Tiger nut 1%	32.8±0.17***	35.0±0.01***	37.2±0.13***	50.6±0.24***
Tiger nut 2%	44.4±0.11***	49.0±0.02***	49.7±0.12***	50.0±0.07***
Tiger nut 5%	43.0±0.13***	36.9±0.01***	41.8±0.11***	36.8±0.07***
Tiger nut 10%	40.8±0.22***	42.7±0.07***	49.0±0.07***	49.2±0.05***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX VIII

Intra dissolution studies

% Release in SIF

Group	10 min	20 min	30 min	40 min
Control	27.4±0.03	28.7±0.06	30.5±0.23	37.7±0.07
Tiger nut 1%	12.6±0.03***	22.5±0.05***	26.9±0.12***	31.8±0.06***
Tiger nut 2%	14.1±0.11***	25.0±0.13***	27.5±0.12***	24.3±0.13***
Tiger nut 5%	26.8±0.20***	27.0±0.13***	30.4±0.13***	35.0±0.12***
Tiger nut 10%	32.4±0.07***	34.9±0.23***	35.4±0.11***	36.8±0.13***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX IX

Extra dissolution studies

% Release in SIF

Group	10 min	20 min	30 min	40 min
Control	44.1±0.11	48.5±0.07	50.4±0.10	51.2±0.15
Tiger nut 1%	9.2±0.13***	10.2±0.05***	11.5±0.09***	15.1±0.16***
Tiger nut 2%	27.4±0.17***	30.5±0.01***	33.3±0.31***	37.3±0.20***
Tiger nut 5%	36.8±0.17***	34.8±0.12***	34.8±0.28***	51.7±0.22***
Tiger nut 10%	41.1±0.12***	43.0±0.13***	46.2±0.27***	48.7±0.02***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX X

Binder dissolution studies

% Release in SIF

Group	10 min	20 min	30 min	40 min
Control	42.7±0.16	43.2±0.10	45.6±0.11	47.2±0.23
Tiger nut 1%	18.8±0.13***	23.8±0.08***	30.4±0.09***	48.8±0.24***
Tiger nut 2%	45.9±0.12***	47.9±0.08***	49.6±0.08***	54.5±0.25***
Tiger nut 5%	13.5±0.09***	24.5±0.04***	31.6±0.03***	32.9±0.15***
Tiger nut 10%	6.0±0.10***	12.4±0.05***	18.6±0.03***	32.8±0.30***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XI

Granule flow rate

Granule flow rate

Group	Intra	Extra	Intra-Extra
Control	7.79±0.06	8.54±0.06	8.13±0.06
Tiger nut 1%	8.64±0.10***	8.32±0.06***	8.55±0.10***
Tiger nut 2%	8.62±0.06***	8.39±0.06***	8.96±0.06***

Tiger nut 5%	8.49±0.10***	8.57±0.10***	8.06±0.06***
Tiger nut 10%	9.09±0.06***	8.67±0.10***	9.12±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XII

Granule flow rate/tensile strength - Binder

Group	Granule flow rate	Tensile strength (*10^5)
Control	10.87±0.12	5.18±0.06
Binder 2.5%	9.06±0.10***	1.98±0.08***
Binder 5%	9.90±0.06***	5.65±0.08***
Binder 7.5%	10.0±0.06***	4.55±0.09***
Binder 10%	10.10±0.06***	8.03±0.07***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XIV

Others for binder

Group	Granule size distribution	Granule density (bulk density)	Granule density (tapped density)	Hardness	Friability (%)
Control	11.78±0.12	0.441±0.09	0.490±0.01	5.70±0.31	0.28±0.06

Binder 2.5%	16.0±0.10***	0.418±0.07***	0.466±0.07***	3.80±0.24***	0.25±0.08***
Binder 5%	15.39±0.06***	0.389±0.01***	0.442±0.17***	6.30±0.02***	0.28±0.08^{NS}
Binder 7.5%	15.96±0.06***	0.449±0.12***	0.490±0.13^{NS}	5.0±0.02**	0.18±0.09***
Binder 10%	14.67±0.06***	0.430±0.12***	0.486±0.13***	9.20±0.04***	0.15±0.07***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XV

Tablet density

Tablet density

Group	Intra		Extra		Intra-Extra	
	Bulk density	Tapped density	Bulk density	Tapped density	Bulk density	Tapped density
Control	0.417±0.06	0.478±0.08	0.413±0.03	0.479±0.06	0.422±0.13	0.452±0.06
Tiger nut 1%	0.421±0.10***	0.486±0.24***	0.413±0.10 NS	0.471±0.10***	0.354±0.10***	0.433±0.06***
Tiger nut 2%	0.413±0.06***	0.481±0.07***	0.387±0.06***	0.489±0.06***	0.370±0.06***	0.438±0.06***
Tiger nut 5%	0.421±0.10***	0.467±0.06***	0.417±0.06***	0.473±0.10***	0.413±0.06***	0.449±0.10***
Tiger nut 10%	0.393±0.06***	0.459±0.10***	0.378±0.10***	0.462±0.06***	0.369±0.10***	0.450±0.10*

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XVI

% size distribution

Group	% size distribution Intra		
	< 1.7µm	< 1.0µm	< 0.7µm
Control	43.73±0.12	40.30±0.03	16.15±0.17
Tiger nut 1%	40.45±0.10***	47.32±0.06***	12.20±0.10***
Tiger nut 2%	33.33±0.06***	51.06±0.14***	15.60±0.15***
Tiger nut 5%	30.30±0.10***	55.05±0.24***	14.65±0.06***
Tiger nut 10%	23.11±0.06***	63.26±0.10***	13.64±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001)

APPENDIX XVII

Group	% size distribution Extra		
	< 1.7µm	< 1.0µm	< 0.7µm
Control	52.77±0.12	36.31±0.03	10.90±0.17
Tiger nut 1%	41.25±0.10***	46.48±0.06***	12.20±0.10***
Tiger nut 2%	44.40±0.06***	40.55±0.14***	15.05±0.15***
Tiger nut 5%	56.19±0.10***	33.90±0.24***	9.90±0.06***
Tiger nut 10%	10.06±0.06***	70.02±0.10***	19.90±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XVIII

Group	% size distribution Intra-extra		
	< 1.7µm	< 1.0µm	< 0.7µm
Control	45.02±0.12	43.10±0.03	11.88±0.17
Tiger nut 1%	7.66±0.10***	71.65±0.06***	20.69±0.10***
Tiger nut 2%	15.27±0.06***	68.91±0.14***	15.82±0.15***
Tiger nut 5%	36.59±0.10***	48.41±0.24***	15.01±0.06***
Tiger nut 10%	46.84±0.06***	42.46±0.10***	10.70±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XIX

Group	% size distribution Binder		
	< 1.7µm	< 1.0µm	< 0.7µm
Control	66.92±0.12	21.29±0.03	11.78±0.17
Binder 2.5%	21.65±0.10***	29.95±0.06***	48.38±0.10***
Binder 5%	44.05±0.06***	40.55±0.14***	15.39±0.15***
Binder 7.5%	33.65±0.10***	50.38±0.24***	15.96±0.06***
Binder 10%	43.84±0.06***	41.49±0.10***	14.67±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XX

	Friability (%)		
Group	Intra	Extra	Intra-Extra
Control	0.19±0.11	0.35±0.09	0.12±0.31
Tiger nut 1%	0.28±0.10***	0.29±0.06***	0.14±0.10*
Tiger nut 2%	0.12±0.06***	0.38±0.06***	0.33±0.06***
Tiger nut 5%	0.16±0.10***	0.53±0.10***	0.21±0.06***
Tiger nut 10%	2.25±0.06***	2.29±0.10***	0.17±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XXI

	Disintegration		
Group	Intra	Extra	Intra-Extra
Control	2.20±0.23	1.92±0.06	3.20±0.22
Tiger nut 1%	3.23±0.10***	7.17±0.06***	5.80±0.10***
Tiger nut 2%	3.12±0.06***	3.78±0.17***	5.10±0.06***
Tiger nut 5%	2.72±0.10***	1.78±0.10***	4.20±0.31***
Tiger nut 10%	2.70±0.06***	1.43±0.10***	2.10±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XXII

Group	Disintegration
Control	6.73±0.12
Binder 2.5%	1.32±0.10***
Binder 5%	5.21±0.06***
Binder 7.5%	10.0±0.06***
Binder 10%	32.0±0.06***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XXIII

Tensile strength of tiger nut

	Tensile strength (*10^5)		
Group	Intra	Extra	Intra-Extra
Control	4.54±0.23	6.03±0.06	7.86±0.22
Tiger nut 1%	5.53±0.10***	6.46±0.06***	5.79±0.10***
Tiger nut 2%	6.46±0.06***	4.98±0.17***	4.96±0.06***
Tiger nut 5%	5.61±0.10***	5.29±0.10***	5.45±0.31***
Tiger nut 10%	7.06±0.06***	5.06±0.10***	8.33±0.10***

Data presented as mean ± S.E.M, values are statistically significant from control at (*p<0.05, **p<0.01, *** p<0.001).

APPENDIX XXIV

% Swelling

	% Swelling		
Time (hr)	Distilled water	SIF (no enzyme)	SGF (no enzyme)
0.0	0.00	0.00	0.00
0.16	0.58	1.00	1.00
0.33	0.63	1.00	1.00
0.50	1.21	1.00	1.00
0.66	1.74	1.00	1.00
0.83	1.74	1.00	1.00
1	1.74	1.50	1.00
24	4.79	2.00	1.00

APPENDIX XXV

% Swelling ï effect of electrolytes

	% Swelling							
	2.0N		1.0N		0.5N		0.1N	
Time (hr)	NaCl	$MgCl_2$	NaCl	$MgCl_2$	NaCl	$MgCl_2$	NaCl	$MgCl_2$
0.0	0	0	0	0	0	0	0	0
0.16	-10	-5	0.5	2	2	0.3	0	0.5
0.33	-10	-10	0	-1	0	0	2	1.0
0.50	-10	-10	-1	-1	-10	0	2	1.0
0.66	-10	-10	0	-1	-10	-8	2	1.1
0.83	-10	-10	-10	-3	-10	-8	2.5	1.2
1	-10	-15	-10	-3	-20	-8	2.3	1.5
24	-20	-15	-20	-3	-20	-10	2.3	1.6

APPENDIX XXVI

Temperature (^{0}C)	Solubility (%)		Swelling Power	
	Cyperus esculentus starch	Corn Starch BP	Cyperus esculentus	Corn Starch BP
55	1.50	5.00	0.80	0.50
65	2.00	6.20	0.81	1.20
75	2.10	9.80	0.86	1.80
85	5.00	11.90	0.90	2.20
95	9.00	18.10	0.92	3.00

APPENDIX XXVII

TABLE SHOWING PERCENTAGE DRUG RELEASED AT DIFFERENT TIMES

TABLET BATCH	% DRUG RELEASE							
	SGF				SIF			
	10MIN	20MIN	30MIN	40MIN	10MIN	20MIN	30MIN	40MIN
CE_3	89.46	89.83	89.58	90.32	27.47	28.70	30.55	37.72
TE_1	90.69	90.32	90.57	90.20	12.65	22.58	26.91	31.85
TE_2	89.65	90.08	90.94	90.02	26.85	27.09	30.43	35.06
TE_3	89.21	89.77	89.58	89.58	26.84	27.09	30.43	35.06
TE_4	25.92	54.07	43.00	63.77	32.47	34.94	35.43	36.85
CX_3	61.49	89.28	93.32	98.17	44.19	48.52	50.49	51.24
TX_1	7.89	18.39	28.94	41.5	9.25	10.24	11.53	15.18
TX_2	93.29	89.39	90.01	90.01	27.47	30.53	33.39	37.35
TX_3	90.26	89.76	90.01	90.57	36.85	34.87	34.81	51.73
TX_4	90.94	90.82	90.82	90.57	41.17	43.03	48.77	48.77
CEX_3	49.88	70.38	92.73	94.27	42.59	30.98	38.83	35.24
TEX_1	71.62	77.23	97.48	95.82	32.89	35.06	37.22	50.68
TEX_2	90.38	91.43	90.08	90.08	44.45	49.08	49.76	50.07
TEX_3	88.47	88.96	89.27	89.52	43.03	36.91	41.85	36.85
TEX_4	59.69	51.30	81.62	95.20	40.80	42.72	49.08	49.14
BC_2	76.24	77.29	76.93	75.63	45.99	47.84	50.07	54.14
BT_2	75.94	75.94	76.37	76.06	45.99	47.90	49.69	54.57
BT_3	9.31	24.74	26.48	56.73	13.57	24.50	31.60	32.96

BT_4	-0.94	3.32	13.94	18.33	6.04	12.46	18.69	32.89

APPENDIX XXVIII

STANDARD BEER'S PLOT FOR PARACETAMOL