# COMPARATIVE EFFECTS OF SUPER-DISINTEGRANT ACTIVITY OF MODIFIED AFRICAN BITTER YAM STARCH IN PARACETAMOL TABLET FORMULATIONS

**By**

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**UNDER THE SUPERVISION OF**

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**DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY**

**FACULTY OF PHARMACY**

**UNIVERSITY OF BENIN**

**BENIN CITY, NIGERIA**

**September, 2023**

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**A DISSERTATION SUBMITTED TO THE DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY, FACULTY OF PHARMACY, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DOCTOR OF PHARMACY (PHARM.D) DEGREE OF THE UNIVERSITY OF BENIN, BENIN CITY, EDO STATE, NIGERIA.**

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# CERTIFICATION

This is to certify that this work was done by **Fredrick Emmanuel Ejeh** in the Department of pharmaceutics and pharmaceutical technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria, in partial fulfillment for the award of the Pharm. D degree of the University.

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**Fredrick Emmanuel Ejeh** **Date**

(Student)

# DEDICATION

This project is dedicated to God Almighty whose loving kindness, infinite mercy has seen me through the period of this study and also to my dad and my late mum, Mrs. Felicia Fredrick for giving me the enablement and providing the resources to undertake this important journey.

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I would like to use this opportunity to appreciate first and foremost, the Almighty God for bringing me thus far. It is a journey I have undertaken backed solidly and continually by my parents, Mr Fredrick Ojile and Late Mrs Fredrick Felicia. Their sacrifices and prayers have provided the solid ground on which I have trod upon.

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Words are not enough to say thank you to my good friends who made my stay in Uniben meaningful especially Christopher, Chucks, God's power, Nonso, Azor, Priscilla, Tracy and my project colleague for their love and assistance, then to the entire 600 level class (2021/2022 session), I love you all.

To all the staff of the Faculty of Pharmacy, University of Benin,I say thank you.

Lastly,I would like to appreciate myself. For not giving up. For not staying down. For seeing this through. For coming this far in what has been a wild ride.

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# ABSTRACT

Objectives: To assess and compare the decomposition performance of carboxymethylated and acid-hydrolyzed bitter sweet potato starch in the formulation of Paracetamol tablets.

Method: Bitter sweet potato starch, extracted from African bitter sweet potatoes, was subjected to modifications through carboxymethylation and acid hydrolysis. Subsequently, various concentrations (5% w/w, 7.5% w/w, and 10% w/w) of carboxymethylated acid-hydrolyzed bitter sweet potato starch were utilized to prepare distinct batches of Paracetamol tablets employing the direct granulation method. The granules were subjected to an evaluation of flow properties, including angle of repose, Carr index, and Hausner ratio, while the tablets underwent assessment for weight uniformity, crush resistance, fragility, disintegration time, wetting time, and solubility.

Results: All particles exhibited free-flowing characteristics with an angle of repose of less than 33 (< 33°), a Hausner ratio of less than 1.5 (<1.5), and a Carr index of less than 25 (< 25%). The tablet weights across all batches ranged from an average of 564 to 630 mg. Tablet hardness fell within the range of 6.9 to 9.1 kp, with a strength value of < 1.0%. Wetting times were consistently < 2 minutes, and decomposition times were < 5 minutes. Dissolution studies revealed that tablets containing bitter sweet potato starch hydrolyzed at 10°F exhibited a drug release rate of 100%, while those with starch hydrolyzed at 10°F displayed a drug release rate of 96.39%.

Conclusion: The findings suggest that both carboxymethylated and acid-hydrolyzed starches result in shorter decomposition times and improved solubility properties. This implies that acid hydrolysis and carboxymethylation enhance the decomposition and solubility characteristics of starch, making it a cost-effective alternative to sodium starch glycolate in pharmaceutical applications.

# CHAPTER ONE

## 1.1 INTRODUCTION

Starch is a versatile compound derived from various plant sources. Its physicochemical properties are significantly influenced by factors such as the plant's origin, environmental conditions during starch development, and the plant's maturity. These elements impact the composition of starch, specifically the content and proportions of amylose and amylopectin. Additionally, they affect the size and distribution of starch granules, as well as the presence and nature of minor components like phosphates and lipids and how they interact with amylose and amylopectin.

When employed as a pharmaceutical excipient, particularly as a binder and disintegrant, the functionality of unmodified starch is directly affected by its physicochemical attributes. These characteristics, primarily their influence on swelling, gelatinization, particle size, and shape, define the properties of the pharmaceutical dosage form in which the starch is used. Consequently, the choice of starch source impacts the qualities of the pharmaceutical dosage form, and this should be taken into account when selecting excipients for drug formulations or considering the substitution of one starch for another.

In its pure form, starch is a colorless, tasteless, odorless, amorphous powder that is insoluble in water and common organic solvents. It is a widespread natural chemical and serves as a form of energy storage in plant materials.

Microscopically, starch comprises colorless, highly refractive granules with size and shape variations influenced by various factors, particularly the starch's source. Starch granules are made up of alternating regions of amorphous and crystalline sheets, forming ring-like structures within the crystalline fraction.

Chemically, starch is a carbohydrate composed of two similar molecules: amylose and amylopectin. Amylose is a linear chain with α-1,4-glycosidic bonds, while amylopectin is a branched polymer with α-1,4-glycosidic bonds and α-1,6-glycosidic bonds connecting branched chains. This structural distinction imparts distinct properties to each of these polymers. For instance, the limited branching in amylopectin at α-1,6-glycosidic linkages contribute to the crystalline portion of the starch grain. In its natural state, starch typically comprises about 20 to 30% amylose and 70 to 80% amylopectin.

Amylose is relatively rigid due to its linear structure, making it insoluble in water but soluble in hot water without forming a gel. In contrast, amylopectin possesses a non-rigid structure, rendering it soluble in water and capable of forming a gel when heated. Starch is primarily synthesized in plant storage organs' amyloplasts or in plant leaves' chloroplasts, often containing small quantities of lipids and phosphate groups.

### 1.2. Pharmaceutical applications of starch

Starch stands out as a highly favored pharmaceutical excipient due to its minimal processing requirements and natural characteristics, making it suitable for various pharmaceutical needs. This biocompatible, non-toxic, and odorless substance is not only readily accessible but also cost-effective. In its unaltered state, natural starch finds applications in diverse dosage forms, with its precise function tailored to the requirements of each specific form. This segment delves into the prevalent roles of starch as a pharmaceutical excipient.

#### 1.2.1 Binder

Starch finds extensive utility as a binding agent in wet screening and granulation processes, crucial stages in the manufacture of tablets, capsules, and other solid pharmaceutical forms. The granulation process, aimed at enhancing the flow of active pharmaceutical ingredients (APIs), typically results in high cohesion. Ensuring a consistent flow rate is imperative to

maintain uniform weight in dosage forms manufactured at high speeds, preventing variations in dosages that may arise from inconsistent flow rates and powder segregation.

In this process, starch serves as a liquid binder, facilitating the formation of agglomerates with favorable flow properties. The creation of pastes involves heating a starch mixture, effectively 'gluing' the formulation's particles together to generate larger agglomerates. This reduces cohesion and enhances flow. The process forms robust bonds between the powder bed's particles, which become sturdy bridges upon drying. The paste's viscosity directly influences the strength of these bridges and the resultant particle size, up to a certain threshold (Asaoka et al., 1984) . Consequently, factors affecting the viscosity of starch paste impact its role as a binder. Studies confirm that starch's origin, chemical composition, and characteristics influence its viscosity (Betancur et al., 1997).

### 1.2.2 Disintegrant

Disintegrants are essential components in pharmaceutical formulations, responsible for breaking down solid dosage forms like tablets or granules into smaller particles. This fragmentation plays a crucial role in drug release and absorption, as it increases the surface area exposed to the surrounding medium, expediting the dissolution, release, and absorption of the drug. Starch, a cost-effective and readily available disintegrant, achieves this by leveraging its swelling properties, which lead to the disruption of inter-particle forces in the dosage form when exposed to water. The extent of swelling is contingent on the starch source and type, determined by the relative proportions and structures of amylose and amylopectin within the starch. Starch's ability to weaken binding forces is indicative of its degradability. Furthermore, the disintegration effect may also involve the creation of channels through which the liquid can penetrate the solid dosage form, facilitating drug dissolution (Blennow et al., 2001; Adebiyi et al., 2011).

### 1.2.3 Diluent

In situations where drugs need to be administered at extremely low doses, making it challenging to process and compress them into the required dosage forms, pharmaceutical formulations may include inert substances that do not possess the drug's pharmacological effects. These inert materials serve to increase the volume of the formulation, facilitating standard processing procedures. Starch is a preferred choice for this role due to its neutral flavor, lack of odor, and digestible nature.

### 1.2.4 Absorbents

Starch is characterized by its hygroscopic nature, capable of absorbing moisture within the range of 10–17% when brought to equilibrium under standard atmospheric conditions (Chabot et al., 1976). Consequently, it is employed as a desiccant in pharmaceutical formulations to maintain powder dryness and safeguard the stability of drugs prone to degradation from processes like hydrolysis and other related chemical reactions.

### 1.2.5 Glidant/lubricant

Starches have been explored for their potential applications as lubricants and glidants (Chan et al., 2009) due to their inherent slipperiness and their capacity to adhere to surfaces.

### 1.2.6 Modified starches

In its natural state, the utility of starch in pharmaceutical applications is constrained by its susceptibility to various processing conditions, including high temperatures, pH shifts, freeze-thaw cycles, degradation, and fragility. However, after undergoing modification, starch becomes exceptionally versatile in pharmaceutical contexts. For instance, acetylation enhances pulp clarity and flow, and augments its swelling capacity (Cheetham et al., 2002). Carboxymethylation, on the other hand, enhances water solubility, lowers gelatinization temperature, and decreases dough stability (Craig and Elaisso 1996). The physicochemical attributes of the specific starch utilized are a pivotal factor in the modification process,

determining the distinctive characteristics of the final modified product. These alterations can be achieved through physical methods such as temperature and humidity exposure, gelatinization, extrusion, spray drying, granulation, or agglomeration. Additionally, starch can be chemically modified by introducing functional groups via techniques like esterification, cationization, cross-linking, hydrolysis, and oxidation, often involving the substitution of some or all hydroxyl groups.

### 1.3. Starch source and its pharmaceutically relevant properties

Starch is a widely distributed natural substance that can be derived from various plant sources. Starch meeting the official compendial quality standards in relevant pharmacopeias is known as official starch. Examples of such starches include those sourced from potatoes, corn, rice, and tapioca. Pharmaceutical-grade starch is generally obtained from different plant sources but must conform to established standards**.**

**Descriptions:** Starch grains' characteristics, such as size, shape, distribution, and the presence or absence of hilum and striations, vary based on the plant material from which the starch is extracted.

**Characteristics:** Key characteristics of pharmaceutical-grade starch include being a fine to very fine powder, typically white with a slight yellowish tint, having no taste, and being insoluble in both cold water and alcohol.

**Identification tests**: involve producing a translucent whitish jelly by cooling 1 gram of starch mixed with 2 ml of cold water, then stirring it into 15 ml of boiling water and gently boiling for 2 minutes. Additionally, adding iodine to a water slurry of the starch results in a reddish-violet to deep blue color**.**

In addition to the standard compendial starches, numerous researchers have explored various plant sources as potential pharmaceutical-grade starch options, using pharmacopeial starches as benchmarks (Emeje et al., 2012).

These investigations reveal that while starch from diverse sources can be employed as excipients, their specific effects, especially in terms of quantity, on formulation properties depend on the source. For instance, the disintegrating effect of yam starch is more pronounced than that of cocoyam starch, which can be attributed to variations in fundamental starch properties like particle size and the amylose/amylopectin ratio. These differences impact functional properties such as swelling, water absorption, and viscosity (Ferguson et al., 1962).

Pharmaceutical-grade starches can originate from underground plant storage organs like tubers, rhizomes, roots, or from grains and cereals. The choice of starch source primarily depends on factors like availability, ease of extraction, and yield, with underground storage organs being preferred due to their minimal extraneous materials. Despite the general physical and chemical properties of starch being consistent, their specific functional attributes are contingent on the particular plant source, which dictates their physicochemical properties. The biological origin of starch is a crucial factor influencing granule shape, size, and morphology (Greenwood et al., 1967). This section aims to explore the impact of specific plant sources on particular physicochemical properties of starch that are pertinent to its utilization in pharmaceutical formulations.

### 1.3.1 Swelling and gelatinization properties

#### 1.3.1.1 Gelatinization

The primary role of starch in pharmaceuticals is as a binder and disintegrant in the production of tablets and other solid dosage forms. Consequently, its behavior in the presence of water

holds paramount importance in the pharmaceutical industry. The decomposition process of starch is chiefly dictated by the interaction between starch granules and water absorption, leading to their swelling before eventual rupture and complete decomposition. When employed as a binder, starch's effectiveness relies on the cohesiveness resulting from a sequence of events leading to the breakdown of starch and the consequent increase in the viscosity of starch paste. The extent of changes experienced by starch granules during heating is contingent on factors like temperature and duration, with the type of starch also playing a significant role (Adebiyi et al., 2011).

Gelatinization denotes the disruption of the granular structure of starch through heating with excess water. In this process, as the suspension is gradually heated, starch granules start to swell laterally (Hirano et al., 1998), and the granular contents, including amylose, gradually seep out, ultimately leading to the rupture of the granule, further increasing viscosity and solubility. Initially, some amylose is retained within the granule, but with prolonged heating, the swollen granules rupture, collapse, and dissolve. This stepwise transformation progressively augments the viscosity of the suspension until the starch granules are entirely decomposed, reaching maximum viscosity (Hofreiter et al., 1987).

This process fundamentally involves weakening the micelle network within resistant granules in suspension by disrupting hydrogen bonds. This facilitates increased hydration and the irreversible swelling of starch granules. These changes involve various irreversible transformations such as particle swelling, the loss of birefringence, amylose leaching, and an increase in both viscosity and solubility, along with lateral granule swelling (Hirano et al., 1998). From a thermodynamic perspective, gelatinization signifies the enthalpy conversion associated with a starch granule, which typically exists in a semi-crystalline form known as a spherulite. The collapse of the crystal structure results in an increase in entropy, contributing to the dislodgment of the hydrogen bond network present in the spherulite.

The apparent viscosity of a starch paste primarily depends on the characteristics of the individual swelling entities, their fragments, the presence of soluble starch, and the interaction or cohesion between the swollen granules.

Gelatinization initiates in areas of the granule where bonds are weakest, and therefore, because the degree of bonding between individual granules varies and is influenced by factors like plant source and environmental conditions during growth, the temperature and nature of gelatinization differ from one starch source to another (Hirano et al., 1998).

#### 1.3.1.2 Retrogradation

Retrogradation refers to the gradual recrystallization of starch components, namely amylose and amylopectin, which occurs when starch undergoes cooling or dehydration (Hofstee et al., 1953). This phenomenon is driven by the extensive molecular chains and the numerous hydroxyl groups present in starch, which strongly encourage the bonding between these chains. As a result, clusters of amylose molecules form, leading to the creation of rigid gels and insoluble precipitates. The rate at which retrogradation occurs in a starch paste is influenced by several factors, including the amylose content, the size of the amylose molecules, and the specific method used to prepare the paste (Hofstee et al., 1953).

#### 1.3.1.3 Factors that affect gelatinization/swelling properties

The resistance of the starch granular structure is determined by the specific characteristics of its constituent molecules, their spatial arrangement, and their interactions with water molecules. As the crystalline region of starch is predominantly composed of amylose, the quantity of amylose plays a crucial role in the gelatinization process. There is a significant relationship between the apparent amylose content and various viscosity parameters, including maximum viscosity (PV), minimum viscosity (MV), final viscosity (FV), degradability (BD), total shrinkage viscosity (TSV), and shrinkage viscosity (SV). The addition of monoester phosphate derivatives enhances the viscosity of starch pastes. Potato starch, which contains a substantial amount of monoester phosphate, exhibits greater resistance to heat and shear compared to cereal starch. However, the stability of the hot dough is compromised when the potassium ions associated with the monoester phosphate are substituted with other cations (Itiola et al., 1991).

Amylopectin primarily contributes to granule swelling and viscosity (Jane et al., 1999). The adhesive properties of starch are influenced by the content of amylose and lipids (Jane et al., 1994). An increase in gelatinization temperature is associated with a higher concentration of amylopectin double helices, resulting in increased rigidity of the amorphous region.

Lipids found in starch, in the form of phospholipids and free fatty acids, tend to form complexes with amylose and the extended branches of amylopectin. This leads to starch granules with limited solubility, resulting in opaque and low-viscosity pastes, significantly reducing the swelling capacity of starch particles. The level of phosphorylation, primarily located in the amylopectin fraction and more abundant in amorphous regions, is lower in cereal starches compared to tuber starches. This lower phosphorylation is associated with increased granule hydration and reduced crystallinity, yielding pastes with higher transparency, viscosity, and freeze-thaw stability (Kunle et al., 2012). The swelling capacity of starch is influenced more by granule structure and chemical composition, particularly the amylose and lipid components, than granule size. Larger quantities of lipid-bound amylose inhibit swelling and gelatinization (Jane et al., 1999).

#### 1.3.1.4 Moisture sorption

The process of moisture absorption by starch, which leads to the swelling of granules, is believed to occur due to the interaction between the hydroxyl groups present in the hexose molecule and water molecules. While water molecules do form hydrogen bonds with both amylose and amylopectin, it has been observed that the physical structure of amylopectin tends to physically trap water molecules. This observation has led to the hypothesis that starch granules rich in amylopectin would possess a greater capacity for moisture absorption. It is worth noting that crystalline polymers are known to have extensive secondary intermolecular bonds, which results in the hydroxyl groups of adjacent glucose units

interacting with each other. Consequently, this reduces the available sites for water molecule absorption. As a consequence of this higher degree of crystallinity, moisture absorption can be diminished (Adebiyi et al., 2011).

#### 1.3.1.5 Effect of growth conditions

The quality and gelatinization characteristics of starch in starch-rich plants are influenced by the environmental conditions during their growth, particularly during the starch maturation phase. For example, it has been observed that barley cultivars grown in cooler conditions tend to exhibit lower gelatinization peak temperatures.

On the other hand, higher temperatures and ample moisture during the formation of starch granules can lead to a phenomenon called annealing, which results in the starch having higher initial gelatinization temperatures and a more confined temperature range for gelatinization (Leah et al., 1967). The temperature conditions during the plant's development significantly impact the swelling properties of the starch particles.

### 1.3.2 Amylose/amylopectin content

The physicochemical properties of starch, particularly its functional characteristics like flow and swelling properties, are primarily determined by the amylose/amylopectin ratio, molecular weight, and fine molecular structure (Lindeboom et al., 2004). These factors are especially critical in understanding the utility of starch in pharmaceutical applications, given its importance in terms of swelling and adhesive properties.

The physicochemical properties of starch in solution are directly linked to the molecular structure of the polymer. This includes aspects such as molecular size, the distribution of unit chain lengths, branching patterns, phosphate substitution degrees, and the size and distribution of starch particles. The thermal properties of starch are significantly influenced by the length of amylopectin branched chains (Morrison et al., 2005).

Numerous factors, both environmental and genetic (Morrison et al., 1993), contribute to the variability in amylose and amylopectin content and their relative proportions in a given starch sample. This ratio can range from around 65:35 to 85:15, and these compositional distinctions have been shown to result in specific physical and functional properties, including differences in crystallinity, granule size, gelling behavior, powder characteristics, and flow properties. The arrangement and association of amylose and amylopectin molecules in starch are influenced by the membrane structure and physical properties of plastids, with amylose content increasing as seeds mature.

The influence of growth conditions on starch gelatinization properties is primarily mediated through their impact on amylose content. For example, research indicates that starch from plants grown in cooler environments, at 15 degrees, exhibits the highest viscosity temperatures, shorter final viscosity (FV), total shrinkage viscosity (TSV), and shorter retention times. This results in an 80% higher peak viscosity compared to starch from plants grown at room temperature. The varying amylose content is responsible for these differences. Elevated growth temperatures tend to increase the gelatinization temperature of wheat starch primarily due to the greater presence of amylopectin double helices, which may lead to increased stiffness in the amorphous region. However, the effect of environmental temperature on amylose content is plant-specific, with some types experiencing an increase and others a decrease. For instance, in rice and corn, high growth temperatures lead to reduced amylose content, while wheat shows a slight increase, emphasizing the importance of plant type. Moreover, exposure to higher temperatures for extended periods results in a greater accumulation of amylose in rice plants. Additionally, starch grain size plays a role in determining amylose content, with larger grains having higher amylose levels.

### 1.3.3 Starch granule size

Particle size plays a significant role in shaping the physicochemical properties of starch, with starches of various plant origins exhibiting distinct morphologies (Reis et al., 1995). It is a crucial parameter that impacts the functional properties of different starches, influencing attributes such as starch composition, gelatinization behavior, paste properties, sensitivity to enzymes, crystallinity, swelling, and solubility.

The membrane structure and physical characteristics of plastids influence the specific shapes and morphologies of starch granules. For example, starch granules derived from tubers and roots often have an oval shape, while those from fruits and seeds display varying shapes. Small granular starch particles typically have an irregular polygonal shape. Small starch granules, when compared to larger ones with similar amylose content, tend to exhibit lower sticking temperatures and release more amylose from intact granules, particularly at temperatures exceeding 55 degrees Celsius. They also show a higher rate of water absorption, quicker hydration, and more substantial swelling. This is attributed to the less crystalline arrangement of polysaccharide chains in smaller starch granules, resulting in a higher proportion of amorphous regions that are more accessible to water. Additionally, factors like the amylose/amylopectin ratio, molecular weight, and fine molecular structure contribute to an increased amylose content with smaller particle size. The length of the branched chains of amylopectin also correlates with particle size and distribution, with reduced granule size associated with decreased amylopectin polymerization and larger, less branched amylose polymers being observed in large starch granules (Stephen et al., 1996).

Interestingly, the dissociation enthalpy of the amylose-lipid complex is higher in small starch particles compared to large ones. This pattern is reminiscent of acid or enzymatic hydrolysis, with small particles undergoing more rapid hydrolysis than larger particles. Enzymatic

digestion patterns also differ between small and large starch granules.The environment can also influence the particle size distribution of starch, as increasing growth temperature tends to reduce both the number and size of starch particles.

### 1.4. Effect of source on the pharmaceutical applications of starch

Extensive research has been conducted to explore the potential of various starches as pharmaceutical excipients, with a focus on their particle morphology, amylose/amylopectin ratio, water absorption capacity, swelling capacity, and gelatinization properties. It has been observed that the physicochemical properties of starch significantly impact the pharmacological properties of dosage forms produced from different starch types (Chan et al., 2016). This holds true irrespective of the specific starch utilized in the formulation.

While many of these novel starch formulations meet pharmaceutical quality standards, they can diverge from the official starch formulations. These differences are often attributed to variations in the physicochemical properties of starch. As previously discussed, starch's utility in pharmaceuticals, particularly in drug formulations, is largely rooted in its water absorption, swelling, and gelatinization characteristics. Although these properties are generally qualitatively similar across starch sources, the previous section has highlighted that the specific or quantitative values of these properties can vary between different starch sources and even among starches from the same source under differing growth conditions. A few examples are cited below to illustrate the impact of these varying properties on dosage form characteristics.

In a comparative study, it was found that taro starch exhibits higher viscosity than yam and cassava starches, and when employed as a binder, it yields tablets that are more brittle compared to other starches, resulting in higher brittleness values (Emeje et al., 2012). Tablets formed via dry granulation with sweet potato starch (large particles) as a disintegrant are

more fragile than those formed with taro starch (small particles), which also display greater hardness. Furthermore, there exists an inverse relationship between starch's swelling ability and the rate and extent of tablet disintegration and dissolution. This suggests that one mechanism for tablet degradation by starch is due to rupture caused by swelling.

The size and shape of starch particles also influence the compaction properties of granules used for tablet formation. For example, sweet potato starch, which is oval-shaped with a larger average diameter, exhibits higher density due to compaction and lower density due to subsequent particle rearrangement under low pressure. In contrast, potato and cassava starch, with smaller diameters and a more rounded shape, show the opposite effect. Yam starch has the highest flow pressure but the lowest tensile strength and brittle fracture index. The gelatinization properties of Tacca starch, as determined by parameters such as gelatinization onset temperature, peak and termination temperatures, crystallinity, and gelatinization enthalpy, are lower than those of corn starch. This implies that Tacca starch has more crystalline regions that are less thermally and structurally stable than corn starch (Adebiyi et al., 2011). These variations in properties result in different compaction behaviors for these starches. Although both undergo plastic deformation, corn starch experiences more extensive deformation because it is less resistant to deformation, leading to the production of stiffer solids. These formulation characteristics are correlated with the properties of the starch used.

Researchers have noted comparable associations between the fundamental properties of starch and its effects on formulation properties (Whistler et al., 1965). Additionally, it has been reported that the functionality of modified starches employed in altered drug formulations is influenced by the origin of the native starch. Investigations utilizing starches sourced from various origins have revealed that the starch's source can impact its performance as a sustained release excipient (Yanagisawa et al., 2004; Zeng et al., 1997).

Starch is a highly accessible natural ingredient with a broad range of applications in various industries, owing to its diverse physical and functional attributes. The presence of numerous hydroxyl groups on its surface allows for modifications and derivatives. In the pharmaceutical sector, starch serves as a crucial excipient, particularly as a disintegrant and binder in the formulation of solid dosage forms. Its effectiveness in this role hinges on its behavior in the presence of moisture, specifically how it interacts and functions when exposed to water. As a disintegrant, starch's insolubility is a key factor, creating pathways within the compacted mass through which water can penetrate to dissolve the active drug ingredient. Additionally, it relies on the swelling of starch granules, which leads to the disruption of solid bridges formed within the compacted mass. The swelling properties of starch are influenced by various factors closely tied to its chemical composition, encompassing amylose, amylopectin, lipids, and phosphates. The proportions of amylose and amylopectin, whether they are linear or branched, play a pivotal role in determining the speed and extent of interaction between water and starch, as they govern the accessibility of water molecules to OH groups within the starch channels. The molecular shape and branching degree also dictate the speed at which water can access and ultimately break the bonds within the starch molecules.

When used as a binder, starch's effectiveness hinges on its state when a starch powder suspension is subjected to high temperatures. These elevated temperatures gradually weaken the bonds between molecules in the starch granules. The continuous supply of heat energy eventually leads to the breakdown of granules, the flow of amylose, and, ultimately, the disintegration of amylopectin. All these processes culminate in increased viscosity, resulting in a viscous gel that imparts binding properties. This is utilized to bind powder particles in drug formulations. After drying, the initially wet globules solidify into sturdy particles that

enhance flow. This process is further influenced by factors such as the amylose-amylopectin ratio, moisture content, and starch production conditions in plants.

The relative proportions of amylose and amylopectin, the branching degree, molecular structure, the presence of phospholipids, interactions between carbohydrates and lipids, particle size, and phosphorylation all reflect the influence of environmental and genetic factors on the fundamental physicochemical properties of starch relevant to its functional role as a pharmaceutical excipient.

In summary, while starches from diverse sources can serve as pharmaceutical excipients, provided they meet the requisite standards, it is essential to acknowledge that their effectiveness in formulations is source-dependent. Since they impact functional properties, particularly swelling and pasting characteristics, it is crucial to gather information on the growth conditions and physicochemical properties of starch to ensure batch uniformity in drug manufacturing. These considerations gain particular significance when contemplating a switch from one starch source to another as an excipient or when formulating new drug preparations.

### 1.5 Carboxy Methyl Starch ( CMS )

Carboxy Methyl Starch (CMS) is a water-soluble polysaccharide that serves as a versatile additive with a growing range of applications. It stands out as a biodegradable and non-toxic product, making it increasingly popular in various industries.

Sodium Carboxy Methyl Starch, referred to as CMS, is a starch ether derivative originating from regular starch. It readily dissolves in water at room temperature, forming a colorless, transparent, and viscous liquid.

CMS finds extensive utility across diverse industrial sectors, offering unique performance characteristics and significant economic advantages as a vital chemical auxiliary. Its

applications encompass serving as a thickener, binder, and emulsifying agent in various contexts.

Applications of CMS in non-food industries include:

I. Textile Sizing and Printing Industry:

Used as warp size: CMS, owing to its excellent emulsifying properties, can be combined with various hydrophilic polymeric compounds. It exhibits strong adhesion to natural fibers and serves as an adhesive sizing material for warp sizing, commonly applied in sizing cotton yarn of small and medium sizes, linen yarn, and blended yarn.

Used as a printing thickener: High-viscosity sodium Carboxy Methyl Starch effectively replaces other printing pastes. It offers advantages such as good cold water solubility, ease of application, strong permeability, vibrant color yield, easy desizing, and cost-effectiveness.

II. Oil Well Drilling Industry:

CMS acts as an economical fluid loss control agent in water-based drilling fluids. Increasing the addition of CMS can enhance the desired viscosity without requiring biocidal treatment in typical drilling fluid operations. It forms a robust and slick filter cake, reducing friction and potentially boosting drilling rates. CMS may be less effective in the presence of high levels of magnesium and cations, and it's recommended to treat these before CMS addition. Normal dosage ranges from 0.3% to 0.5%.

III. Paper-Making Industry:

In the paper-making and dyeing sectors, CMS is valued for its moisture-retaining and fluidizing properties. CMS colloid exhibits transparency and delicacy, making it suitable as a

drying agent, wet-end additive, and sizing agent for paper production. It can be combined with PVA to form oil-resistant and water-soluble coatings.

IV. Detergent Industry:

CMS is used in detergents to replace CMC (Carboxymethyl Cellulose) due to its similar anionic characteristics. The utilization of CMS in detergent production offers significant advantages, enabling the complete substitution of CMC and a portion of polyacrylates. This replacement enhances the biodegradability of the final product.

V. Electric Welding Rods Industry:

Thanks to its high build and cohesiveness, Carboxy Methyl Starch serves as a binding element and propping agent in the electric welding rods industry.

CMS's versatile and eco-friendly properties make it a valuable asset in these industries, contributing to enhanced performance and environmental sustainability.

**Other Miscellaneous Applications:**

CMS can be used in Adhesives, paints, water treatment, Mining Industries etc.

## 1.6 Acid modification

Treating starch with acid without significantly changing the grain form produces modified starch with commercially valuable properties. This chapter will also discuss the usefulness of acid modification as a step in the production of other modified starches and the acid treatment of granular starches in liquids other than water. Acid transformation of starch occurs due to preferential acid attack on the amorphous part of the granule. Acid modification can be used as a pre-modification step in some cases or as a post-modification step in others. The use of acid-modified starch, still the dominant starch in the textile industry, has declined over the past decade. Acid-modified starch behaves like a chain.

Sizing agent to increase fiber durability and abrasion resistance during the weaving process. Acid modified starch is used in the production of gypsum board for the construction of drywall. Acid-modified wax starch has been shown to be useful in the production of corrugated cardboard.

Modified starches, also known as starch derivatives, are prepared by treating natural starch physically, enzymatically or chemically to change its properties. Modified starches are used in most starch applications, for example in food products as thickeners, stabilizers or emulsifiers; in pharmaceuticals as a disintegrant; or as an adhesive in coated paper. They are also used in many other applications.

Modified food starch packet, a type of food additive prepared by processing starch or starch granules. Starches are modified to improve their performance in various applications. Starches can be modified to increase their stability against extreme heat, acids, shear, time, cooling or freezing; change their texture; reduce or increase their viscosity; prolong or shorten gelatinization time; or to increase their viscosity.

### 1.7 Sodium starch glycolate

Sodium starch glycolate is a widely used superdisintegrant employed to facilitate the rapid disintegration and dissolution of immediate-release (IR) solid dosage forms. It is produced through the chemical modification of starch, specifically carboxymethylation to enhance hydrophilicity and cross-linking to reduce solubility. Literature reports suggest that the functionality of sodium starch glycolate can be influenced by factors such as the source of starch, particle size, the amount of sodium chloride (a by-product of the reaction), viscosity, degree of substitution, and cross-linking.

Conventional chemical analyses provide an accurate assessment of the chemical quality of the excipient, but they may not adequately characterize its physical properties. Physical

characterization of sodium starch glycolate, as per the United States Pharmacopeia (NF), reveals variations in particle size, surface area, porosity, surface morphology, and viscosity among two of the three tested sources. Automated liquid absorption testing conducted under neutral and acidic conditions demonstrates similar initial absorption rates, although the extent of liquid absorption varies among the tested degradable powders. Additionally, differences are observed in the settling volume between the digestates from the two sources. Reducing the pH of the medium leads to a decrease in both the rate and extent of liquid absorption and settling volume in all cases. Notably, smaller sieve fractions tend to exhibit a higher degree of liquid absorption and settling volume in both media.

Although variations are also noted in axial and radial disintegration force measurements of pure disintegrating compacts, there are no significant differences observed in the disintegration and dissolution of a model drug, hydrochlorothiazide, from either a soluble core or insoluble matrix when comparing multiple sources.

Starches from different plant sources, including corn, potato, rice, and tapioca (cassava), were assessed for their properties in direct compression. Rice starch stands out with its superior compatibility compared to corn, potato, and tapioca starch. Furthermore, its binding capacity remains relatively unaffected when combined with magnesium stearate. In contrast, significant reductions in the crushing strength of potato starch pellets are observed when lubricants are added. The compressibility of starch is notably influenced by the equilibrium moisture content, which, in turn, depends on the relative humidity of the storage environment. All tested starches exhibit sufficient water absorption capacity to act as disintegrants. Rice starch's decreased flowability is attributed to its finer particle size in comparison to other starches. The granulation of rice starch makes it a promising binder in tablets prepared via direct compression.

Starch and its derivatives, such as natural starch and modified starch (e.g., sodium starch glycolate), are primarily employed as disintegrants in pharmaceutical tablet formulations. They also serve as diluents, binders, and thickeners. Disintegrants are pharmaceutical excipients added to tablet formulations to aid in the rapid breakdown of tablets into smaller pieces when exposed to an aqueous environment. Enhanced tablet disintegration in aqueous media improves the solubility, absorption, and bioavailability of orally administered drugs. Other substances used as disintegrants in pharmaceutical formulations include cellulose and its derivatives (e.g., microcrystalline cellulose, croscarmellose sodium, and low-substituted hydroxypropyl cellulose), resins and their derivatives, starch derivatives, and crospovidone.

Natural starches derived from plant sources are commonly used as disintegrants in pharmaceutical tablet formulations, typically at concentrations ranging from 2 to 10% w/w. The addition of starch and other disintegrants to tablet formulations can be done intragranular (within granules), extragranular (outside granules), or as a combination of intragranular and extragranular techniques. In intragranular addition, starch is mixed with the powder and granule blend, while extragranular addition involves adding dry starch powder to the preformed granules. In the case of intragranular and extragranular supplementation, half of the starch introduced into the tablet formulation is intragranular, and the other half is extragranular. The manner in which a disintegrant is incorporated affects its disintegration efficiency, with extragranular addition generally leading to faster disintegration than intragranular addition. However, disintegrants provided in granular or granular form yield the most effective results. Other factors influencing disintegration efficiency include particle size, moisture content, and the applied compaction force.

Various disintegration mechanisms have been proposed, including swelling, capillary or wicking action, tension recovery, heat interaction, and breaking of particle-particle bonds.

Swelling is considered the primary mechanism for the disintegration of starch and its derivatives.

The main natural starches used in tablet formulations are typically derived from corn, potatoes, and wheat. However, natural starches may not possess the ideal properties for tablet formulation. For instance, natural starch has poor compaction properties and requires relatively high concentrations (10-15% w/w) to be effectively disintegrated compared to modified starch. Genetic, physical, and chemical engineering techniques have been applied to alter the granular structure of natural starches to optimize their performance as pharmaceutical excipients. Research institutions such as the Crop Research Institute of Ghana (CRIG) are using genetic engineering to develop new cassava varieties with specific starch, fiber, nutrient, and functional characteristics.

This study aimed to assess the disintegration properties of both natural starch and modified starch in Paracetamol tablet formulations. Paracetamol is chosen as a model drug due to its poor compression and flow properties, a tendency for capping and rolling, and a lack of inherent disintegration activity. The study evaluates how starch disintegrants influence the mechanical properties and drug release of Paracetamol tablets.

## 1.8 FORMULATION OF COMPRESSED TABLETS

The process of creating compressed tablets involves the preparation of granules through granulation and then compressing these granules into tablet form. These tablets are shaped by compressing a particulate solid inside a die. This is achieved by applying force using two punches: the lower punch moves up and down within the die, while the upper punch descends into the die to apply compressive force. After compression, the upper punch withdraws to allow the tablet's ejection. The formulation of tablets takes into account various key factors:

I. The specific drug substance utilized, including its chemical and physical characteristics, and the intended route of administration.

II. The selection of the appropriate manufacturing process is crucial in tablet formulation

III. Consideration is given to how the tablet will be used, whether it is meant to be swallowed whole or dissolved in water, and so on.

IV. Various types of compressed tablets exist, each with names that reflect their designated usage instructions.

## 1.9 TYPE OF TABLETS

### 1.9.1 Oral Tablets

Oral tablets are designed to be ingested with water and should readily disintegrate in the gastrointestinal system after swallowing. Examples of drugs delivered in this form include paracetamol, aspirin, and chloroquine phosphates.

### 1.9.2 Lozenges

Lozenges are compressed tablets, typically with a diameter of at least 18mm, that do not contain a disintegrant. They are meant to be sucked on and dissolved in the mouth. There are two main types of lozenges, depending on their intended purpose. The first type produces a local effect in the mouth or throat and often contains an antiseptic or antibiotic. These lozenges need to be palatable and dissolve slowly. The second type produces a systemic effect and may contain vitamin supplements.

### 1.9.3 Buccal Tablets or Sublingual Tablets

Buccal tablets are small, flat oral tablets designed for buccal administration. They are placed in the buccal pouch to dissolve or disintegrate slowly. These tablets are formulated and

compressed with enough pressure to create a hard tablet. Glycerin is an example of such a tablet.

### 1.9.4 Implant Tablets

Implant tablets consist of drug substances only, without excipients. They are typically very small pellets, about 2-3mm in diameter, which are surgically inserted into body tissue. These pellets are absorbed slowly over a period of months.

### 1.9.5 Effervescent Tablets

Effervescent tablets are soluble tablets that contain sodium bicarbonate and an organic acid such as tartaric or citric acid. When they come into contact with water, these additives react, releasing carbon dioxide, which acts as a disintegrant and creates effervescence.

### 1.9.6 Controlled Release Tablets

Controlled release tablets are formulated to release the drug slowly over an extended period.

### 1.9.7 Solution Tablets

Solution tablets are intended to be used for preparing solutions or imparting specific characteristics to solutions before administration. They should be clearly labeled "Not to be swallowed." Examples include Halazone tablets for solution and potassium permanganate tablets for solution.

### 1.9.8 Chewable Tablets

Chewable tablets are designed for patients who have difficulty swallowing tablets whole or for children who have not yet learned to take tablets with water. Mannitol is commonly used as a chewable base diluent due to its pleasant cooling sensation in the mouth, which can help mask the taste of certain medications.

## 1.10 GRANULATION PROCESS

Granulation is a crucial process in the production of pharmaceutical dosage forms, particularly tablets and capsules. During this process, small particles are transformed into larger agglomerates known as granules. The granulation typically begins after initial dry mixing of the necessary powder ingredients, including the active pharmaceutical ingredient (API), to ensure even distribution of each component in the powder mixture. These granules, which typically fall in the size range of 0.2-4.0 mm, serve as intermediaries and can be packed as a dosage form or mixed with other excipients before tablet compaction or capsule filling.

The production of granules serves several purposes, such as enhancing the uniformity of the API in the final product, increasing the blend's density for efficient storage and shipment, aiding in metering or volumetric dispensing, reducing dust during the granulation process to minimize toxic exposure and process-related hazards, and improving the product's appearance. Ideal granules should have a spherical shape to facilitate flow, a narrow particle size distribution for content uniformity and volumetric dispensing, sufficient fines to fill void spaces for better compaction, and adequate moisture and hardness to prevent breakage and dust formation during processing.

The properties of granules acquired after the granulation process depend on factors such as particle size of the drug and excipients, the type, concentration, and volume of binders and/or solvents, granulation time, the type of granulator, and drying rate (temperature and time). Various mechanisms are involved in the formation of agglomerated granules, including solid

bridges, sintering, chemical reactions, crystallization, deposition of colloidal particles, and the use of high-viscosity binders. The mechanisms involved include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage.

The granulation process can be categorized into three main types:

I. Dry granulation

II. Wet granulation

III. Direct compression or slugging

These categories depend on the methods used to facilitate the agglomeration of powder particles. Dry granulation employs mechanical compression or compaction to agglomerate dry powder particles, while wet granulation uses a granulation liquid (binder/solvent) to create a wet mass through adhesion. Although wet granulation involves multiple unit processes, it is the most widely used method, despite its complexity, time consumption, and expense, which require considerable space and multiple equipment.

### 1.10.1 Granulation by Direct Compression

This method is also known as the "slugging" method. It involves blending the active ingredient with other excipients and compressing them into "slugs" or "cakes" under controlled humidity and pressure. These slugs are then broken down into appropriately sized granules through screening or milling, which are subsequently compressed into tablets. This method is suitable for materials like aspirin, ascorbic acid, and certain antacids.

## 1.11 Compression of Granules

The granules obtained from the aforementioned methods can be compressed into tablets using the appropriate force and weight. A tableting machine consists mainly of a hopper, feed shoe, punches (upper and lower), and a die cavity. The punch, under regulated pressure, presses the granules into compacts, which are then ejected.

In the pharmaceutical industry, there are primarily two types of tableting machines:

I. Single punch machine

II. Multiple punch machine

### 1.11.1 Single Punch Machine

Single punch machines are manually operated and consist of a single punch and die. They are primarily used for experimental runs in tablet manufacturing.

### 1.11.2 Multiple Punch Machine

Multiple punch machines, often of the rotary type, are used for large-scale tablet production. They can produce approximately 1,500 tablets per minute and are commonly found in pharmaceutical industries. These machines offer the advantage of producing tablets with more uniform size and weight.

## 1.12 RELEVANCE OF THE STUDY

1. To develop starches that could be used as an alternatives to sodium starch glycolate as a super disintegrant

2. To develop fast orally disintegrating tablet such as risperidone

### 1.12.1 OBJECTIVES OF THE STUDY

Modified starches enhances thermoplasticity, solubility and flow properties. Modified starches have shown excellent potentials and are, thus, incorporated in several pharmaceutical formulations either as binder or disintegrant. Various researches has been carried out on the effect of modified starches in tablets formulations. Hence the objective of this study are;

1. To evaluate and compare the disintegrant activities of carboxymethylated and acid hydrolyzed bitter yam starches in paracetamol tablet formulation

2. To determine the flow properties of the granules and post compression parameters of the tablets of paracetamol

3. Investigate the dissolution profiles of the formulated acid hydrolyzed and carboxymethylated paracetamol

4. To compare the disintegrant activities of the modified bitter yam starches with sodium starch glycolate as the standard.

# CHAPTER TWO

## MATERIALS AND METHODS

### 2.1 MATERIALS

Paracetamol powder was gotten from a shop at main gate university of Benin, Benin City, Nigeria, hydroxypropyl methylcellulose (HPMC) (QualikemsPvt Ltd, Delhi, India), sodium hydroxide (CDH Ltd, New Delhi, India), sodium starch glycolate, α-lactose monohydrate, magnesium stearate and talc (BDH Chemicals Ltd, Poole, England), monochloroacetic, isopropyl alcohol, 6% hydrochloride acid, glacial acetic acid. Native African bitter yam (Dioscorea Dumetorum) was purchased from a local farmer in Benin City, Edo State, Nigeria.

### 2.1 EQUIPMENT

I. Laboratory test sieves Gallen Kamp, England. 710um, 1.70mm;

II. Manesty single punch tableting machine. Type F3 Manesty Machines Limited, Liverpool, Englang

III. Manesty Tablet Disintegrating unit L24, 9LQ, Manesty Machines LImited, Liverpool, England.

IV. Electronic balance

V. Tablet hardness tester

VI. Hot air oven, Kotterman, Germany

VII. Tablet Friabilator

## 2.3 Extraction of bitter yam starch

To process the native African bitter yam, a full sack bag of yams was initially peeled and thoroughly washed to eliminate any foreign materials. Once peeled and cleaned, the yams were then milled into a paste using a milling machine. This paste was mixed with an adequate amount of water and subsequently strained through a muslin cloth to separate the yam chaff. Additional water was introduced to the resulting paste-like starch, allowing it to settle for approximately six hours. Following this settling period, the clear supernatant fluid was decanted, while the sedimented starch was collected. The collected starch was spread out to dry under sunlight for a duration of two days. Once dried, the starch lumps were further processed into a fine powder using a blender.

## 2.4 Acid-modification of extracted starch

A quantity of 250 grams of the extracted native African bitter yam starch powder was subjected to hydrolysis by immersing it in a solution consisting of 500 ml of 6% HCl at a temperature of 23 ± 1.00°C. This hydrolysis process was allowed to proceed for a duration of 8 days, and no stirring was involved in this phase [Atichokudomchai et al., 2003]. Following the hydrolysis period, the suspension was neutralized using a 10% w/v NaOH solution. Subsequently, the starch slurry underwent a series of five washes with distilled water. The resulting starch was then subjected to drying in a hot air oven set at 40°C for a period of 24 hours. Once completely dried, the starch was further processed into a powdered form using a laboratory ball mill and sifted through a 125 μm mesh sieve.

## 2.5 Carboxymethylation Of Starch

Approximately fifty grams of native African bitter yam starch were dissolved in 150ml of isopropyl alcohol. Following this, approximately 50ml of an aqueous sodium hydroxide (NaOH) solution was introduced, and the mixture was stirred at a temperature of 30 degrees Celsius for a duration of 10 minutes. Subsequently, around 25ml of monochloroacetic acid solution was added and continuous stirring was maintained for a period of 6 hours. The pH of

the solution was then adjusted to 5 (acidic) by the gradual addition of 50% glacial acetic acid. The carboxymethylated starch was subsequently subjected to washing with 80% ethanol and underwent a drying process at a temperature of 50°C for 6 hours. The obtained starch was sifted through a 150-mesh sieve and stored in an airtight container, away from light.

**Table:1** Formula of prepared paracetamol powder mixes and tablets

| **Ingredients** | **Batches** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **I** | **J** | **K** |
| Paracetamol (mg) | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Sodium starch glycolate (%w/w) (mg) | 30 (5%) | 45 (7.5 %) | 60 (10 %) | - | - | - | - | - | - | - | - |
| Carboxylated bitter yam starch (%w/w) (mg) | - | - | - | 30 (5%) | 45 (7.5 %) | 60 (10 %) | - | - | - | - | - |
| Acid-hydrolyzed bitter yam starch (%w/w) (mg) | - | - | - | - | - | - | 30 (5%) | 45 (7.5 %) | 60 (10 %) | - | - |
| Native bitter yam starch (%w/w) (mg) | - | - | - | - | - | - | - | - | - | 30 (5%) | 60 (10 %) |
| Hydroxylpropyl methyl cellulose (HPMC) (mg) | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Lactose (mg) | 49 | 34 | 19 | 49 | 34 | 19 | 49 | 34 | 19 | 49 | 19 |
| Talc (mg) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate (mg) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |

## 2.6 Preparation of granules and tablets

Eleven batches of paracetamol granules and tablets were produced using the formula described in Table 1. The required amounts of ingredients for each batch were weighed and passed through a 710mm sieve. Paracetamol and lactose powders were combined through dry mixing in a mixer for 5 minutes. Subsequently, the other ingredients, except for the lubricant and glidant (which were pre-mixed separately), were added to the powder mix in specified proportions and thoroughly blended. The resulting powder blend was processed into slugs using a robust tableting machine from Kilian and Co, GmbH, located in Köln, Germany. These slugs were then further reduced to granules with a mortar and pestle. Magnesium stearate and talc, both of which had been screened, were incrementally integrated into the granules and mixed meticulously. Prior to compression into tablets using the direct compression method, the granules underwent compatibility studies between the drug and excipients, along with assessments of various flow properties. The produced tablets were sealed in an airtight container for subsequent evaluation.

## 2.7 Pre-compression (granule flow) evaluations

### 2.7.1 Bulk Densities

To determine the bulk density, 30 grams of the granules were gently poured into a measuring cylinder, and the volume occupied by the granules was measured.

### 2.7.2 Tapped Densities

For tapped density, the measuring cylinder containing the 30 grams of granules was tapped 100 times on a wooden platform. The volume after tapping was recorded for calculating the tapped density.

### 2.7.3 Carr's Index

The Carr's index was calculated by finding the difference between the tapped and bulk density of the granules, dividing it by the tapped density, and expressing the result as a percentage.

### 2.7.4 Hausner's Ratio

Hausner's Ratio was determined by calculating the ratio of the tapped density to the bulk density of the granules.

### 2.7.5 Angle of Repose

The angle of repose was measured using the fixed funnel and free-standing cone method. A glass funnel was clamped 2.7 cm above a flat horizontal surface. Granules were poured through the funnel until the heap formed by the granules touched the tip of the funnel. The height of the heap and the diameter of the cone base were measured, and the angle of repose was calculated using Equation 1.

$\theta = \tan^{-1}(h/r)$ .... (1) Where h is the height of the heap of granules and r is the radius of the circular base

### 2.7.6 Flow Rate

The flow rate was determined using the funnel method. A glass funnel was clamped at a specific distance from a horizontal surface, and about twenty-five grams of granules were poured into the funnel with the orifice initially blocked by a glass sheet. The glass sheet was then removed, allowing the granules to fall freely under gravity. The time taken for all the granules to pass through the orifice was recorded, and this process was repeated in triplicate to calculate the mean values.

## 2.8 Post compression (tablet) evaluations

The following tests were conducted on the compressed tablets in accordance with established procedures, as outlined in the British Pharmacopoeia (2003):

### 2.8.1 Weight Uniformity

The weight of 20 tablets from each batch was individually determined using an electronic balance (College B154, Mettler Toledo, Switzerland). The mean weight and standard deviation were calculated**.**

### 2.8.2 Friability

Four pre-weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany), which rotated at 25 rpm. After 4 minutes, the tablets were removed, de-dusted, and reweighed. The percentage loss in weight was calculated, and this process was performed in triplicate to determine the mean and standard deviation.

### 2.8.3 Crushing Strength

The crushing strength of ten individual tablets per batch was measured using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India) through diametric compression. The mean and standard deviation values were computed.

### 2.8.4 Disintegration Time

The time required for six tablets from each batch to disintegrate in distilled water at 37 ± 0.5 °C was determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean disintegration time and standard deviation were calculated.

### 2.8.5 Wetting Time

A tablet with a known weight was placed on cotton wool that had been soaked, and a small amount of amaranth powder was placed on the tablet's upper surface. The wetting time was defined as the time it took for a red color to appear on the tablet's upper surface. This process was repeated three times, and the average wetting time and standard deviations were calculated.

**2.8.6 Dissolution Studies**

The dissolution profiles of the paracetamol tablets were investigated using a USP dissolution test apparatus (Type II) for the various tablet batches (Labindia-DS 8000, Mumbai, India). The dissolution medium consisted of 900 ml of 0.1N hydrochloric acid solution, maintained at 37 ± 0.5°C, with a paddle revolution rate of 50 rpm. At specific time intervals (5 min, 10 min, 20 min, 30 min, 45 min, and 60 min) within a 1-hour period, a 5 ml volume of the dissolution medium was withdrawn, and an equivalent volume of fresh dissolution medium (0.1N HCl) at the same temperature was added. The samples withdrawn were filtered and suitably diluted with 0.1N hydrochloric solution. The absorbances of these solutions were measured at the λmax of 297 nm using a spectrophotometer (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug released at each time interval were determined by reference to a standard calibration plot obtained from pure drug samples.

# CHAPTER THREE

## RESULTS AND DISCUSSION

### 3.1 Pre-compression parameters

The results pertaining to the granule flow properties for all the batches are summarized in Table 2. These include measurements of bulk and tapped density, Carr's index, Hausner's ratio, and flow rates. It's evident that as the quantity of disintegrants increased in all the batches, there was a decrease in the degree of compactness in the granules. Furthermore, the flow rate of the granules exhibited variability, which correspondingly increased with the higher quantities of disintegrants. Notably, the angle of repose values fell within the range of 27.02 to 32.15, signifying excellent flow properties of the granules.

Bulk properties encompass characteristics related to the density, consolidation, and flow of a powdered mass. These properties also shed light on the ease with which the starch powders can be compressed. Smaller particle sizes tend to resist free flow due to adhesion between the particles (as discussed by Eraga et al., 2014). The results suggest that the bitter yam starches under investigation possess satisfactory bulking properties for pharmaceutical applications, primarily owing to their favorable flow properties.

Carr's index and Hausner ratio both provide insights into the compressibility of the starch powder, while the angle of repose reflects the flow properties of powders and their interparticle resistance to movement. In general, the bitter yam starches demonstrated commendable flow properties, as indicated by Carr's index, Hausner ratio, and the angle of repose values.

**Table 2:** Pre-compression properties of the different batches of paracetamol granules

| Batch | Weight (mg) | Flow rate (sec) | Angle of repose | Bulk volume | Tap volume | Bulk density | Tap density | Hausner Ratio | Carr Index |
|---|---|---|---|---|---|---|---|---|---|
| A | 23.83 | 23.11 | 28.72 | 35.00 | 27.00 | 0.68 | 0.88 | 1.29 | 22.73 |
| B | 23.96 | 28.55 | 29.25 | 37.00 | 28.00 | 0.65 | 0.86 | 1.32 | 24.42 |
| C | 24.88 | 31.00 | 31.45 | 37.00 | 28.00 | 0.67 | 0.89 | 1.33 | 24.72 |
| D | 24.74 | 25.27 | 30.74 | 37.00 | 28.00 | 0.67 | 0.88 | 1.33 | 23.86 |
| E | 26.12 | 27.11 | 30.87 | 39.00 | 31.00 | 0.67 | 0.84 | 1.25 | 20.24 |
| F | 24 | 20.93 | 27.45 | 36.00 | 27.00 | 0.67 | 0.89 | 1.33 | 24.72 |
| G | 23.99 | 30.27 | 31.43 | 35.00 | 27.00 | 0.69 | 0.89 | 1.29 | 22.47 |
| H | 24.86 | 29.11 | 32.15 | 36.00 | 27.00 | 0.69 | 0.92 | 1.33 | 25.00 |
| I | 22.79 | 26.58 | 31.01 | 34.00 | 26.00 | 0.67 | 0.88 | 1.33 | 23.86 |
| J | 22.18 | 14.00 | 27.02 | 32.00 | 26.00 | 0.69 | 0.85 | 1.23 | 18.82 |
| K | 25.24 | 26.1 | 29.91 | 35.00 | 28.00 | 0.72 | 0.90 | 1.25 | 20.00 |

## 3.2 Post-compression parameters

### 3.2.1 Weight Uniformity

The purpose of this standard is to ensure consistency in drug content among the tablets within a sample. In Table 3, you can find the results of the tablet weight uniformity test. All the tablets produced, utilizing various concentrations of disintegrants, adhere to the specifications outlined in the British Pharmacopoeia (B.P.).

The weight measurements of the paracetamol tablets fell within the range of 580 - 620 mg, and there were no significant differences in tablet weights, both within and across batches. These values align with the requirements set by the British Pharmacopoeia, which stipulates that no more than two individual tablet weights should deviate from the average weight by more than ±5%, and none should deviate by more than ±10% [British Pharmacopoeia Vol. III].

The results reveal that only four tablets from three different batches displayed variations in tablet weights exceeding ±5% of the calculated mean weight, but these differences remained below the stipulated ±10%.

**Table 3:** Weight Uniformity

| **Batch** | **Average weight of 20 tablets (mg)** | **Mean weight** ±5% | **No. of tablets that deviated** |
|---|---|---|---|
| A | 598.3 | 569-628 | 1 |
| B | 597.7 | 568-628 | 1 |
| C | 600.2 | 570-630 | 0 |
| D | 595.5 | 566-625 | 0 |
| E | 596.2 | 566-626 | 0 |
| F | 591.2 | 562-621 | 0 |
| G | 595.6 | 566-625 | 0 |
| H | 601.5 | 570-630 | 0 |
| I | 594.6 | 564-624 | 0 |
| J | 596.7 | 566-626 | 2 |
| K | 602.8 | 570-630 | 0 |

### 3.2.2 Friability and crushing strength

Tablet hardness is an essential surface property that assesses a tablet's strength and its capacity to endure various stresses without deformation. Tablets need to possess a balance between robust tensile strength to withstand pressures during handling, film-coating, and packaging, while also being sufficiently weak to facilitate drug release upon administration. Typically, as the starch concentration increased, the tensile strength of the tablets decreased.

**Table 4:** Fraiability and crushing strength

| Batch | Friability (%) | Crushing strength (kp) |
|---|---|---|
| A | 1.15 | 8.5 |
| B | 0.51 | 7.45 |
| C | 0.5 | 6.95 |
| D | 0.71 | 9.1 |
| E | 0.42 | 7.68 |
| F | 0.17 | 7.2 |
| G | 2.78 | 8.95 |
| H | 0.17 | 8.83 |
| I | 0.34 | 8.15 |
| J | 0.53 | 8.3 |
| K | 0.70 | 7.73 |

**Disintegration and wetting times**

These parameters are critical for the evaluation of fast-disintegrating tablets, as they pertain to the tablet's mechanical strength. Most of the tablet batches yielded acceptable friability values below 1.0%, with the exception of batch A and G. The slightly higher values in these batches could be attributed to the low compressibility of the tableting machine or the relatively low disintegrant content in the granules. According to the British Pharmacopoeia, a loss in weight ranging from 0.8% to 1.0% during the friability test, without exhibiting issues like capping, lamination, or breaking, is considered acceptable.

Friability is closely related to the tablet's crushing strength or hardness, and while it is not an official test, it provides insights into a tablet's susceptibility to powdering, chipping, or fragmenting during transportation and handling [WHO Document QAS/11.414 FINAL S.3.1 Tablet Friability]. The average crushing strength values of the tablets fell within the range of 6.9 to 9.1 kp, with the highest values observed in Batch D tablets. These hardness values were deemed acceptable, as a crushing strength exceeding 6 kp is considered satisfactory for tablets.

Disintegration and wetting times are crucial because they assess how effectively the compressed tablet can break apart when it comes into contact with bodily fluids. According to the British Pharmacopoeia (1993), uncoated oral tablets should disintegrate within a maximum time limit of 15 minutes.

**Table 5:** Disintegration time and Wetting time

| Batch | DISINTEGRATION TIME (sec) | WETTING TIME (sec) |
|---|---|---|
| A | 136 | 63 |
| B | 126 | 56 |
| C | 44 | 50 |
| D | 145 | 45 |
| E | 86 | 40 |
| F | 66 | 36 |
| G | 144 | 60 |
| H | 94 | 52 |
| I | 63 | 42 |
| J | 150 | 68 |
| K | 91 | 51 |

All prepared tablets disintegrated within 15 minutes (Table 3), as specified in the British Pharmacopoeia for uncoated tablets (2009). Tablets prepared from bitter sweet potato starch originating from Africa showed the longest shelf life. Decomposition time decreases with increasing decomposition concentration. As rapidly disintegrating tablets, only tablets C, F and I have excellent disintegration properties when disintegrating within 1-minute, European Pharmacopoeia 3rd edition (2001). The tablet wetting time is directly related to the liquid absorption rate of the tablet. The rate of absorption of this liquid is influenced by the type of disintegrant and the mode of action of the disintegrant, i.e. whether the disintegrant causes the tablet to disintegrate upon contact with liquid by capillary effect (suction) or swelling or not. In general, the shorter the wetting time of the tablet, the shorter the disintegration time. The wetting time of tablets is correlated with their disintegration time, as the tablets with the shortest wetting time also have the shortest disintegration time.

**Dissolution studies**

Disintegration, i.e., the fragmentation of solid dosage forms into small, discrete particles, is an important prerequisite for drug dissolution. The rapid rate of disintegration accelerates tablet dissolution by exposing the large surface area of the solid particles to the dissolution medium. The drug release characteristics of the Paracetamol tablet formulations are shown in Figure 3. All tablets released drug rapidly, with more than 80% of the drug released within 30 minutes. Solubility depends on wetting and decomposition time; they are therefore essential for the dissolution properties of quick release tablets. There is a direct relationship between wetting time, disintegration time and drug release properties of tablets.

Block F tablets have the shortest wetting and disintegration time giving the highest drug release efficiency in 5 minutes, while block J tablets have the longest wetting and disintegration time giving the highest drug release efficiency in 5 minutes. minute. The slow release of this batch J pill may be due to the slow swelling of the primary granules of natural

millet starch due to poor water absorption by the starch granules leading to slow release of the drug. This observation is consistent with a study involving super degradants that operate primarily through swelling, in which it was found that the poor water absorption capacity of the swollen decomposers led to Longer wetting and decomposition times.

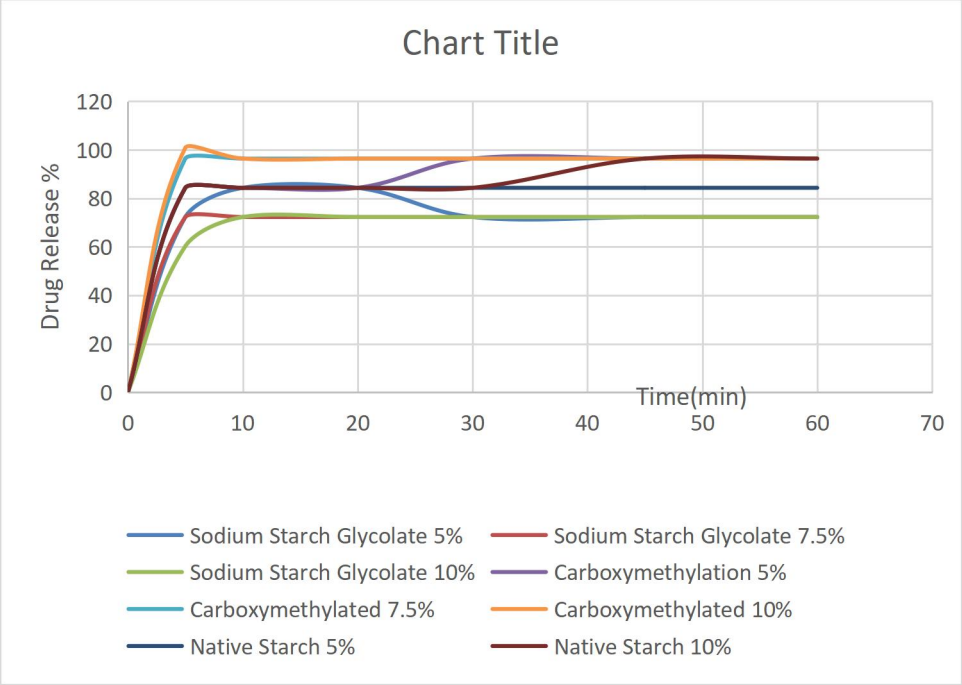


**Fig 1:** Dissolution graph among native starch, sodium starch glycolate and carboxymethylated bitter yam starch

From the above dissolution profile, the 10% carboxymethylated starch has the highest peak of drug release of 100% within the first five minutes of dissolution and the rate of drug release dropped to 96.39% after 10 minutes and later to 84.34% after 45 minutes. While the 7.5% carboxymethylated starch showed a drug release of 96.39% in the first five minutes. Sodium starch glycolate had a drug release of 72.29% within the first five minutes of dissolution.

The carboxymethylated starch having an extremely rapid initial drug release of 100.8% within the first five minutes might be attributed to its high water solubility profile or disintegration properties. Hence it can be considered as a super disintegrants in the formulations of fast orally disintegrating tablets such as risperidone. However, the subsequent drop to 96.39% after 45 minutes suggests that there might be some control over the drug release with time. On the other hand, sodium starch glycolate had a more moderate initial drug release of 72.29% which indicates that it has a slower dissolution rate compared to carboxymethylated starch.

This implies that the carboxymethylated starch has a high super-disintegrants activities when compared with sodium starch glycolate in the formulations of paracetamol tablets.

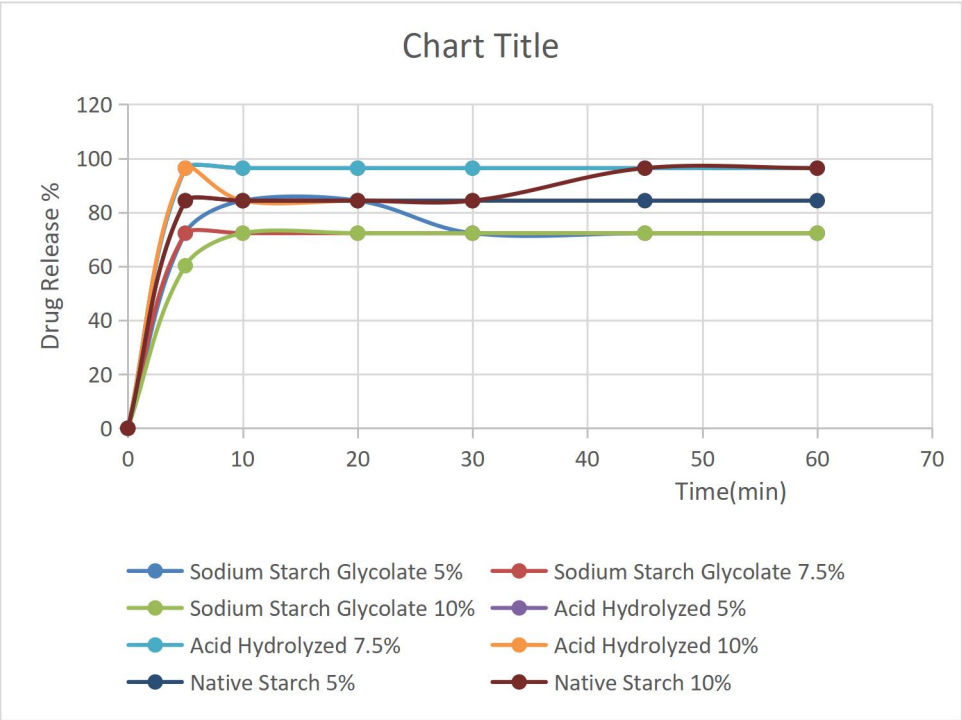


**Fig 2:** Dissolution graph among native, sodium starch glycolate and acid modified bitter yam starch

The dissolution profile revealed distinct characteristics among the different starch types used in the formulations. The tablet containing 10% acid-hydrolyzed starch exhibited the highest initial drug release, reaching 96.39% within the first five minutes. Subsequently, the rate of drug release decreased to 84.34% after 10 minutes and remained at 84.34% over the next 60 minutes. This exceptionally rapid initial drug release can be attributed to the high water solubility and disintegration properties of acid-hydrolyzed starch. This starch type can be considered a potent super-disintegrant in the formulation of fast orally disintegrating tablets. The gradual decrease in drug release rate after the initial peak suggests a degree of control over drug release with time.

In contrast, sodium starch glycolate displayed a more moderate initial drug release of 72.29%, indicating a slower dissolution rate compared to carboxymethylated starch. Therefore, the acid-hydrolyzed starch exhibits superior super-disintegrant properties when compared to sodium starch glycolate in the formulation of paracetamol tablets.

# CHAPTER FOUR

## CONCLUSION

The study revealed that both acid-modified bitter yam starch and carboxymethylated starch substantially reduced disintegration time and improved the dissolution profile when compared to native bitter yam starch in paracetamol tablets. This indicates that acid modification enhances the disintegration and dissolution properties of starch.

Moreover, acid-modified bitter yam starch and carboxymethylated starch can serve as cost-effective alternative disintegrants to sodium starch glycolate due to their similar disintegration times and dissolution profiles. This research also reaffirmed the direct correlation between wetting times and disintegration times in compressed tablets.

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# APPENDIX

## APPENDIX 1

### Standard Calibration Curve Values for Paracetamol

| Concentration(ug/ml) | Absorbance |
|---|---|
| 0.1 | 0.007 |
| 0.05 | 0.007 |
| 0.025 | 0.006 |
| 0.0125 | 0.004 |
| 0.00625 | 0.003 |
| 0.003125 | 0.002 |
| 0.0015625 | 0.001 |
| 0.00078125 | 0.001 |
| 0.000390625 | 0.001 |
| 0.0001953125 | 0.001 |

## APPENDIX 2

Standard calibration curve for paracetamol