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Oryza sativa Starch
Co-Processed with

Dioscorea dumentorum Starch in Directly Compressed Paracetamol Tablet
Formulations

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EVALUATION OF THE DISINTEGRANT PROPERTIES OF SILICIFIED *ORYZA SATIVA* STARCH CO-PROCESSED WITH *DIOSCOREA DUMENTORUM* STARCH IN DIRECTLY COMPRESSED PARACETAMOL TABLET FORMULATIONS

ABSTRACT

Starch is a readily available excipient which finds application in the pharmaceutical industry as binders, diluents and disintegrants. The use of starch is however limited by its poor flow characteristics. Co-processing exploits the desirable attributes of excipients, while masking the undesirable properties. Co-processed starch, thus presents great potential for use in formulation of directly compressed tablets which require materials with strong inherent cohesive and free flowing properties. In this study, *Dioscorea dumentorum* (Family: *Dioscoreaceae*) Starch (DdS) is co-processed with silicified rice starch (SRS) obtained from *Oryza sativa*; Family: *Poaceae* was incorporated as a disintegrant in directly compressed paracetamol tablet formulations in comparison with silicified rice starch and Avicel® as the official standard.

Rice and DdS were extracted following standard procedures. The rice starch was silicified using colloidal silicon dioxide and co-processed with DdS in the ratio SRS:DdS (1:2). The DdS, SRS and SRS:DdS (1:2) were characterized using FTIR, particle size, angle of repose, bulk and tapped densities, Hausner ratio and Carr's index. Paracetamol powder was directly compressed into tablets incorporating the co-processed excipient (SRS:DdS; 1:2) as disintegrants alongside Avicel®, SRS and DdS at varying concentrations (10% w/w, 15% w/w, 20% w/w, 25% w/w). The properties of the tablets were evaluated using friability, crushing strength and disintegration as the assessment parameters. Measurements were made in triplicates and the results were statistically analyzed.

The yield of the starches was 41% w/w and 39% w/w for rice starch and DdS respectively. Silicifying the rice starch markedly improved the flow of the starch with a change of Carr's index and Hausner ratio from 16.7 and 1.32 to 2.33 and 1.02 respectively. Tablets containing Avicel® had better crushing strength and friability values than those containing SRS:

DdS at all disintegrant concentrations. The disintegration times for Avicel® and SRS: DdS compared favourably at all concentrations of disintegrant and at 15% w/w disintegrant, SRS: DdS showed better disintegrant properties than Avicel®.

Key words: Disintegrant, Silicification, Co-processing, *Dioscorea dumentorum* starch, *Oryza sativa* starch

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

A drug is a substance or mixture of substances intended for use in diagnosis, mitigation, treatment, cure, or prevention of diseases in both man and animals. Drug substances (i.e. active pharmaceutical ingredients) are usually administered as part of a formulation together with one or more non-medicinal which serves various specific functions in the formulation. These non-medicinal agents are referred to as excipients and they confer uniqueness to pharmaceutical drug products, giving rise to different means of administration of drugs, referred to as dosage forms (Nishath *et al*, 2011).

A pharmaceutical dosage form is therefore a pharmaceutical drug product containing the active pharmaceutical ingredient and excipients for the intention of administration to the patient. In the design and formulation of a pharmaceutical dosage form, the physical, chemical and biological characteristics of all the pharmaceutical ingredients must be put into consideration. This is to ensure that the final drug product is of the right quality with respect to its potency and purity.

1.2. IMPORTANCE OF DOSAGE FORMS

a) To provide a mechanism for the safe, convenient and effective administration of drugs. As a result of the potent nature of some drugs and the low doses required to produce therapeutic effect, there is the problem of obtaining accurate doses without the formulation of drugs into dosage forms. For drugs like digoxin and nitroglycerine, with

drug contents of 0.125mg and 0.3mg respectively, it is almost impossible to obtain accurate doses all the time during the duration of therapy if a dosage form is not formulated.

b) Protection of the drug substances from environmental influences such as oxygen and humidity through specialized dosage forms e.g. coated tablets.
c) Protection of drug substances from the destructive effects of gastrointestinal juices as in enteric coated tablets.
d) Masking the bitter, offensive or unpleasant tastes or odors of drug substances through the formulation of flavored and sweetened drug products.
e) Provision of liquid preparations of drug substances in form of solutions or suspensions.
f) Provision of a rate-controlled delivery of drug substances.
g) Provision of a means of inserting drugs into body orifices (rectal and vaginal suppositories).
h) Provision of optimal drug action through inhalation and topical administration of drugs as in inhalants, ointments, transdermal patches, ophthalmic preparations, ear and nasal preparations.

1.3. SOLID DOSAGE FORMS

Solid dosage forms constitute the largest percentage of dosage forms employed clinically in drug delivery (Jones, 2008). Drugs presented in solid dosage forms are usually administered orally and in their dry state (Kalyan Babu *et al*. 2017). Examples of solid dosage forms include: powders, granules, capsules, etc.

1.4. TABLETS

Tablets are hard solid dosage forms containing the active pharmaceutical ingredient (API) and appropriate excipients. Tablets are formulated in different weights, shapes, sizes, hardness and thickness. In order to perform their pharmacotherapeutic uses, there is a need for tablets to rupture or breakdown and dissolve to release the API (Adedokun and Itiola, 2013). These characteristics and other unique qualities are conferred on the tablet by the types of excipients added in the formualation of the tablet.

1.4.1. Types of Tablets

The types of tablets available include: compressed tablets, multiple compressed tablets, film coated tablets, sugar coated tablets, gelatin coated tablets, enteric coated tablets, chewable tablets, effervescent tablets, buccal and sublingual tablets, and immediate release tablets (Allen and Ansel, 2014).

a) Compressed Tablets

Compressed tablets constitute the most commonly prescribed and administered tablets in clinical use. These tablets consist of API and excipients mechanically compacted into dosage forms using a punch and die system. They are formulated to produce quick disintegration of the compact and thus effect rapid release of the medicament from the tablet. The rate of disintegration and subsequent release of medicament from compression tablets depend on the nature and types of tablet excipients employed in the formulation of the tablet. Addition of appropriate disintegrants for example enhances the disintegration of the tablets (Allen and Ansel, 2014).

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1.4.2. Properties of Tablets

a. Tablets should be physically and chemically stable to maintain the integrity of the tablet over its shelf life.
b. The tablet should have an elegant appearance, free from cracks, discoloration and chips.
c. The active ingredient should be released in a controlled and reproducible manner.
d. Tablets should be mechanically stable to withstand the stress of handling.
e. Tablets should contain the correct amount of active ingredient.

1.4.3. Advantages of Tablets

a) Tablets are convenient to use, requiring no special skill to administer.
b) Tablets are relatively cheap compared to other dosage forms.
c) Tablets can be produced to contain more than one medicament.
d) Tablets are less prone to physical, chemical and microbiological degradation.
e) Tablets provide a means of masking objectionable taste and odour of medicaments.
f) Identification of tablets is made easier by imprints engraved on tablets.

1.4.4. Disadvantages of Tablets.

a) Tablets are sometimes difficult to swallow, especially for children and the elderly
b) They cannot be administered to unconscious patients
c) There is slow absorption of medicaments in tablets relative to other dosage forms
d) Low bioavailability due to first pass metabolism.

1.5. MANUFACTURE OF TABLETS

The manufacture of tablets involves a number of unit processes in which the starting materials used in the manufacture undergo a number of physical changes until the final dosage form is produced. A number of methods are employed in the manufacture of tablets. The methods include:

a. Wet Granulation
b. Dry Granulation
c. Direct Compression

The choice of the method of manufacturing tablets is influenced by factors such as: compression properties of the therapeutic ingredients, particle size of the therapeutic agent and excipients and the chemical stability of the therapeutic agent and excipients during the process.

1.5.1. Direct Compression

The processes involved in direct compression of tablets includes: premilling of the individual pharmaceutical ingredients, mixing of the active ingredients with the excipients and compression of mixed ingredients into tablets. In direct compression, the powdered materials are mixed together and compressed directly. This method of tablet manufacture is used for chemicals which have strong inherent cohesive and free-flowing properties which facilitate the compaction without the need for granulation (Chowdary and Ramya, 2013). For active ingredients that lack cohesive and free flowing properties, there is need to add excipients to cater for these properties and make direct compression

possible. Some of these excipients include fillers (e.g. microcrystalline cellulose, mannitol), disintegrants (e.g. sodium carboxymethyl starch, sodium starch glycolate), lubricants (e.g. magnesium stearate, polyethylene glycol) and glidants (e.g. fumed silicon dioxide, talc). Direct compression of tablets is a preferred method for manufacture of heat-sensitive or moisture sensitive materials.

1.6. EXCIPIENTS IN TABLET MANUFACTURE

Pharmaceutical formulations are seldom manufactured in isolation. The materials which are added to active pharmaceutical ingredients to aid formulation are called excipients, adjuvants or formulation additives. Excipients are defined according to The International Pharmaceutical Excipients Council (IPEC) as "substances, other than the active drug substance of finished dosage form, which have been evaluated for safety and are included in a drug delivery system during its manufacture to protect, support, enhance stability, enhance bioavailability, enhance patient acceptability, assist in product identification or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" (Apeji *et al*, 2011).

Excipients play very key roles in tableting technology. They play a critical role in processing, safety, stability, and performance of tablets (Apeji *et al*, 2013). The choice of excipients to be employed in tablet manufacture depends on the process involved. They can be categorized as excipients that aid compression (diluents, binders, lubricants and glidants) and those that aid bioavailability (disintegrants).

1.6.1 Diluents

Diluents (also known as fillers) are added to tablets to increase the mass of the tablet, especially for tablets with low concentration of therapeutic ingredient. Addition of diluents to tablets ensures the manufacture of reasonably sized tablets which render the manufacturing process reliable and reproducible. Ideal diluents should exhibit good compression properties and should be inexpensive. Examples of diluents include: anhydrous lactose, lactose monohydrate, spray-dried lactose, starch, microcrystalline cellulose, dicalcium phosphate, mannitol, etc (Allen and Ansel, 2014).

1.6.2. Binders

These are majorly polymeric components employed in the manufacture of tablets through granulation. They are added to the formulation to promote the cohesive properties of individual powder particles. Binders are used either as solution or as powder. Examples of commonly used binders include: sucrose, acacia, microcrystalline cellulose, polyvinylpyrrollidone, hydroxypropylcellulose (Allen and Ansel, 2014).

1.6.3. Lubricants

During the compression process, there is the tendency for powdered material to stick to the surface of the punch or dies. Lubricants in pharmaceutical tablet formulation act at the interphase between the face of the punch and die and the surface of the tablet, thus preventing adherence to these surfaces and subsequently enhancing smooth ejection of tablets. Insufficient addition of lubricants to tablet ingredients produces tablets with pitted surfaces due to adherence of material to die surface. Examples of lubricants

employed in tablet manufacture include: magnesium stearate, stearic acid, glycerybehenate, polyethylene glycol, lauryl sulphate salts (Allen and Ansel, 2014).

1.6.4. Glidants

In tablet compression, powdered ingredients or granules are fed in through the hopper. The flow properties of the powder within the hopper go a long way in predicting the quality of tablets produced. Glidants are added to tablet formulations to enhance the flow properties of the powdered ingredients or granules within the hopper into the die. Glidants act by occupying the spaces between powder or granule particles thereby ensuring smooth flow of materials. Examples of glidants commonly used include: talc and colloidal silicon dioxide (Allen and Ansel, 2014).

1.6.5. Sweetening Agents

Some active ingredients are characterized by very obnoxious tastes and thus would discourage acceptability. Sweetening agents are added to control or mask the tastes of tablet ingredients and thus ensure acceptability of the tablets. These are especially important in the formulation of chewable tablets. Examples of sweetening agents used are: aspartame, glycerin, dextrose, sorbitol and peppermint oils (Allen and Ansel, 2014).

1.6.6. Colourants

In order to improve the aesthetic appearance of tablets or to enhance identification and patient acceptabilitfy, colourants are added to tablets. Addition of colourants to tablets should however be done with care to ensure even distribution of the colour on the tablets produced. Examples of colourants used include: amaranth, caramel, sunset yellow (Allen and Ansel, 2014).

1.6.7. Disintegrants

To elicit its therapeutic effect, the tablet must disintegrate or break up into smaller particles to dissolve. Typically, on entering the gastrointestinal tract, an uncoated tablet should breakup into fragments within 15 minutes (BP, 2009). Disintegrants are added to tablet formulations to facilitate the breakdown of the tablet into smaller particles, promoting the release of the active ingredient. Disintegrants elicit their action by a number of mechanisms, which are:

a) **Increasing porosity and wettability of tablet matrix:** By increasing the porosity and wettability of the tablet matrix, gastrointestinal juices more readily penetrate the tablet matrix and cause a breakdown of the tablet. By this mechanism, the disintegrant must be homogenously dispersed within the table. Examples of disintegrants in this category include: starch and sodium starch glycolate.
b) **Swelling:** Some disintegrants elicit their action by swelling when in contact with aqueous fluids. This increases the internal pressure within the tablet matrix, causing it to burst open. Examples of disintegrants in this group are: crospovidone, sodium starch glycolate and pre-gelatinized starch.

c) **Evolution of Gas:** This is the mechanism of disintegration in effervescent tablets. Upon contact with water, the disintegrant undergoes a chemical reaction in which gas is evolved. With evolution of gas, the tablet gets disintegrated.

1.7. CO-PROCESSED EXCIPIENTS

A co-processed excipient is defined by IPEC as "any mixture of compendia or non-compendial excipients that has been designed to be physically co-processed in a way which results in functional performance attributes when used in a drug application and which are not seen if the excipients are combined using simple mixing" (Folttmann, 2015). In co-processing excipients, only physical interactions such as hydrogen bonding or ionic interactions should be involved.

Co-processing of excipients involves the incorporation of one excipient into the particle structure of another in a bid to mask some undesired properties of individual excipients while retaining or improving desired properties of individual excipients. This results in an overall improvement of performance of the excipient (Folttmann, 2015).

1.7.1. Methods of Co-processing

The vast availability of excipients provides numerous possibilities to produce tailor-made co-processed excipients, meeting functional requirements. The methods employed in co-processing include:

a) Spray drying
b) Solvent evaporation
c) Crystallization

d) Melt extrusion

e) Granulation/Agglomeration

f) Co-milling

g) Co-transformation

a) Spray Drying

Spray drying enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. The feed can be in the form of solution, suspension, dispersion or emulsion. Spray drying is a continuous particle processing drying operation and the dried product can be in the form of powders, granules, or agglomerates depending on the physical and chemical properties of the fee, the dryer design and the final powder properties required (Ajay *et al* 2012).

b) Solvent Evaporation

Solvent evaporation involves the use of liquid as a manufacturing vehicle. It is a form of microencapsulation process in which the coating excipient is dissolved in a volatile solvent which is immiscible with the liquid vehicle phase. The excipient to be used as core material is dissolved in the coating polymer solution and with agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated to evaporate the solvent (Liew *et al*, 2019). After evaporation of the solvent, the liquid vehicle temperature is reduced to ambient temperature with continued agitation. By this time, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may either be water-soluble or water insoluble materials.

c) Crystallization

Crystallization is the process of formation of solid crystals precipitating from a solution, melt or rarely deposited directly from a gas. Crystallization is also a chemical solid-liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs. Crystallization only occurs from a solution that is supersaturated and it can be achieved by various methods including:

a) Solution cooling
b) Addition of a second solvent to reduce the solubility of the solute
c) Chemical reaction
d) Change in pH

d) Melt Extrusion

Melt extrusion is a process of formation of small beads or pellets from the molten mass which is extruded through an extruder. The extruder consists of one or two rotating screws which are either co-rotating or counter rotating inside a stationary cylindrical barrel. It involves the pumping of materials at elevated controlled temperature and pressure through a heated barrel.

The procedure for melt extrusion can be summarized thus:

Feeding of material through the hopper to the extruder.

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Mixing, grinding, venting and kneading.

↓

Flow of materials through the die

↓

Extrusion from the die.

e) Granulation

Granulation is the act of forming grains. Granules typically have a size range between 0.2 to 4.0mm depending on their use. This method is widely used to improve physical properties such as flowability, wettability, bulk density and product appearance. Two types of granulation techniques may be employed: wet granulation and dry granulation.

f) Co-milling

Co-milling or dry grinding may be carried out in a roller mill, ball mill, bead mill, jet mill or hammer mill. The excipients are premixed and passed through a high speed milling machine. The excipients interact and form bonds when subjected to the milling force (Liew *et al*, 2019).

g) Co-tranformation

This involves the application of heat or a solvent to open up the particles of one excipient temporarily then adding another excipient into the opened up particles. This method has been employed in the production of superdisintegrants with improved compressibility (Sujatha Kumari *et al*, 2013)

1.7.2 Advantages of Co-processed Excipients

The main goal of co-processing excipients is to produce excipients with superior qualities when compared to the individual ingredients. Some of the advantages of co-processed excipients are:

a) **Improved flow properties:** The controlled particle size and particle size distribution of co-processed excipients ensures that they have superior flow properties with no need for addition of glidants to formulations. Though the particle size range of co-processed excipients is similar to that of the individual excipients, co-processed excipients posses a much better flow. This is exemplified in the comparative study of cellactose, an excipient co-processed from cellulose and lactose. Cellactose has better flow properties compared to cellulose and lactose (Sreekanth Babu *et al*, 2012).

b) **Improved compressibility:** Direct compression as a method of tableting is limited by the incompressibility of active ingredients and excipients. Co-processing of excipients produces excipients with marked increase in flow properties and compressibility profiles of excipients, enabling them to be directly compressed (Ajay *et al*, 2012).

c) **Better dilution potential:** Dilution potential is the ability of the excipient to retain its compressibility even when it is diluted with another material. Active pharmaceutical ingredients (APIs) are usually poorly compressible and as such excipients used in combination with APIs should have good dilution potential to retain compressibility when combined with active ingredients. Co-processed excipients have better dilution potential than individual excipients (Sreekanth Babu *et al*, 2012).

d) **Fill weight variation:** Fill weight variation is a consequence of poor flow property. Materials for direct compression usually show high fill weight variation as a result of

their poor flow properties. Co-processed excipients having good flow properties thus have fewer fill weight variation problems. This is achieved through the impregnation of one ingredient into the matrix of another, reducing the rough particle surfaces and creating a near optimal size distribution. The result being a better flow and ultimately low fill weight variation (Ajay *et al*, 2012).

e) **Reduced lubricant sensitivity:** Co-processed excipients usually consist of a relatively large amount of brittle material and a smaller amount of plastic material. The plastic material provides good bonding properties by creating a continouos matrix with a large surface for bonding. The larger brittle material provides low lubricant sensitivity by preventing the formation of a coherent lubricant network through the formation of newly exposed surfaces after compression. This breaks up the lubricant network (Ajay *et al*, 2012).

f) **Absence of chemical changes:**The chemical properties of excipients after co-processing have been shown to remain intact. This is of great importance to formulations because excipients though usually inert impact on the properties of active ingredients (Sreekanth Babu *et al*, 2012).

1.8. EVALUATION OF TABLETS.

Tablets must be made to meet both physical and quality standards. This can be with respect to apparent or embedded features. All of these must be controlled both during the production and after the production to ensure that the right quality standard is

met for each given product. This is the basis for why evaluation of tablet quality is carried out. Some criteria for evaluation of tablet quality include:

1.8.1. General appearance

The general product elegance of a tablet is important not just to improve consumer acceptance but to also control lot-to-lot and tablet-to-tablet uniformity. Evaluation of the general appearance of a tablet would include measurement of the size, shape, colour, presence or absence of odour, taste, etc. the same tablets must not have thickness variations greater than 5% and the colour distribution for coloured tablets must be uniform with no mottling.

1.8.1.1. Tablet thickness

This is determined by the diameter of the die used in tableting, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the pressure applied during compression. In order to produce tablets with uniform thickness, the fill, die and pressure must be carefully monitored. Tablet thickness is measured using a gauge whether hand held or automated.

1.8.1.2. Tablet hardness

The hardness of a tablet is a subject of the amount of pressure employed during the compression process. Generally, the greater the pressure applied, the harder the tablets produced. Some tablets are intended to be hard, like lozenges which are meant to slowly dissolve and release medicaments whereas others are meant to be soft. Tablets should

generally be hard enough to resist mechanical stress and soft enough to disintegrate to release their medicament. Tablet hardness is measured using a hardness tester.

1.8.2. Weight and content uniformity

The amount of material fed into the die system determines the weight of the tablets to be formed. Weight uniformity is therefore subject to the filling efficiency and the calibration of the machine. The United States Pharmacopoeia, USP describes a test for the determination of weight uniformity for uncoated tablets using weight variation as a parameter. Twenty (20) tablets are weighed individually and the average weight is determined. The individual weights of the tablets are then compared to the average weight. The tablets pass the test if no more than two tablets fall outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

In content uniformity, 10 randomly selected tablets are assayed individually. The tablets pass the test if 9 of the 10 tablets have between 85-115% of the labeled drug content and the 10^{th} contains not less than 75% and not more than 125% of the labeled drug content. This holds true for all tablets unless it has been specifically stated in the monograph of the drug.

1.8.3. Friability

A tablet's friability is the tendency for a tablet to crumble when exposed to mechanical stress. This is determined using equipment called a friabilator. The equipment

determines the friability of the tablet by allowing the tablet to roll and fall within a drum. The tablets weight before and after a specified number of rotations is determined, and the difference in weights between the initial tablets and the tablets after rotation is evaluated. Significant loss of tablet material is indicative of inability to withstand abrasion in handling, packaging and transport. A tablet passes the friability test if less than 0.5-1% of loss is recorded.

1.8.4. Tablet disintegration and dissolution.

In eliciting their action, tablets must first disintegrate to release the active pharmaceutical ingredient into body fluids for absorption. Disintegration is defined as a state in which any residue of the unit remaining on the screen of the test apparatus is a soft mass having no palpably firm core. This holds true for all materials except fragments of insoluble coating or capsule shell. Disintegration is also important for drugs which are not absorbed into systemic circulation but which act locally in the gastrointestinal tract e.g. antacids as the drugs need to break up into smaller particles, increasing the surface area for activity. Disintegration is carried out using a disintegration apparatus consisting of a basket and rack assembly containing six open-ended transparent tubes of specified dimensions, held vertically upon a 10-mesh stainless steel wire screen. A tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in the immersion fluid at 29-32 cycles per minute with the wire screen always below the level of the fluid. Distilled water (at 37°C) is usually employed as the immersion fluid unless otherwise stated by the monograph of the drug.

Uncoated tablets are officially expected to disintegrate within 30 minutes or the set time for individual drugs according to their monographs.

The rate of tablet disintegration is important in determining the dissolution rate. The dissolution test measures the rate at which the drug gets into solution and the U.S.P. specifies two apparatus for the dissolution rate test. A tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. Into a 100ml flask containing the medium for dissolution medium is immersed. The flask is kept at 37±0.5°c. The second apparatus operates like the first except that the basket is replaced by a paddle.

A number of factors can affect the disintegration and dissolution of tablets and they include:

a) Particle size of the drug substance
b) Solubility of the formulation
c) Hygroscopicity of the formulation
d) Type and concentration of the disintegrants, binders and lubricants used,
e) Method of manufacture.

1.9. STARCH

Starch is a carbohydrate and is abundant in leaves, flowers, fruits, stems and roots (Alcazar-Alay and Meireles, 2015). It is the most abundant organic compound found in nature after cellulose and serves as a source of energy and carbon. Starches are obtained from different sources including wheat, maize, rice, potato, yam, sorghum and banana.

They differ in their granular morphology, molecular weight, composition and physicochemical properties depending on the sources of the starch. As a result of this difference in source, starches also have different properties leading to a variety of ways in which starches are applied in improving consistency, stability, and other properties of materials. Starch forms the bulk of human diet but also has wide applications in the biomedical and pharmaceutical, and many other industries. This is as a result of its biocompatibility, biodegradability, non-toxicity, and abundant sources. In the biomedical industry, starch is a potentially useful material in tissue engineering of bone, bone fixation, and carrier for hormones. The applications of starches in the pharmaceutical industry cannot be overemphasized as starch finds application as binders, diluents and disintegrants (Mohammed *et al*, 2011). Its application in these areas is as a result of its adhesive, thickening, gelling, swelling and film forming properties.

Starch is composed of two polysaccharides: amylose and amylopectin. Amylopectin is branched and amylose is linear however, both polymers consist of linear α-1,4 linked D-glucose residues interconnected through α-1,6 glycosidic linkages which form branches in the polymers (Bertoft, 2017). Amylopectin constitutes more than three quarters of common starch while amylose constitutes one quarter of common starch (Alcazar-Alay andMeireles, 2015). Amylopectin and amylose can be arranged in a semicrystalline structure forming a matrix of starch granules with alternating amorphous material from amylose and crystalline material from amylopectin.

1.9.1. Properties of Starch

a.) Morphology, size, composition and crystallinity

Depending on the botanical source of the starch, its morphology may vary between different shapes as oval, ellipsoidal, spherical, smooth, angular or lenticular. The size of starches varies in diameter between 0.1-200µm with particle size distribution of unimodal, bimodal or polymodal (Alcazar-Alay, Meireles, 2015).Starches are composed of different quantities of amylose and amylopectin even within the same source because of differences in geographic origin and cultural conditions. Some non-carbohydrate materials are also contained in starch like phosphorus. Phosphorus exists in starch as monoester phosphates or phospholipids. The crystallinity or amorphous nature of a starch is dependent on the content of the two polysaccharides; amylose and amylopectin in the starch. A higher proportion of amylopectin in a starch confers greater crystallinity to the starch.

b.) Birefringence.

The ability of a material to doubly reflect polarized light is termed birefringence. Starch granules produce birefringence proportional to the content of amylopectin in the starch. It represents the radial arrangement of amylopectin molecules with their chains forming 90° angles with the reduced ends in the direction of the starch center. By implication, a disorganization of the crystalline region i.e. the amylopectin component will result in weak birefringence patterns (BeMiller and Whistler, 2009).

c.) Swelling and Solubility

On heating starch molecules in excess water, its semi-crystalline structure is broken down and water molecules associate by hydrogen bonding to hydroxyl groups exposed on

the amylose and amylopectin molecules. This results in swelling, increased granule size and solubility of the starch. The swelling capacity and solubility of starch illustrates the interactions of the amorphous and crystalline fractions of the starch.

d.) Gelatinization and Retrogradation

Gelatinization occurs as a transition phase when starch is heated in excess water. Every starch has a characteristic temperature interval for which gelatinization occurs. Gelatinization occurs when water diffuses into the granule which then swells due to hydration of the amorphous phase resulting in loss of crystallinity and molecular order (Jimenez *et al,* 2012).

The molecular interaction produced after gelatinization and cooling of the paste formed is known as retrogradation. Starch exhibits lower gelatinization and enthalpy after retrogradation because of its weakened crystalline structure.

e.) Pasting

Continuous heating of starch in excess water with stiring causes the starch granules to swell and burst as a result of a breakage of the starch structure. Amylase leaches out and the starch granules disintegrate to form a viscous material called a paste (Wani et al, 2012). Pasting occurs together with or after gelatinization and it determines the behavior of starch during processing.

1.9.2. Yam Starch

Yam is the second most important root and tuber crop in Africa (Otegbayo*et al,* 2011). Yam is a general name for plant that form tubers and belong to the genus

Dioscorea of the monocot family Dioscoreaceae. There are hundreds of species belonging to the genus *Dioscorea* but only about 10 are staple species (Zhu, 2015). Variations in chemical composition of yam exist not only between different species but also within same species (Ezeocha and Okafor, 2016).

Yam starch is composed of amylose and amylopectin in different proportions. Variations in the amylose content of starch from different species reflect on the properties and uses of the starch. Great variations in amylose content of different yam species exist with contents ranging from 1.4%-50%. The amylose content of yam starch is quantified based on a number of methods such as iodine binding spectrophotometry, enthalpy changes of amylose-lysophospholipid inclusion complex transition, size exclusion chromatography of whole starch by high performance size-exclusion chromatography coupled to multi-angle laser light scattering and differential refractometric index and size-exclusion chromatography of debranched starch. Colorimetric methods apply the principle that amylose forms a complex with iodine, changing its colour to blue-black. Other minor components of starch include protein, lipid, phosphorus-containing compounds and ash which affect the functionality of the starch despite their small quantities. High lipid content for example significantly reduces the value of amylase content by forming inclusion complexes with amylose. It has an amylose content of about 15% which is rarely affected by the harvesting time of the yam (Zhu, 2015). Granules from *Dioscorea dumentorum* are very small (0.8μm) thus reflecting the amount of amylose which increases with granule size.

1.9.3 Rice Starch

Rice (*Oryza sativa*; Family: *Poaceae*) is consumed as food by over half the population of the world. Starch makes up 80% of the total constituents of rice (Wani *et al*, 2012). As a result of wide diversity in rice starch, there can be isolation of its starch with different functionalities. The physicochemical properties of the starch depend on the variety, isolation procedure, climatic and soil conditions during development (Gayin, 2015). Starch obtained from rice is creamy, spreadable, and smooth to feel and has no distinct taste. The starch granules are the smallest in cereals ranging between 2 to 7 μm although starch granules have smooth surfaces, they posses angular or polygonal shapes. In the pharmaceutical industry, rice starch has gained acceptance as a result of its digestibility, hypoallergenicity, bland flavor, small granules, white colour, increased freeze-thaw stability of pastes, grater acid resistance and wide range of amylose: amylopectin ratios.

As with all other starches, the major components of rice starch are amylose and amylopectin with the physicochemical properties of rice starch being most affected by the amylose content of the starch. Other minor components of rice starch include lipids and proteins which may be contained on the surface or inside the granule. Phosphorus in the form of phosphate mono-ester and phospholipids as well as calcium, potassium, magnesium and sodium in their ionic form are also present.

1.9.4. Modification of Starch.

The use of starch in its native form is uncommon and limited due to its instability with respect to changes in temperature, pH and shear forces (Alcazar-Alay and Meireles,

2015). As a result of this, they possess functional properties unfavourable for industrial use.

Starch is modified by altering the structure of starch including hydrogen bonding capacity in a controlled manner in order to improve and broaden the application of starch industrially (Mohammed, 2017). Starch modification alters the physicochemical properties of starch through physical, chemical and enzymatic methods. In the physical methods, heat and moisture are employed whereas introduction of functional groups is done in chemical methods (Alcazar-Alay and Meireles, 2015).

1.9.4.1 Physical Modification of Starch.

Physical modification of starch reduces the size of the starch granules and improves its water solubility. Physical modification is especially important for products meant for human consumption because no chemical or biological agents are employed. Other advantages of physical modification include simplicity, cost effectiveness and safety. Some methods of physical modification include;

a) Pregelatinization
b) Annealing
c) Hydrothermal Treatment
d) Non-thermal Modification

a) Pregelatinization: This is the simplest method of modification carried out by heating the slurry, roll drying, spray drying or extrusion (Mohammed, 2017). The starch undergoes a cooking process until gelatinization occurs then there is a simultaneous drying process. Pregelatinization is designed to improve adhesiveness of starches and produce starch with

good flow, binding and compressibility. Pregelatinization however destroys the granular structure of the starch, causing fragmentation of the granules and loss of birefringence. The functionality of pregelatinized starch is dependent on its cooking conditions, drying and source of starch (Ashogbon and Akintayo, 2014).

b) **Annealing:** Annealing involves the soaking of native starch in excess water between 40-60% w/w at predetermined temperatures for a specific period of time. In annealing, moisture, temperature and heating time determine the product. Hydration of the starch granules in annealing causes a transition from a glassy state to a static state, thereby increasing the mobility of the amorphous regions to a crystalline state. These changes generate physicochemical modifications which increase chain interaction in the crystalline region (Chen *et al*, 2014). Annealing increases starch granule size, thermal stability and improves availability of starch to digestive enzymes.

c) **Hydrothermal Treatment:** This involves the application of heat in the presence of limited amount of water for a process time of between 15 minutes to 16hours. Hydrothermal treatment impacts changes in the crystalline structure, swelling capacity, gelatinization, paste properties and retrogradation of the starch. The changes resulting from hydrothermal treatment are affected by the source of the starch granules with respect to the composition and organization of amylose and amylopectin in the starch. Hydrothermal treatment also causes structural modifications into the amorphous and crystalline regions on the granules which make the granules susceptible to chemical and enzymatic modifications as well as hydrolysis (Zavareze and Dias, 2011).

d) **Non-thermal Modification:** This method involves the use of high pressure, ultrasound, microwaves and electric pulses in the treatment of starches. Non-thermal modification in

addition to restricting swelling capacity eliminates pathogenic microorganisms and spores.

1.9.4.2 Chemical Modification of Starch.

This involves the addition of functional groups onto starch without disturbing the morphology or size distribution of the granules. Chemical modification is extensively used in industrial starch modification as it significantly impacts on the gelatinization capacity, retrogradation, pasting property and general starch behavior.

a) **Cross linking:** Cross linking of the starch polymer occurs when hydrogen bonds present between the starch grains are replaced by stronger permanent covalent bonds (Mohammed, 2017). Sodium trimetaphosphate, sodium tripolyphosphate, epichlorohydrin and phosphoryl chloride are examples of agents used in cross linking. Starch modified by cross linking produces acid, heat and shear stability but causes starch to lose water solubility. Distarch phosphate is a commonly used example of a cross-linked starch.

b) **Cationization:** Modification by cationization occurs by the reaction of starch with compounds containing tertiary or quaternary ammonium, imino, amino, sulphuric or phosphate groups. Cationization can be carried out by wet, dry or semi-dry methods and starches produced have increased viscosity peaks and reduced pasting temperature.

c) **Acetylation:** Acetylation of starch involves the addition of functional acetylated groups which react with free hydroxyl groups in the branched chains of the starch polymer to produce esters (Sweedman *et al*, 2013). Acetylation increases the swelling capacity and solubility of the modified starch.

d) **Acid hydrolysis:** This is the reaction of acid with the starch, resulting in de-polymerization of the amorphous region of the starch granules. As a result, the granules rupture quickly when the starch is heated beyond its gelatinization temperature (Mohammed, 2017).

e) **Oxidation:** Oxidation is carried out by treating starch with sodium hypochlorite or peroxide. Starches produced from this method are mainly used as sizing agents or coating binders (Forssell *et al* 1995).

1.10. PARACETAMOL

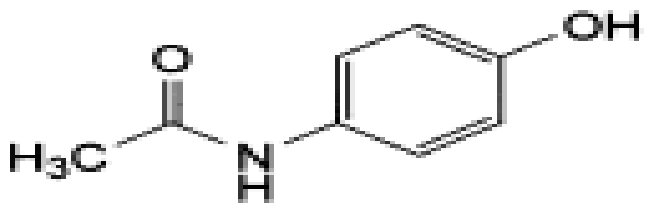


Fig 1.1.: Structural formula of paracetamol (N-(4-Hydroxyphenyl) acetamide)

Paracetamol (also known as acetaminophen), belongs to the class of drugs known as aniline analgesics. It is also referred to as a non-opioid analgesic. Paracetamol has both analgesic and antipyretic activity and unlike non steroidal anti-inflammatory drugs (NSAIDs) it does not posses anti-inflammatory action. Paracetamol is indicated for mild to moderate pain, headache and fever (Twycross *et al*, 2013). It has a central analgesic effect mediated by the activation of descending serotonergic pathways. Its mechanism of action is however not very well understood. Debate exists about its site of action being the inhibition of prostaglandin synthesis or through an active metabolite influencing cannabinoid receptors (Anderson, 2008).

1.10.1. Pharmacology of Paracetamol

Paracetamol can be administered by oral, intravenous or rectal routes and at therapeutic concentrations, the pharmacokinetics of paracetamol are linear and constant with repeated administration. Upon oral administration, paracetamol is rapidly absorbed with a peak plasma concentration of 2.1 mcg/ml and a volume of distribution of 1 L/kg. Its onset of action is 30minutes to 1hour after oral administration and it is 10-25% bound to plasma proteins. Paracetamol is metabolized in the liver by the microsomal enzyme system and through conjugation by glucoronic acid or sulphuric acid. Metabolites of paracetamol metabolism include N-acetyl-para-benzoquinone imine (NAPQI) and N-acetylimidoquinone. NAPQI is further metabolized through conjugation with glutathione. It is excreted in urine as acetaminophen glucoronide and acetaminophen sulphate or mercaptate.

1.11 Objectives of the study

i. To extract and purify yam and rice starches from tubers of *Dioscorea dumetorum* and cereals of *Oryza sativa*, respectively.
ii. To co-process the rice starch with colloidal silicon dioxide to obtain ratio (rice starch:colloidal silica) of 97:3
iii. To co-process the silicified rice starch with yam starch at a ratio of 1:2
iv. To characterize the native yam and rice starch powders, silicified rice starch and co-processed rice and yam starches using FTIR, angle of repose, particle size and density, bulk and tapped densities, Carr's index and Hauner's ratio as assessment parameters.

v. To incorporate native yam starch, native rice starch and co-processed silicified rice and yam starches as directly compressible disintegrants in paracetamol tablet formulations at concentrations of 10% w/w, 15% w/w, 20% w/w and 25% w/w in comparison with similar formulations containing official micro-crystalline cellulose (Avicel®).

vi. To evaluate the mechanical properties of the paracetamol tablets using tensile strength and friability as assessment parameters.

vii. To evaluate the disintegrant properties of unmodified yam starch, unmodified rice starch and co-processed silicified rice and yam starches in paracetamol tablet formulations using disintegration test as assessment parameter.

1.12 Justification of the Study

Silicification is expected to enhance the flow properties of rice starch, while the choice of co-processing silicified rice and yam starch is expected to have better disintegrant properties than the individual powders when incorporated as a disintegrant in directly compressed paracetamol tablets. Moreover, paracetamol cannot be tableted on its own and requires a disintegrant and other excipients to be formulated as a tablet.

CHAPTER TWO

MATERIALS AND METHOD

2.1 MATERIALS

The materials used are *Dioscorea dumentorum* starch obtained from *Dioscorea dumentorum* (Family: *Dioscoreaseae*) yam tubers, rice starch obtained from grains of *Oryza sativa* (Family: *Poaceae*) and authenticated at the herbarium of the department of Pharmacognosy, University of Ibadan. Distilled water was obtained from the laboratory of the department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan. Other materials include; colloidal silica, paracetamol powder, corn starch BP, Lactose BP and Magnesium stearate.

2.2 METHODS

2.2.1 Collection, extraction and purification of yam starch

The *Dioscorea dumentorum* tubers were peeled, washed with distilled water and cut into tiny pieces before milling to a pulp. Sufficient distilled water was added to dilute the slurry and sieved until all the starch was fully extracted. The resultant mixture was allowed to stand for 48 hours then it was decanted, leaving the sediment behind. Distilled water was added to the sediment with subsequent decantation twice in a day for four days. The extracted starch was dried at 50 °C for 48 hours, dry blended and stored in an air tight container.

2.2.2 Collection, extraction and purification of rice starch

Starch obtained from *Oryza sativa* were washed and soaked in distilled water for 48 hours to soften the grains. The grains were then milled to a pulp and sufficient distilled water was added to dilute the slurry. This slurry was sieved until all the starch was extracted, leaving only the chaff. The mixture was allowed to stand for 48 hours after which it was decanted leaving the sediment starch behind. Distilled water was added with subsequent decantation twice in a day for four days. The starch was then dried at 50 °C for 48hours, powdered and stored in an air tight container.

2.2.3 Silicification of rice starch

Exactly 300 g of suspension containing 40% w/v of *Oryza sativa* starch was prepared in a 500 mL beaker using 180mL distilled water. Exactly 3.7 g colloidal silica was weighed and dispersed in the slurry with stirring for 5 minutes. The mixture was then transferred to a thermostatic water bath set at 54 °C for 15 minutes with stirring. It was taken off the water bath and allowed to cool to room temperature the Ethanol 150 mL was added to precipitate the silicified starch. The silicified starch was separated and spread on a tray to dry in open air. It was passed through a 1.00 mm sieve and dried at 40 °C until drying was complete.

2.2.4 Co-processing of *Dioscorea dumentorum* and silicified *Oryza sativa* starch

Exactly 6 g of silicified rice starch (SRS) as well as *Dioscorea dumentorum* Starch (DdS) were weighed into a mortar and triturated to produce an even mix of a 1:2 ratio of the two starch samples.

2.3. Characterization of Starch

2.3.1. Identification of Starch

The presence of starch in *Dioscorea dumentorum* and *Oryza sativa* was confirmed using iodine. A small quantity of *Dioscorea dumentorum* starch was placed on a glass slide and 2 drops of iodine added to the sample. The colour change from the reaction was recorded accordingly. The process was repeated for *Oryza sativa* starch.

2.3.2. Fourier Transform Infrared (FTIR) Spectroscopy

Small quantities (10mg) each of *Dioscorea dumentorum* Starch (DdS), silicified rice starch (SRS), SRS:DdS (1:2), Paracetamol (API) and SRS:DdS (1:2) with API were used to obtain spectra using a Magna-IR, 560 spectrophotometer (Perkin Elmer, USA).

2.3.3. Particle Size Determination

The particle size of each of the samples: *Dioscorea dumentorum* Starch (DdS), silicified rice starch (SRS) and SRS:DdS (1:2), was determined using a microscope with the aid of a calibrated eyepiece.

2.3.4. Bulk density

The bulk densities of *Dioscorea dumentorum* Starch (DdS), silicified rice starch (SRS) and native rice starch were determined using 30g of powdered sample each. The

powder was poured into a 100 mL measuring cylinder and the volume occupied by the powder was recorded. The bulk density was calculated using the formula:

$$\text{Bulk density} = \frac{\text{mass}}{\text{volume}} (\text{gcm}^{-3}) \qquad \text{Eq (i)}$$

2.3.5. Tapped density

The tapped densities of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and native rice starch were determined using 30g of powdered sample each. The sample was poured into a 100 mL measuring cylinder and tapped for 3 minutes at 2 seconds intervals. The volume at the end of 3 minutes was recorded and the tapped density determined using the following formula:

$$\text{Tapped density} = \frac{\text{mass}}{\text{Tapped volume}} (\text{gcm}^{-3}) \qquad \text{Eq (ii)}$$

2.3.6. Carr's index

From the bulk and tapped densities of each of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and unmodified rice starch, the Carr's compressibility index was calculated using the following formula:

$$\text{Carr}'\text{s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \qquad \text{Eq (iii)}$$

2.3.7. Hausner ratio

For each of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and native rice starch, Hausner ratio was calculated using the following formula:

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density} \qquad \text{Eq (iv)}$$

2.3.8. Angle of repose

Exactly 10g each of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and native rice starch was poured through a funnel clamped on a retort into an open ended glass tube placed on a flat surface. The tube was removed producing a cone. The height of the resultant cone and the radius was determined using a ruler and a pair of dividers. The angle of repose was then calculated using the formula:

$$\text{Angle of repose}, \theta = \tan^{-1}\frac{h}{r} \qquad \text{Eq (v)}$$

Where h= hypotenuse of cone obtained from Pythagoras theorem

r= radius of cone.

2.3.9. Particle density

The particle density of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and native rice starch was determined using the liquid pycnometer method with xylene as the replacement fluid. The 50mL capacity pycnometer was dried and weighed empty (W), filled completely with xylene, closed up and the excess solvent wiped. The pycnometer filled with xylene was weighed and recorded (W_1). The weight of the xylene (W_2) was determined as the difference between W and W_1. Each sample (2 g) was weighed (W_3) and transferred into the pycnometer. The pycnometer was closed up and

excess solvent wiped off. It was weighed and recorded (W_4). The density was evaluated using the following formula:

$$\text{Particle density} = \frac{W_2 W_3}{50(W_3 - W_4 + W_2 + W)} \qquad \text{Eq (vi)}$$

2.4. Preparation of powder mix

The basic formulation for preparing the powder mix is shown in Table 2.1. Exactly 25 g powder mix was prepared by weighing dry powders into a dry mortar and triturating using a pestle until a uniform mix was obtained. The different batches of powder were stored in air-tight containers.

2.5. Production of tablets

Using the Carver hydraulic hand press (model C Carver Inc., Menomonee Falls, Wisconsin, USA) , 500mg $\pm$ 20mg paracetamol tablets were produced using a 10.5mm diameter die with flat faced upper and lower punches at a compression pressure of 1 metric tonne for 30 seconds.

The mixed powder for each formulation was weighed carefully and poured into the lower punch fitted with the die. The upper punch was then fitted to enclose the powder mix and place on the hydraulic press. The tablet was compressed by lowering the pressing head until a pressure of 1 metric tonne was reached and maintained for 30 seconds. The pressure was then released and the formed tablet ejected from the die and stored appropriately for 24 hours before evaluation was carried out on the tablets.

2.6. EVALUATION OF TABLETS

2.6.1. Uniformity of weight

Twenty tablets produced in a batch were weighed individually using a weighing balance (Mettler PC 440 Delta RangeR, CH-8606 Griefennsee Zurich, Switzerland) and their mean weights and standard deviation determined.

2.6.2. Tablet thickness

The thickness of three tablets selected at random from each batch was determined using a micrometer screw gauge (MItutoyocode no 7301 micrometer screw gauge). The mean thickness of three determinations and standard deviation for each batch was also calculated and recorded.

2.6.3. Crushing strength

The crushing strength of three randomly selected tablets was determined using the semiautomatic hardness tester (Copley Scientific Industries, U.K. Serial no: 23571). Each of the tablets was placed between the anvil and spindle of the hardness tester and the knob of the tester screwed to apply pressure on the tablet after tarring the tester. The pressure at which the tablet was crushed was recorded in triplicates and mean thickness and standard deviation evaluated for each batch.

2.6.4. Friability test

Three tablets selected at random from each batch were used to evaluate the friability of each batch using the Tablet Friability Tester FRV (Copley Scientific Industries, U.K. Serial no: 27912) set at a speed of 25rpm. The weight of the three tablets was determined and then transferred into the friabilator. The friabilator was started and set to rotate at 25rpm for 4 minutes. At the end of 100 rotations, the tablets were dusted, reweighed and the percentage weight loss evaluated.

2.6.5. Disintegration time test

The disintegration time of each batch of tablets was determined by placing the tablets in distilled water at 37 $\pm$ 2°C in the Tablet Disintegration Tester DTG 4000 (Copley Scientific Industries, U.K. Serial no: 24700). The disintegration time was recorded when the entire tablet had passed through the mesh.

Table 2.1: Basic formulation for preparation of 500mg Paracetamol tablets

Component	Ingredient	Batch 1 (%w/w)	Batch 2 (%w/w)	Batch 3 (%w/w)	Batch 4 (%w/w)
API	Paracetamol	50	50	50	50
Binder	Corn starch	20	20	20	20
Disintegrant	Avicel® or SRS or DdS or SRS:DdS (1:2)	10	15	20	25
Filler	Lactose	19.5	14.5	9.5	4.5
Lubricant	Magnesium stearate	0.5	0.5	0.5	0.5

Code: API= Active Pharmaceutical Ingredient,
SRS=Silicified Rice Starch
DdS=*Dioscorea dumentorum* Starch

CHAPTER THREE

RESULTS

3.1. Characterization of Starch

3.1.1. Starch Yield

The yield of *Dioscorea dumentorum* was 39 %w/w and while that of *Oryza sativa* was 41 %w/w.

3.1.2. Identification of Starch

The starch from both *Dioscorea dumentorum* and *Oryza sativa* were identified using iodine. A blue-black colour change confirmed the presence of starch in the two samples of the starch powders used.

3.1.3. Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra obtained for *Dioscorea dumentorum* Starch (DdS), silicified rice starch (SRS), SRS:DdS(1:2) are shown on Figs. 3.1, 3.2 and 3.3

3.1.4. Particle size

The particle size distribution as well as the morphological characteristics of *Dioscorea dumentorum* Starch (DdS), silicified rice starch (SRS) and SRS:DdS (1:2) are shown in Table 3.1 and Fig. 3.4 respectively.

3.1.5. Bulk and Tapped densities

The bulk and tapped densities of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and native rice starch samples are shown in Table 3.2

3.1.6. Carr's index

The Carr's indices of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and unmodified rice starch samples are shown in Table 3.2

3.1.7. Hausner ratio

The Hausner ratios of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and unmodified rice starch samples are shown in Table 3.2

3.1.8. Particle density

The particle densities of *Dioscorea dumentorum* Starch, silicified rice starch (SRS) and unmodified rice starch samples are shown in Table 3.2.

3.2. EVALUATION OF TABLETS

The results of weight uniformity, thickness and diameter of the tablets are shown in Table 3.3. The crushing strength, friability, crushing strength-friability ratio (CSFR) and disintegration time tests are shown in Table 3.4.

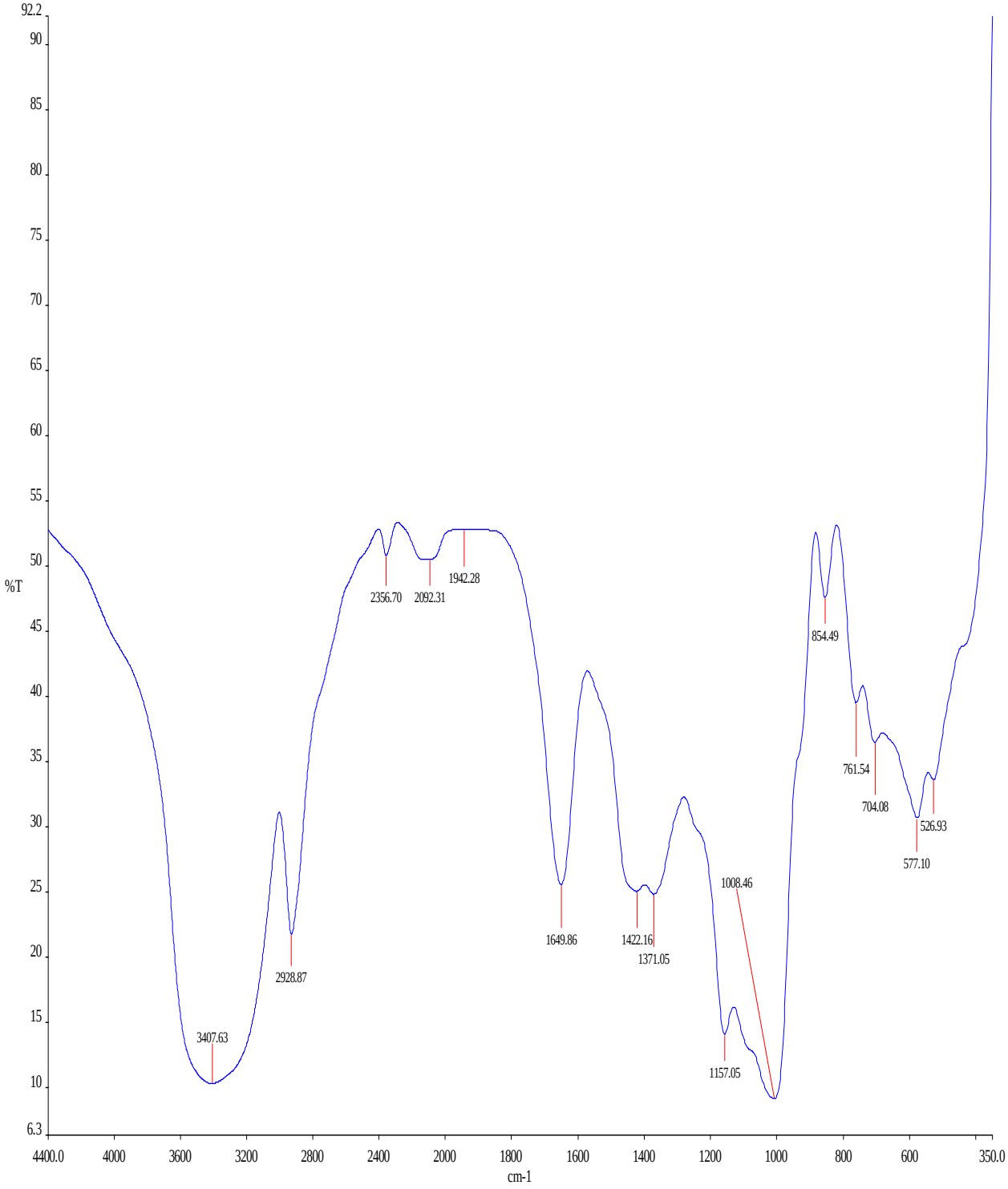


Fig 3.1:FTIR Spectroscopic pattern for *Dioscorea dumentorum* Starch (DdS)

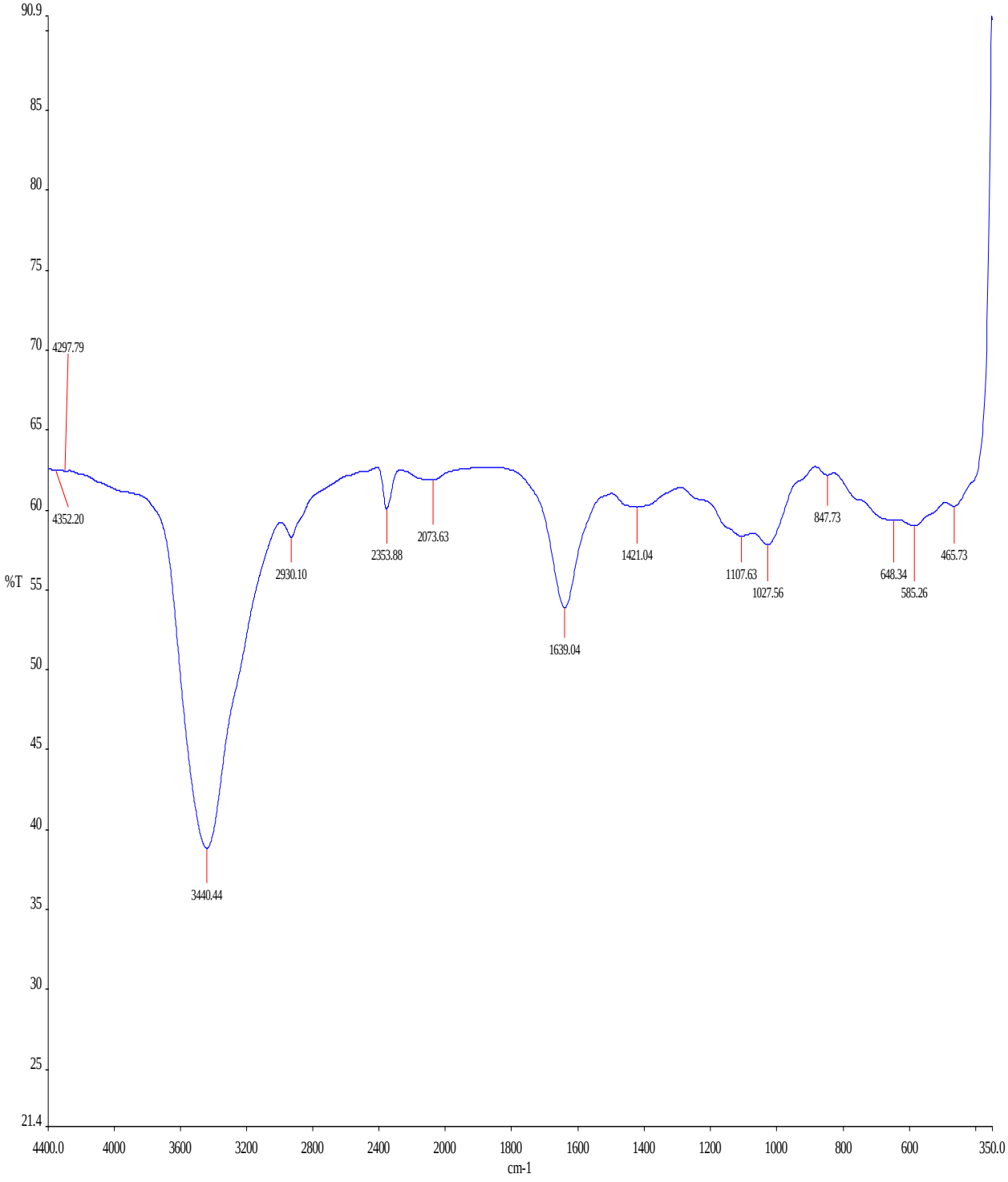


Fig 3.2: FTIR Spectroscopic pattern for silicified rice starch (SRS)

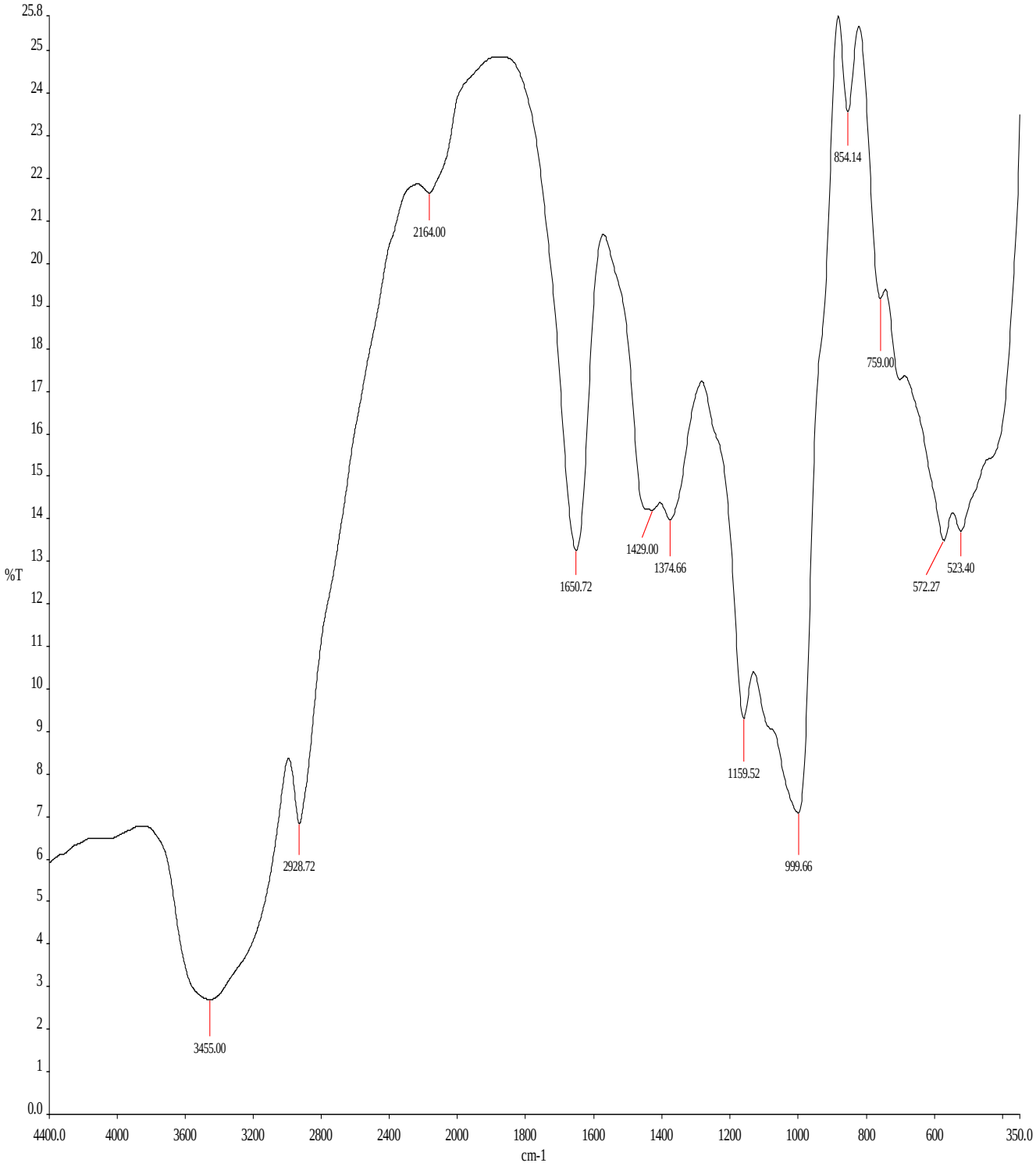
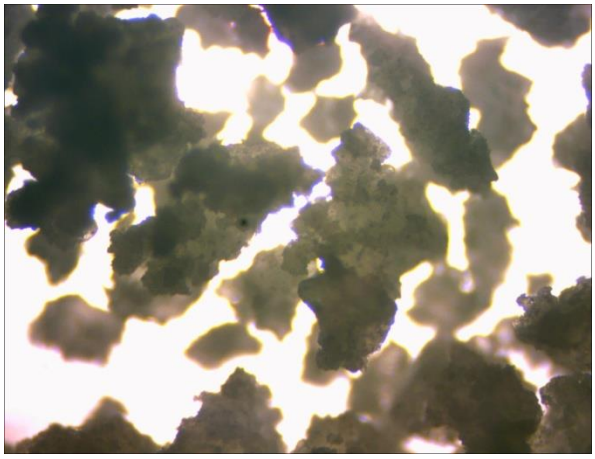
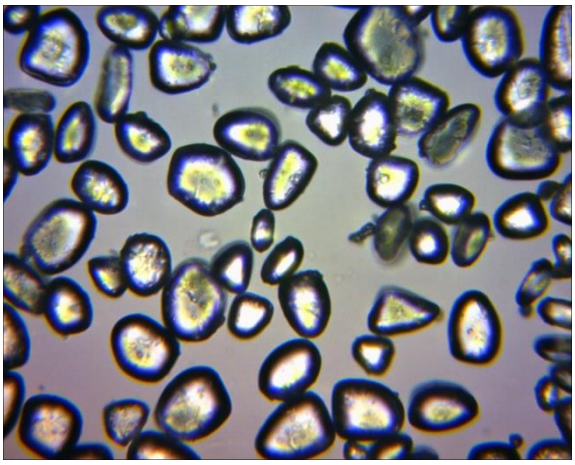


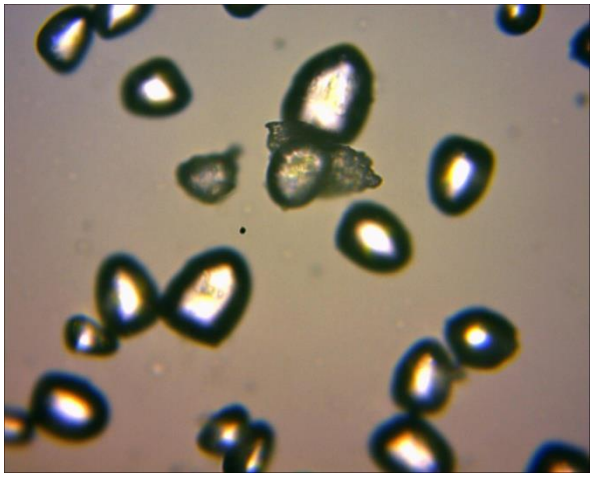
Fig. 3.3: FTIR Spectroscopic pattern for SRS:DdS (1:2)



SRS



SRS: DdS (1:2)



Dioscorea dumentorum starch

Fig. 3.4: Photomicrograph (x 100) of silicified rice starch (SRS), *Dioscorea dumentorum* starch (DdS) and co-processed starch (SRS:DdS, 1:2)

Table 3.1: Particle size distribution of silicified rice starch, *Dioscorea dumentorum* starch and co-processed starch (SRS:DdS, 1:2)

Statistical Quality	**Silicified Rice Starch (SRS)**	***Dioscorea dumentorum* starch**	**SRS:DdS (1:2)**
Number of values	100	100	100
Minimum (μm)	122	10.62	4.66
Maximum (μm)	677	42.49	43.35
Mean (μm)	324	22.67	17.84
Standard Deviation(μm)	122	7.17	6.741
Standard error	12.20	0.72	0.67

Table 3.2: Powder properties of *Dioscorea dumentorum* Starch, silicified rice starch and unmodified rice starch.

Powder property	***Dioscorea dumentorum* starch**	**Unmodified rice starch**	**Silicified rice starch**
Bulk density (gcm^{-3})	0.67	0.69	0.42
Tapped density (gcm^{-3})	0.83	0.83	0.43
Carr's index	18.28	16.87	2.33
Hausner ratio	1.24	1.32	1.02
Angle of repose (°)	59.42	54.73	52.67
Particle density (gcm^{-3})	1.47	1.49	1.43

Table 3.3.: Values of uniformity of weight, diameter and thickness of 500 mg paracetamol tablets

Disintegrant	Concentration (% w/w)	Uniformity of weight (g)	Uniformity of diameter (mm)	Tablet thickness (mm)
Avicel ®	10	0.50±0.01	10.90±0.03	4.98±0.07
	15	0.50±0.01	10.91±0.07	5.23±0.04
	20	0.50±0.01	10.88±0.06	5.20±0.04
	25	0.50±0.01	10.90±0.09	5.10±0.09
SRS:DdS (1:2)	10	0.50±0.01	10.86±0.05	4.76±0.02
	15	0.50±0.01	10.92±0.06	5.03±0.03
	20	0.49±0.01	10.93±0.03	4.84±0.04
	25	0.49±0.01	10.82±0.09	4.93±0.24
SRS	10	0.50±0.01	10.93±0.02	5.01±0.02
	15	0.49±0.01	10.93±0.02	5.10±0.20
	20	0.52±0.01	10.88±0.10	5.19±0.10
	25	0.50±0.01	10.91±0.03	4.97±0.20
DdS	10	0.49±0.01	10.92±0.03	4.85±0.10
	15	0.50±0.01	10.85±0.08	5.41±0.06
	20	0.49±0.01	10.93±0.03	4.95±0.15
	25	0.50±0.01	10.91±0.03	5.05±0.16

Table 3.4: Values of Disintegration time, Crushing Strength, Friability, crushing strength-friability ratio (CSFR) of Paracetamol tablets

Disintegrant	Concentration (% w/w)	Disintegration time (secs)	Crushing strength (N)	Friability (%)	CSFR
Avicel®	10	28	14.23±1.01	19.83	0.72
	15	24	24.37±1.40	12.21	2.00
	20	26	25.66±0.83	13.00	1.97
	25	27	40.13±1.66	11.50	3.49
SRS : DdS (1:2)	10	29	10.57±0.42	27.89	0.38
	15	21	22.63±1.82	20.25	1.12
	20	26	13.83±1.80	29.72	0.47
	25	28	9.43±1.29	34.53	0.27
SRS	10	34	21.23±2.37	20.01	1.06
	15	34	6.73±0.70	49.55	0.14
	20	32	13.30±1.2	37.70	0.35
	25	29	10.77±1.80	38.07	0.28
DdS	10	34	10.63±0.93	33.95	0.31
	15	29	7.53±1.66	34.96	0.22
	20	34	11.97±0.46	39.89	0.30
	25	30	7.63±0.49	41.26	0.18

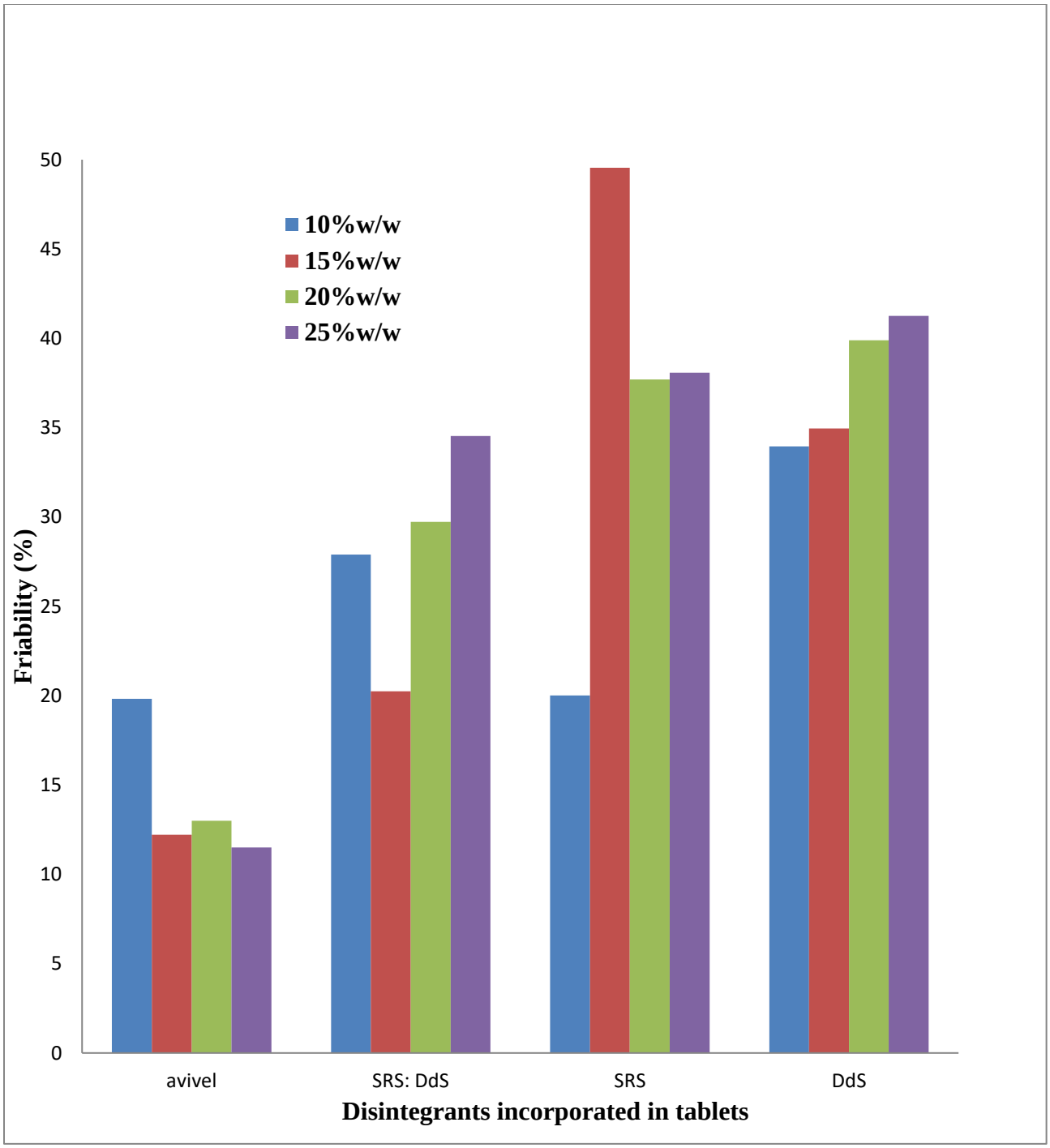


Fig. 3.5: Plot showing the effect of Disintegrant (%w/w) on Friability (%)

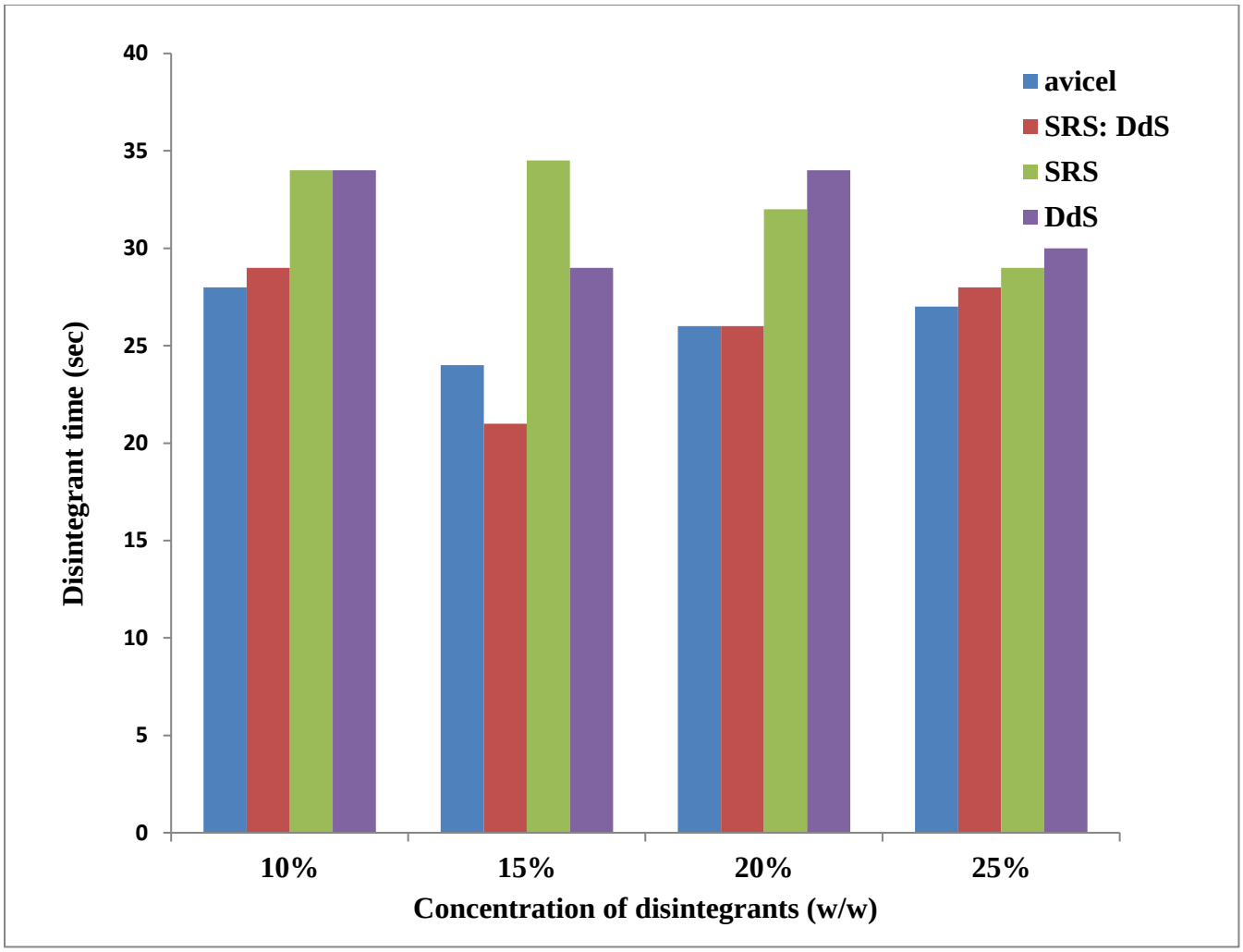


Fig. 3.6: Plot showing effect of disintegrant concentration (%w/w) on disintegration time (sec)

CHAPTER FOUR

DISCUSSION

4.1. Starch yield

Starch yield or recovery from yam tubers depends on factors such as the starch content in the original tubers, structure and composition of the tubers, postharvest storage conditions and the efficiency of the method of isolation (Daiuto *et al,* 2005). Starch from *Dioscorea dumentorum* is composed of small granules and more difficult to extract than those from other yam species (Otegbayo *et al,* 2014). This can be as a result of two (2) reasons; small granules settle more slowly during extraction and get entrapped in the fibrous matrix more easily than starches of larger granules. The yield of the *Dioscorea dumentorum* starch was obtained to be 39% w/w comparable with the starch content in dried flour which ranges from 41-63 % (Akinoso and Biodun 2013).

The starch component of rice makes up 80% of its total constituents, other minor constituents include proteins, lipids and phosphorus (Wani *et al,* 2012). The yield of the starch was however obtained to be 41%w/w which could have been as a result of spillage during the extraction process. Both the starch powders produced a blue-black colouration on addition of N/50 iodine, confirming the presence of starch in the powders. This is because, amylose forms a complex with iodine, which changes its colour to blue-black (Wani *et al,* 2012).

4.2. Fourier Transform Infrared (FTIR) Spectroscopy

Ganim *et al* (2008) documented the use of Fourier Transform Infrared (FTIR) spectroscopy in analyzing the secondary and tertiary structures of compounds based on harmonic oscillations associated with the bending and stretching of bonds. Significant changes in a sample can be detected from significant changes in functional groups that are associated with the sample as a result of bending and stretching of bonds due to intimate cohesion of the sample with other components.

The FTIR spectra for the silicified rice starch (Fig. 3.2) indicates characteristic peaks (3440.44 cm^{-1}, 2930.10 cm^{-1} and 2353.88 cm^{-1}) in the functional group region, which can be assigned to O-H stretching vibration in CH_2=C-H, stretching vibration in CH_3, CH_2.andC-H stretching vibration in C-O-C respectively. Other significant peaks are shown in the fingerprint region within the range 1421.04 cm^{-1} and 465.73cm^{-1}; peaks within this range are associated with aromatic C-H bending vibrations. Co-processing of silicified rice starch (SRS) with *Dioscorea dumetorum* starch (DdS) did not affect the integrity of SRS as relatively all the characteristic peaks were replicated in the FTIR spectra for SRS:DdS (1:2) as seen in Fig. 3.3. For example, the peaks occurring at 3440.44 cm^{-1} and 2930.10 cm^{-1}in the FTIR spectra for SRS are now occurring at 3455.00 cm^{-1} and 2928.72 cm^{-1} respectively in the FTIR spectra for SRS:DdS (1:2).

4.3. Mechanical properties of starch powders

4.3.1. Bulk and Tapped densities

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume expressed in

grams per millilitre (g/mL). The bulk density is therefore a subject of the powder properties and the arrangement of the particles in the powder bed (International Pharmacopoeia, 2018). Reproducibility is often a problem with bulk density because slight disturbance of the powder bed changes the bulk density.

The bulk density of a powder determines its packing behavior during die filling, mixing, granulation and compression (Odeku and Okunlola, 2009). Light powders leave large gaps between individual particles and have low bulk densities whereas heavy powders have smaller particles sitting between larger particles with resultant high bulk density. Tapped density is obtained by mechanically tapping a graduated measuring cylinder containing the powder sample. The tapped density of a powder determines the rate and extent of packing during the unit operations of tableting.

From the results obtained, the ranking of the bulk and tapped densities was Unmodified Rice Starch (URS)>*Dioscorea dumentorum* Starch (DdS) > Silicified Rice Starch (SRS). Silicified Rice starch had the lowest values, indicating a high fill volume.

4.3.2. Flow and Compressibility Properties.

The flow property of a powder is a key consideration in the formulation of tablets. The flow of the powder from the hopper into the die determines the weight, hardness and content uniformity of the tablets (Shah *et al*, 2008). Angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner ratios are evaluated as measures of flow. The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. It is a function of the strength of the interparticulate forces, flatter cones having weaker interparticulate forces. The smaller

(more acute) the angle, the better the flow properties of the powder (Copley, 2008).Powders have excellent, good, fair, passable, poor, very poor, very very poor flow when they have values 25-30°,31-35°, 36-40°, 41-45°, 46-55°, 56-65° and >66°. The ranking of the angles of repose was Silicified rice starch, SRS< Unmodified rice starch, URS <*Dioscorea dumentorum* starch, DdS.

Carr's index is the ratio of the difference between the tapped density and the bulk density to the tapped density. Hausner ratio is the ratio of the tapped density to the bulk density of the powder. From the results, the ranking of the Carr's index and Hausner ratio was SRS<DdS< URS.

4.3.3. Uniformity of weight of Tablets

Tablet weight is influenced by factor such as the tableting machine, pressure, machine speed and flow properties of the powder. From the results, the diameter and weight of the tablets showed insignificant deviations with the highest being 0.1 mm. The highest deviation from mean thickness of the tablets was 0.24 mm. Uniformity of weight of tablets is a measure of homogeneity of distribution of constituents in the formulation.

All the tablets fell within the acceptable limit of weight variation ($\pm$ 5%) allowed for tablets weighing $\pm$250 mg (British Pharmacopoeia, 2009).

4.4. Mechanical Properties of Tablets

4.4.1. Crushing Strength

Crushing strength of a tablet is a measure of the tablet hardness and it is the force required to break up a tablet. The crushing strength of a tablet is dependent on the

concentration of the binder, type and concentration of lubricant, compression force and the powder/granule properties. Crushing strength as a property of tablets does not have officially set limits for acceptance or rejection. This is because the acceptable crushing strength is dependent on the intended use of the tablet.

From the results, Avicel® had the highest average crushing strength at all the disintegrant concentrations used and *Dioscorea dumentorum* starch had the least. The ranking of the average crushing strengths of the tablets is Avicel®>SRS :DdS>SRS >DdS. The variation between the crushing strengths ranged from 0.49- 2.37 N.

4.4.2. Friability

Friability is a measure of the tendency for a tablet to chip, crumble or break following compression. Friability testing is employed to determine the physical strength of compressed and uncoated tablets upon exposure to mechanical shock and attrition (Saleem *et al,* 2014). Thus it tells how much mechanical stress tablets can withstand during manufacture, distribution and handling (Iwuagwu *et al,* 2013). According to the British Pharmacopoeia, friability values of less than 1% are considered acceptable. From the results obtained however, all the tablets failed the friability test with the least value of friability being 11.50 %. This high friability could be as a result of insufficient binder or small compression pressure.

Avicel® had the least disintegration values across all the disintegrant concentrations. At 15%w/w disintegrant concentration, the friability of the tablets ranked Avicel® <SRS: DdS (1:1) <DdS<SRS.

4.4.3. Disintegration

Disintegration is the mechanical breakdown of a tablet into smaller particles as a result of the breakage of inter-particle interactions generated during tablet compression (Silva *et al*, 2018). If disintegration does not occur, only active ingredients near the surface of the tablet dissolves and so are available for absorption and activity. Disintegration is thus an important prerequisite for dissolution and absorption of tablets (Silva *et al*, 2018). From the results of the study, all the paracetamol tablets had disintegration times much lower than the Pharmacopoeia specification of < 15 minutes with disintegration occurring in seconds (British Pharmacopoeia, 2009). This rapid disintegration time could be exploited in the formulation of immediate release tablets.

The disintegration times for Avicel® and SRS:DdS compared favourably at all disintegrant concentrations with SRS: DdS having a lower disintegration time than Avicel® at 15%w/w concentration.

CHAPTER FIVE

CONCLUSION

This study was aimed towards evaluating the disintegrant properties of silicified rice starch (*Oryza sativa*) co-processed with *Dioscorea dumentorum* starch in directly compressed paracetamol tablet formulations. From the results obtained, the following conclusions can be made:

i. Silicification of rice starch markedly improved the flow properties of the starch when compared with the unmodified starch without affecting the integrity of the starch.

ii. Co-processing of silicified rice starch with yam starch did not affect the functional integrity of the individual starches as shown by FTIR spectroscopy.

iii. Tablets containing Avicel® as disintegrant had better crushing strength and friability values than those containing silicified rice co-processed with *Dioscorea dumentorum* starch (SRS:DdS) at all disintegrant concentrations.

iv. Avicel® and SRS:DdS had relatively comparable disintegration times. However, at 15%w/w concentration, SRS:DdS exhibited better disintegrant properties than Avicel®.

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