UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

THE EFFECT OF NATIVE CASSAVA STARCH ON THE DISINTEGRATION OF FORMULATED PARACETAMOL TABLETS

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QUOTE

If you don't like something change it; if you can't change it, change the way you think about it.

----------Mary Engelbreit----------

DECLARATION

I declare that this is my original work and the work has not in any form or way been submitted to any other institution for examination purposes or otherwise.

Signature..... Date..30/09/2013.....

Supervised by;

Dr. Lucy. J. Tirop

Signature..... Date..30/09/2013

DEDICATION

To The Almighty God who has been my aid and my guide for this long and has made me rise over the many challenges.

ACKNOWLEDGEMENTS

I am overwhelmed by the input accorded to me by my supervisor Dr. Tirop, my mentor Dr. Karumi and the pharmaceutical technologists, School of Pharmacy, who have seen me through the realization of my project. I would also like to appreciate highly my uncle David Wanjohi who has seen me through my years of undergraduate study.

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ABSTRACT

The project involved the use of extracted cassava starch from raw cassava tubers as a disintegrant in the manufacture of tablets. However, there was also manufacture of tablets using industrial corn starch. The tablets obtained were tested for comparison. Other physico-chemical tests were conducted on the locally acquired cassava starch.

The extracted cassava starch was also subjected to tests such as solubility, cyanogenic glycoside, iodine, tannin, angle of repose, bulk density, swelling capacity, and moisture content. The starch was confirmed and found to be insoluble in water and ethanol, cyanogenic glycosides were present, no tannins were present and bulk density, swelling capacity and moisture content results were recorded accordingly.

Wet granulation was then done to make granules that would be used to make the tablets. Small granules were then formed by passing them through different sieves viz:710um,500um,355um,250um,180um,125um.The granules weights were then recorded and results tabulated. The granules were then used to make corn and cassava tablets for comparison tests.

The comparison of the tablets formed by the cassava and corn starches was then done in the form of different tests done viz; disintegration, mechanical strength, friability, hardness and uniformity of weight. This tests were done following relevant Standard Operating Procedures as they were stipulated.

The use of locally acquired starches such as cassava was a noble approach however the rates of disintegration, friability, mechanical strength and other tests done on the tablets showed corn starch was the preferred disintegrant and that it was the disintegrant of choice as it served as a staple food for the country thus its availability. A risk of using cassava was evident due to it containing cyanogenic glycosides as evidenced by the test.

The tablets seemed not to pass friability and disintegration tests as the compression was not adequate during tableting.Most tablets passed the uniformity of weight test.Deviations from the mean weight were presented in table format.

CHAPTER ONE

1. INTRODUCTION

1.1. SOLID DOSAGE FORMS

Solid dosage forms are defined as solid formulations comprising an active pharmaceutical ingredient (API) and excipients. Solid dosage forms may be administered orally or via other different routes such as the buccal, rectal or even vaginal routes. However, oral solid dosage forms especially tablets and capsules have gained much popularity due to their easy mode of administration and also portability.

1.1.1. TABLETS

The term tablet is from the Latin word 'tabuletta' and is associated with appearance of the dosage form i.e. a tablet is a small disc-like or cylindrical specimen. Moreover, 'compressi' also a Latin name envisages the fact that the dominating process of tablet production is powder compression in a confined space. Alternative procedures used in tablet production include molding and freeze drying. Tablet-like preparations formulated by freeze drying are called oral lyophilisates. Molding, is the shaping and hardening of a semi-solid mixture of active substances and excipients (Reference 1).

A tablet may consist of one or more drugs, APIs, as well as a series of other substances, known as excipients, used in the formulation. The European Pharmacopeia defines a tablet as solid preparation each containing a single dose of one or more active ingredients and usually obtained by compressing uniform volumes of particles. Tablets may be swallowed whole, chewed or dissolved in water before being administered. Other tablets e.g., buccal tablets are retained in the mouth where the active ingredient is released.

Tablets may be used for systemic or local drug delivery. Systemically, the drug must be released from tablet i.e. dissolved in the fluids of the mouth, stomach or intestines and thereafter be absorbed into systemic circulation by which it reaches its site of action. In the case of local drug delivery, the mouth or gastrointestinal tract are sites of action e.g., anti-acid tablets act locally in the stomach where they are used to increase the stomach pH momentarily.

The popularity of tablets for drug administration is due to the following factors;

a) The oral route represents a convenient and safe way of drug administration.

b) In comparison to liquid dosage forms, tablets exhibit better chemical and physical stability.

c) Tablets enable accurate dosing of the drug.

d) Tablets are convenient to handle and can be prepared in a versatile way with respect to their use and the delivery of the drug.

e) Tablets can be mass produced relatively cheaply with robust and quality controlled production procedures giving elegant preparations of consistent quality.

However, drawbacks to tablets as a dosage form include concerns regarding the bioavailability of poorly water-soluble or poorly absorbable drugs. In addition, some drugs may cause local irritancy to the gastrointestinal mucosa.

Tablet attributes enabling fulfillment of a number of specifications regarding chemical, physical and biological properties include;

a) Tablets should include correct dose of the active pharmaceutical ingredient (API)

b) Tablet appearance should be elegant

c) Tablet weight, size and appearance should be consistent

d) The API should be released from the tablet in a controlled and reproducible manner

e) Tablets should be biocompatible i.e. not include excipients, contaminants or microbes that could cause harm to patients

f) The tablet should be of sufficient mechanical strength to withstand fracture and erosion during handling at all stages of its lifetime.

g) The tablet should be formulated and packed in a manner presentable to the patient.

1.1.1.1. EXCIPIENTS

Excipients are substances other than the API or prodrug which are included in the manufacturing process and contained in the final dosage form. Excipients are added as they ensure tabletting runs satisfactorily with quality tablets being produced. These excipients, which are classified depending on their different roles include;

i) Fillers

Fillers, otherwise known diluents, are used to increase the bulk volume of powder and hence facilitate tablet formulation. Generally, tablets weigh more than 50mg and therefore a low dose of a potent drug requires incorporation of fillers. However, the filler may not be necessary if the dose of drug per tablet is high. Ideal fillers should be chemically inert, non-hygroscopic, biocompatible, cheap, have acceptable taste and possess good technical properties i.e. compatibility and dilution capacity. Substances used as fillers include lactose, sucrose, glucose, mannitol, sorbitol, calcium phosphate, cellulose and calcium carbonate.

ii) Binders

A binder, also sometimes called an adhesive, is added to a drug-filler mixture to ensure granules and tablets can be formed with required mechanical strength. Examples of binders include gelatin, plant gums, starch, sucrose, cellulose, and methylcellulose.

iii) Glidants

The role of a glidant is to improve flowability of the powder. Glidants are added to the powder/granules before tabletting to ensure that sufficient flowability of powder/granules from the hopper to the die. Examples of lubricants include silica, magnesium stearate and talc.

iv) Lubricants

A lubricant is a substance added in tablet formulation that ensures that tablet formation and ejection can occur with low friction between the powder/granulate and die wall. High friction may cause flaking, capping and other tablet defects. Examples of lubricants include liquid paraffin, sodium stearyl fumarate, sodium lauryl sulphate, stearic acid and polyethylene glycol.

v) Anti-adherents

Anti-adherents are substances added to a tablet formulation to reduce adhesion or sticking of the particles from the powder bed to the punch faces. Tablet defects such as sticking or picking happens mostly if the tablet punches have markings or the powder has a high moisture content. Examples of anti-adherents include talc, starch, cellulose and magnesium stearate.

vi) Adsorbents

Adsorbents are substances capable of eliminating moisture by way of sorbing some quantities of fluid in an apparent dry state. This sorbents include silica or microcrystalline cellulose.

vi) Flavors

Flavouring agents are added into formulations to mask any unpleasant taste. Some flavors are thermolabile and thus should not be added to an operation involving heat. Examples of flavors include orange and banana flavors.

vii) Colorants

Colorants are added to formulation to aid in identification of tablets, improve aesthetic appeal and enhance patient compliance. Coloring is often accomplished during coating but colourants can also be included in the formulation prior to compaction.

viii) Disintegrants

Disintegrants are included in the formulation to ensure that the tablet, upon contact with liquids breaks up into small fragments, thus promoting rapid drug dissolution. The tablet should ideally disintegrate into smaller drug particles in order to obtain the largest possible effective surface area during dissolution. Examples of disintegrants include, starch, cellulose, sodium carboxymethyl cellulose and sodium starch glycolate.

Native starches are extensively used as disintegrants in tablet formulation. Starches act via swelling or capillary action when wetted with aqueous liquids. Starches are isolated from raw materials of different origins including rice, banana, cassava, sorghum, millet, maize, oat, wheat and potato just to mention a few. These starches therefore have different physiochemical properties such as particle size, swelling and hydration capacity. These differences could modify their functioning as tablet disintegrants.

Pharmaceutical industries have trusted in the reliability of natural starches since the early beginnings. The latest technology, roquette, transforms three key crops (maize, wheat and potatoes) into essential and high quality excipients in pharmaceutical industry. Maize starch, extra white maize starch, wheat starch and potato starch are long-known and reliable excipients used as insoluble diluents/fillers in the formulation of tablets and capsules and as powder for sachets, all while retaining a disintegration function (reference 2).

In recent years several newer agents, known as super disintegrants, have been developed. These super disintergrants are very effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water, super disintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. Super disintegrants offer significant improvements over traditional disintegrants.

Some factors affecting the disintegration time of the tablet include:

a) Type of disintegrant

b) Amount of disintegrant

c) Compression force used to manufacture the tablets

The disintegrants play an opposing role to tablet binders and the physical forces that are employed during tablet compression. Ideally, disintegrants should cause the tablet to disrupt, not only into granules from which it was compressed, but also into the powder particles from which the granules were prepared.

While rapid disintegration of tablets don't necessarily ensure fast bioavailability, slowly disintegrating tablets almost always exhibit slow bioavailability. The ability to interact strongly with water is essential to the disintegrant's function. Swelling and/or wicking and/or deformation are the main mechanisms of disintegrant action.

A disintegrant used in granulated formulations can be more effective if used both 'intergranularly' or 'extragranularly' thereby acting to break the tablet into granules and breaking the granules in powder particles. Disintegrant added intragranularly (in wet granulation process) is usually not as effective as that added extragranularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since the compaction process does not involve its exposure to wetting and drying, the disintegrant used extragranularly tends to retain good disintegration activity. This therefore shows distinct ways in which the incorporation of disintegrant is done. The methods, by way of addition, thus include:

a) Internal addition (intragranular)

b) External addition (extragranular)

c) Partly internal and external

In the external addition method, the disintegrant is added to the prepared granules prior to compression. With the internal addition method, the disintegrant is blended with other powders before wetting the powder mixtures with the granulating fluid, thus the disintegrant is incorporated within the granules. Apart from these two methods, part of the disintegrant can be added intragranularly and part extragranularly. The extragranular disintegrant ensures immediate disruption of the tablet into previously compressed granules, while the disintegrating agent within the granules produces further erosion of granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding disintegrant to the granulation surface only.

Disintegrants typically act via one/more of the four mechanisms outlined below;

a) Swelling; It should be noted that tablets with high porosity show poor disintegration due to inadequate disintegration force. Sufficient swelling force is exerted in tablet with low

porosity. It is worthwhile also to understand if packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slowed down.

b) Wicking (capillary action); Disintegration by capillary action is always the first step in tablet disintegration. When the tablet is put into suitable aqueous media, the medium penetrates the tablet and replaces the air adsorbed on the particles weakening the intermolecular bonding and breaking tablet into fine particles. Water uptake by tablet depends upon hydrophobicity of the drug/excipient and on the tablet conditions e.g., porosity. The disintegrant's maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary as this helps in disintegration by creating a hydrophilic network around the drug particles.

c) Particle/particle repulsive forces; Non-swelling particles also cause disintegration of tablets by the electric repulsion forces generated between particles in contact with water. It was noted that this electrical repulsion is secondary to wicking-phenomenon by Guyot-Hermann (Reference 3).

d) Deformation; During tablet compression, disintegrated particles get deformed and only resume their general structure upon hydration. For example, the swelling capacity of starch is improved when granules are extensively deformed during compression. The size increase of the deformed particles on hydration produces disintegrant forces breaking up the tablet.

1.2. TABLETTING

Tablets are basically prepared by compression which involves forcing particles/granules into close proximity to each other, which enables particles to cohere into a porous, solid specimen of defined geometry.

The rationale of granulation of powders prior to tabletting includes;

a) Improved compactibility of powder by adding a solution binder which is effectively distributed on particle surfaces.

b) Improved flowability of powder to ensure tablets with a low and acceptable tablet weight variation can be prepared.

c) Improved mixing homogeneity and reduction of segregation.

d) Ensures homogeneous color on a tablet by adding color in a manner that ensures its effective distribution over particle surfaces.

The process of tabletting can be divided into three stages;

i. Die filling

This is done by gravitational flow of powder from a hopper via the die table into the die (although pressure based flow employed in centrifugal die filling). The die is closed at its lower end by the lower punch.

ii. Tablet formation

Upper punch descends and enters the die and the powder is compressed to form a tablet. During the compression phase the lower punch can be stationery or can move slightly upwards in the die. After maximum applied force is reached, the upper punch is raised thus decompressing the powder bed.

iii. Tablet ejection

During this phase the lower punch rises until its tip reaches the level of the top of the die subsequently ejecting the tablet from the die. The tablet is then removed from the die table by a pushing device. Tablet presses used in tabletting include the single punch press (eccentric press), the rotary press and the computerized hydraulic press (compaction simulator).

1.3. DRUG OF STUDY

Paracetamol, the drug to be used in this study, is a common analgesic with overwhelming demand worldwide. It is known by tradenames such as Panadol®, Acetaminophen®, Betamol®, and Sonamoja®. Paracetamol is an over the counter drug, requiring no prescription to purchase, hence its popularity.

Statistics show of a population of seventeen million people (worldwide) who use analgesics, majority popularly choose paracetamol as an API to relieve pain sensation. This indeed stipulates the need to have more studies in the improvement of bioavailability of paracetamol tablets while maintaining their quality.

The metabolism of paracetamol involves a series of enzymes that inactivate the compound. Paracetamol dosage should not exceed 4 g a day for any individual as this may lead to hepatotoxicity brought about by paracetamol metabolites. Dosage for adolescents and adults is normally 1 g (two tablets of 500 g) thrice daily (TDS). Pediatrics, due to palatability and swallowing problems may receive a liquid dosage form at a dosage of 100 mg TDS (Reference 4).

CHAPTER 2

2. LITERATURE REVIEW

Cassava (*Mannihot esculenta*) is one of the plants that has drawn very huge attention in terms of increasing diversity in food production. Other scientific names of cassava include *Mannihot ultissima phol* and *Mannihot aipi phol.* Cassava also has common names viz: yucca, mwanga, muhogo, mogo and manioc root, just to mention a few. Cassava is a native shrubby plant initially from South America. It is extensively cultivated in tropical and subtropical regions for its edible starchy tuberous root (Figure 2.1), a major source of carbohydrates. When dried and milled it forms a starchy, powdery extract called tapioca, which upon fermentation forms garri (Reference 5).

Figure 2-1: Photograph of cassava tubers

2.1. TAXONOMICAL CLASSIFICATION OF CASSAVA

Kingdom; Plantae

Phylum; Angiospermae

Class; Eudicots

Order; Malpaghiales

Family; Euphorbiacae

Subfamily; Crotonoideae

Tribe; Manihotae

Genus; Manihot

Species; *Mannihot esculenta*

2.2. FLOWERING CHARACTERISTICS OF CASSAVA

Cassava bears separate male and female flowers on the same plant making it monoecious. Male and female flowers are borne in a single branched panicle, with female flowers at the base and male flowers towards the tip. The flowers are small, with the male flower being about 0.5 cm in diameter, and female flower slightly larger (Reference 6).

2.3. CASSAVA TOXICITY

Cassava is famous for free and bound cyanogenic glycosides i.e. linamarins and lotaustralin. They are converted to HCN (hydrogen cyanide) in presence of linamarasea, a naturally occurring enzyme that acts upon rupture of cells. All plant parts contain cyanogenic glycosides with the leaves having the highest concentration than the interior. In the past cassava was classified as either sweet or bitter signifying the absence or presence of toxic cyanogenic glycosides. Sweet cultivars can produce as little as 20mg of HCN per kilogram of fresh roots, while bitter ones produce fifty times as much. Bitterness is identified by taste and smell.

2.4. RECENT STUDIES EMPLOYING CASSAVA STARCH AS A TABLET DISINTEGRANT

Apart from cassava starch being used as a disintegrant, studies show of it also being used as a binder and/or as filler. Maize starch is mainly used as a disintegrant in many tablet formulations. Recent studies on starch disintegration properties have been carried out on metronidazole tablets whereby cassava starch is extracted and subjected to modification by controlled acid hydrolysis to produce microcrystalline cassava starch. Both the unmodified and microcrystalline cassava starch was tested for hydration and swelling capacities. Comparison of unmodified cassava starch and maize starch B.P. are used as a basis of comparison with the microcrystalline cassava starch.

Metronidazole granules were prepared by wet granulation and were evaluated for moisture content, size distribution and flow properties while tablets were assessed for friability, crushing strength, weight uniformity, disintegration time, dissolution rate and content of active ingredient. The yield of microcrystalline cassava starch was 66%. The unmodified and microcrystalline cassava starches displayed hydration and swelling capacities of 2.21 and 2.24 respectively; values that doubled those produced by maize starch B.P. Granules formed were free flowing. The tablets formulated using 7.5% w/w concentrations of unmodified cassava starch, microcrystalline cassava starch and maize starch as disintegrant, disintegrated at 3.24, 1.7 and 2.07 minutes respectively. Microcrystalline starch derived from cassava displayed superior disintegration properties than the unmodified cassava starch and maize starch B.P used (Reference 7).

Another study in Nigeria involved the use of official maize and potato starches and locally produced cassava starch as disintegrants in sodium salicylate tablet formulations. The disintegrants were added intragranularly in each batch. Concentration range of 5% to 15% w/w of each disintegrant was used. In vitro dissolution profile, weight uniformity and hardness tests were also performed. The mean disintegration times obtained at 5% w/w disintegrant concentrations were 32.33, 33.83 and 41.50 minutes for tablets formulated with maize, cassava and potato starches respectively. At 10% w/w starch concentration, the mean disintegration times were 28.66, 34.67 and 32.33 minutes for tablets formulated with maize, cassava and potato starches respectively, while at 15% w/w, results were 33.33, 46.67 and 42.67 minutes for tablets formulated with maize, cassava and potato starches respectively. T50% (time required for dissolution of 50% of the drug) obtained for all the batches of tablets produced, indicates that all the tablets released up to 50% of active ingredient within 18 minutes. An order of the efficiency of the various starches as tablet disintegrants was established i.e. maize>potato>cassava, with maize and potato starches being optimum disintegrants at 10% w/w while the locally produced cassava starch was an optimum disintegrant at 5% w/w in the sodium salicylate tablet formulations (Reference 8).

Cassava starch was also used in a study in Thailand in the University of Nakhon Pathon. Native yam starch and carboxymethyl yam starch (CMS) were evaluated as tablet disintegrants in comparison with various starches viz; maize, tapioca and rice starch. The tablets were made by direct compression having calcium phosphate as a filler and each of the starches used as a disintegrants between 3-15% w/w and magnesium stearate as a lubricant. Hydrochlorothiazide (HCTZ) was used the active pharmaceutical ingredient. Properties such

as friability, hardness, disintegration and dissolution were evaluated. Tablet hardness seemed to increase on addition of more starch. Yam and rice starch containing tablets were harder as compared to tablets containing other native starches, with tablets formulated with yam CMS exhibiting remarkable hardness. Native yam starch showed faster disintegration properties as compared to tapioca, rice and corn starches. The increase of native starch concentration in the tablets led to faster tablet disintegration. Up to a concentration of 9% w/w CMS and yam starch, tablets showed similar disintegration times. It was therefore concluded that native yam starch with its carboxymethyl derivative can be used as superior disintegrants in tablet formulations (Reference 9).

2.5. JUSTIFICATION

Most tablet formulations have prioritized the use of maize starch as a disintegrant and also the emerging super disintegrants. This may be a contributing factor to the exclusion of other starches such as yam, cassava, potato and other starches. Evaluation of this other starches is important thus the need for the study. Moreover, different plants may give different starches that exhibit different properties due to the varying climatic conditions at their specific ecological niches i.e. cassava, maize or yam starches of a particular region may show different nutritional properties or characteristics compared to other regions thus the need to evaluate them.

Furthermore despite availability of the raw materials, many industries in the developing world rely on imported pharmaceutical excipients. Local production of pharmaceutical excipients may contribute to the reduction in tablet prices and thus provision of efficient and affordable healthcare.

2.6. MAIN OBJECTIVES

To compare the disintegrant properties of native cassava starch, extracted from tubers obtained locally, and pharmaceutical grade maize starch in formulated paracetamol tablets.

2.7. SPECIFIC OBJECTIVES

a) Extraction and characterization of cassava starch from tubers obtained locally

b) Preparation and evaluation of paracetamol granules

c) Preparation of paracetamol tablets using both native cassava starch and pharmaceutical grade maize starch as disintegrants

d) Evaluation of prepared paracetamol tablets using tests such as uniformity of weight, hardness, friability among others

2.8. HYPOTHESIS

The disintegration of tablets prepared using native cassava starch is comparable to that of tablets prepared using pharmaceutical grade maize starch.

CHAPTER 3

3. MATERIALS & METHODOLOGY

3.1. MATERIALS

a) Paracetamol

b) Lactose (filler)

c) Maize starch (disintegrant)

d) Acacia mucilage (10%w/v)

e) Magnesium stearate (lubricant)

f) Cassava tubers

g) Distilled water

3.2. APPARATUS

i) Tabletting machine (make of Liverpool from the United States of America)

ii) Friability tester

iii) Disintegration tester machine

iv) Weighing balance

v) Sieves

vi) Grater

vii) Knife

viii) Monsanto tester

3.3. EXTRACTION OF STARCH

Cassava starch was freshly extracted by wet milling the raw tubers. The cassava starch needed to be extracted immediately to avoid perishability and enzymatic degradation, processes that are responsible for the deterioration in 1-2days. Five kilograms of cassava tubers were peeled, washed and grated. A pulp was then formed by addition of water (water added to gratings in the ratio of 2:1). The mixture was then sieved with the gratings being retained. Thereafter, the gratings were washed three to four times with distilled water.

The starch extracted was allowed to sediment after which the water was decanted off and the starch rewashed with distilled water to remove any fiber remaining. The starch was then dried

in open air for two days at room temperature. The powdery starch was then stored in an air tight container to prevent contamination and moisture. The percentage yield of starch was then calculated (Reference 10).

3.3.1. TESTS CARRIED OUT ON EXTRACTED STARCH

a) Solubility test

It involved the addition of 1g of the cassava starch in 100ml of distilled water and stirring of the mixture. Turbidity or a clear solution were the parameters used to check for solubility of the starch.

b) Cyanogenic glycoside test

0.5g of the cassava starch was put in a test-tube and few drops of water added. A strip of sodium nitrate paper was suspended in the mixture. The mixture was then heated gently to 37 degrees centigrade and allowed to stand. Liberation of a gas and the colour of the sodium nitrate paper were checked and noted.

c) Iodine test

Both starches (2g of both maize and cassava) were subjected to a few drops of iodine solution after addition of a few drops of water and the colour changes noted.

d) Tannin test

2g of the cassava starch was subjected to 20ml of water and filtered, a few drops solution of ferric chloride was added and colour changes noted.

e) Angle of Repose

A 30g sample of the cassava starch was poured into a plugged paper funnel, which was 10cm above a flat surface. The starch was allowed to flow freely through the orifice of the funnel forming a heap whose height and diameter were determined. The angle of repose was calculated using the formulae: Tan o=height/radius. This test was also carried out on the maize starch for comparison purposes.

f) Bulk density

A sample of the cassava starch was weighed and poured in a 100ml cylinder and volume recorded. The bulk density (BD) was calculated using formulae;

BD=M/V

where M=Mass of the powder and V=Volume of the powder

This test was also carried out on the maize starch for comparison purposes.

g) Swelling capacity

The tapped volume (Vd) occupied by 10g of the cassava starch in a 100 mL measuring cylinder was noted. The powder was then dispersed in 85ml of distilied water and the volume made to 100 mL with more water. After around 15 hours of standing, the volume of sediment (Vw) was noted and the starch swelling capacity computed as follows:

Swelling capacity = Vw-Vd

This test was also carried out on the maize starch for comparison purposes.

h) Moisture content

A 3g weight of the cassava starch was heated to 125 degrees centigrade and then weighed again for the determination of moisture content.

3.4. GRANULATION

Granulation was carried out by wet/moist granulation where the granules were formed by adding granulating liquid to the powder then forcing the mass through sieve apertures of suitable size i.e. 710 microns. The excess moisture was removed by drying the granules at room temperature overnight. Table 3.1 presents the composition of each tablet.

Table 3.1: Composition of ingredients in each tablet

For each tablet: *Intragranularly*	
Paracetamol powder	300mg
Lactose (filler)	57.5 or 47.5 or 37.5 mg
Maize starch (disintegrant)	20 or 25 or 30 mg
Acacia (10% w/v) binder	1mg
Extragranularly	
Maize starch	20 or 25 or 30 mg
Magnesium stearate	2.5mg

Table 3.2 presents the composition of each ingredient in each tablet batch obtained by taking each amount in milligrams multiplied by fifty .i.e. the number of tablets per batch.

Table 3.2: Composition of each ingredient in fifty tablets

Intragranularly	
Paracetamol	15g
Lactose	2.875 or 2.375 or 1.875 g
Maize starch	1, 1.25 or 1.5 g
Acacia mucilage 10%w/v (binder)	0.05g
The powders were properly mixed and 10ml of water added for wet granulation. The granules were then dried followed by extragranular addition of lubricant and disintegrant.	
Extragranularly	
Maize starch	1g, 1.25 or 1.5 g
Magnesium stearate	0.125g

The procedure was repeated this time using extracted cassava starch as the disintegrant in the three concentration ratios (of 20mg, 25mg and 30mg intra and extragranular addition per tablet respectively) representing the different batches made.

3.4.1. TESTING OF GRANULES

Evaluation of granules is mainly a quality control parameter that aids to check compliance so as to maintain Good Manufacturing Practices (GMP). It involved two other aspects:

i) Size distribution

This constituted the passage of the dried granules through a series of sieves of different pore sizes i.e. 710, 500, 355, 250, 180 and 125 microns. The granules remaining on the sieve were given a positive value (oversize) and that which passed through a negative value (undersize) to the corresponding sieves in question.

ii) Angle of repose

The dried granules were passed through a funnel resting on a sheet of paper thus forming a cone shaped heap. The height and diameter of the cone formed by the granules was obtained, and values used for calculation of the angle of repose.

iii) Bulk density

The dried granules were weighed and then poured into a plastic measuring cylinder. The volume occupied by the granules was measured and used to calculate the bulk density of the granules.

3.5. TABLET MANUFACTURE

A tableting machine is a volumetric device thus granules filled into the die occupy similar volume dimensions. Thus the flowability, average size and size distribution of granules are therefore important for tablet weight uniformity after compression.

3.5.1. COMPRESSION OF GRANULES

The compression of granules to form tablets involved prior selection of the weight, shape and dimensions of the tablets as well as optimum compression force. The set of punches and die used were of known diameter with flat-faced punches. Diameter was controlled as per the B.P. 2010.

Tabletting involved compression of granules to form tablets. The granules were filled in the die and the punches used to produce tablets by way of compression. The tabletting machine was a single stroke press of model LIVERPOOL from the United States of America.

3.6. TESTING OF TABLETS

3.6.1. UNIFORMITY OF WEIGHT

Uniformity of weight is a general requirement for tablets except for the sugar-coated or enteric coated. Compliance to this test results from enhanced GMP and quality assurance. Poor machine maintenance, lack of production control may lead to excessive variations in tablet weight leading to incorrect dosages administered. The B.P. provides guidelines for the uniformity of weight test;

I. 20 tablets were weighed and average weight calculated
II. Single tablets were weighed
III. For tablets weighing between 80-250 mg not more than two tablets were expected to deviate from average tablet weight by more than ± 7.5% and no tablet by more than ± 15%
IV. The deviation was calculated by taking;
(Individual tablet weight – average tablet weight) ÷ average tablet weight × 100%.

3.6.2. DISINTEGRATION TEST

It involves the measure of the tablet disintegration rate which may be either fast, slow or in a delayed manner in the case of slow releasing tablets. The disintegration test involved:

i) Temperature and agitation conditions of apparatus were checked.i.e.37 degrees and the liquid media used was distilled water.

ii) 6 tablets were placed in the basket and the time required for disintegration recorded

iii) A guided disk was used as defined in B.P. if necessary, and tablets checked if they disintegrated within B.P specified times.

iv) The disintegration times were recorded for disintegrant analysis.

3.6.3. MECHANICAL STRENGTH

It is a test done to measure the tablet resistance to mechanical failure. Inadequate mechanical strength may lead to tablet breaking upon coating, handling or even transportation, while excessive mechanical strength may lead to tablets that may exhibit poor disintegration and dissolution characteristics. There no pharmacopeia or compendia standards for mechanical strength.

Measurement of strength involved use of instruments that are of metal and planar surfaces. Compressive or crushing forces were applied on edges of the tablets across its diameter.

The following procedures were followed;

i) The tablets were dusted off and each tablet placed on the two edges of the Monsato equipment. The device was screwed in and compressive pressure applied.

ii) The tablet hardness was then deduced and recorded after the tablet was crushed into fragments.

iii) The recording was done in kg/cm^2

3.6.4. FRIABILITY TEST

It involved the use of a friability test machine where the following procedures were followed;

a) Friability tester was rested on a flat surface

b) Friability tester was then connected to power

c) Power was switched on

d) Drum was unscrewed and the cover removed

e) 20 dusted tablets of known weight were placed on the drum

f) Drum was then covered and screwed back to its position

g) A speed of 25 revolutions per minute was set and the machine left to run for four minutes, making a total of 100 revolutions

h) After the revolutions were complete, the tablets were collected, dusted and reweighed

i) The percentage weight loss after the test was calculated

CHAPTER 4

4. RESULTS AND DISCUSSION

4.1. EXTRACTION OF STARCH

Starch was extracted and the percentage yield calculated as follows:

$$percentage\ yield = \frac{Final\ weight\ of\ starch}{Weight\ of\ Cassava\ tubers} \times 100$$

$$percentage\ yield = \frac{1.5kg}{5kg} \times 100$$

The percentage yield obtained was 30%, which was well within the expected range (20-32%) according to the International Starch Institute for Cassava.

Summary of starch extraction process

The extraction of cassava starch involved a series of processes summarized in the flow chart below (Figure 4.1).

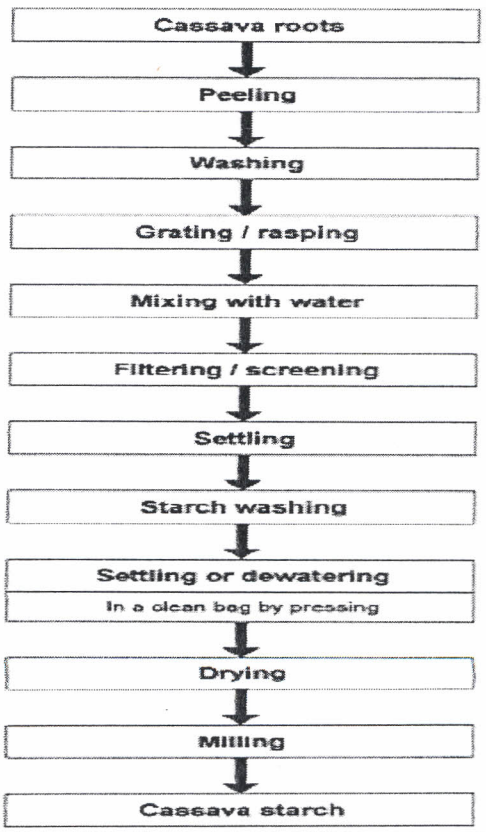

Figure 4-1: Flowchart showing stages involved in starch extraction from cassava

4.2. CHARACTERIZATION OF EXTRACTED STARCH

i) Solubility test

Upon adding the cassava starch to distilled water, it was properly shaken for around two minutes. Turbidity was present even after shaking thus revealing that the starch was insoluble in water. The starch was also insoluble in ethanol.

ii) Cyanogenic glycoside test

In this test there was evolution of a gas that turned the sodium nitrate paper to reddish purple thus showing presence of the cyanogenic glycosides which are poisonous both to animals and man. Therefore the extracted starch would require further purification to remove these cyanogenic glycosides.

iii) Iodine test

The powder turned blue-black after addition of iodine solution, confirming the presence of starch.

iv) Tannin test

The water-starch mixture assumed the colour of the ferric chloride solution indicating absence of tannins.

v) Angle of Repose

The radius of the heap was 5cm in height and 6cm in radius thus the angle of repose came to 39.81° which was calculated as per the formula given in Chapter 3. This value falls within the acceptable range for pharmaceutical powders of below 40°.

vi) Bulk density

The mass of the powder being 30g and the volume occupied being 60mL, the bulk density was 0.5g/mL.

vii) Moisture content

The percentage moisture content, obtained by determining weight loss after drying, was 2%. The starch was therefore less prone to microbial attack and interaction with drugs due to the relatively low moisture content.

viii) Swelling capacity

The swelling capacity of the cassava starch was 4 thus it showed that it was highly efficient in low concentrations due to its high swelling capacity.

4.3. GRANULATION AND TESTING OF GRANULES

Paracetamol granules were successfully prepared by wet granulation. They were white in colour and looked gritty on the surface.

The following key is used in presentation of results;

Batch 1G - Granules containing 1g of maize starch intragranularly
Batch 2G - Granules containing 1.25g of maize starch intragranularly
Batch 3G - Granules containing 1.5g of maize starch intragranularly
Batch 4G - Granules containing 1g of cassava starch intragranularly
Batch 5G - Granules containing 1.25g of cassava starch intragranularly
Batch 6G - Granules containing 1.5g of cassava starch intragranularly

i) Particle size distribution

Particle size analysis results obtained by sieving the granules are presented in Tables 4.1-4.2 and Figures 4.2-4.3.

Table 4.1: Particle size distribution of granules prepared using maize starch

Particle size	Batch 1G	Batch 2G	Batch 3G
+710um	9.67g (79.98%)	9.46g (77.04%)	12.25g (71.72%)
+500um	0.7g (5.78%)	1.57g (12.79%)	1.24g (7.25%)
+355um	0.5g (4.14%)	0.44g (3.58%)	1.16g (6.78%)
+250um	0.4g (3.56%)	0.38g (3.09%)	1.0g (5.85%)
+180um	0.33g (3.31%)	0.13g (1.05%)	0.6g (3.51%)
+125um	0.37g (3.06%)	0.2g (1.63%)	0.7g (4.09%)
< 125 um (fines)	0.12g (0.99%)	0.1g (0.81%)	0.13g (0.76%)
Total weight of granules	12.09g	12.28g	17.08g

Most of the granules were retained in the 710um sieve as stipulated in the graph. However, no significant trend was evident. It was expected that larger granules were a hindrance to hardness of tablets and smaller granules would form well hardened tablets due to the surface area available for bonding. On the other hand, larger granules have better flow properties than smaller granules. Determination of granule size and size distribution is important as it helps predict flow properties and resultant tablet hardness.

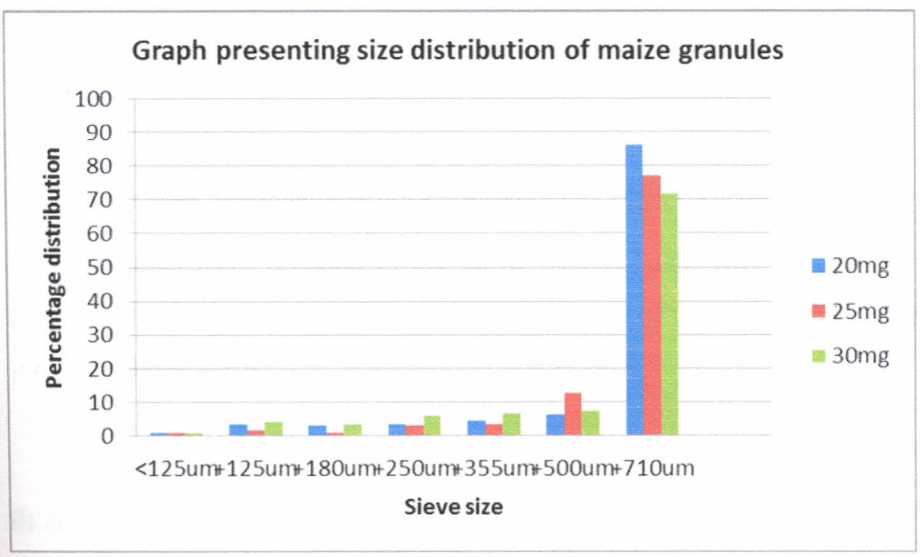

Figure 4-2: Graph presenting particle size distributions of granules prepared using maize starch

Here the increase of the disintegrant concentration intragranularly has no conclusive effect on size distribution of the granules

Table 4.2: Particle size distribution of granules prepared using cassava starch

Particle size	Batch 4G	Batch 5G	Batch 6G
+710um	10g (69.15%)	9.6g (73.61%)	9.5g (72.07%)
+500um	1.91g (13.21%)	0.96g (7.36%)	1.6g (12.14%)
+355um	0.9g (%)	0.71g (5.44%)	0.75g (5.69%)
+250um	0.6g (6.22%)	0.65g (5.024%)	0.6g (4.55%)
+180um	0.35g (2.42%)	0.47g (4.98%)	0.2g (1.52%)
+125um	0.5g (3.46%)	0.55g (4.22%)	0.4g (3.03%)
<125um	0.2g (1.38%)	0.1g (0.767%)	0.13g (0.98%)
Total weight of granules	14.46g (100%)	13.04g (100%)	13.18g (100%)

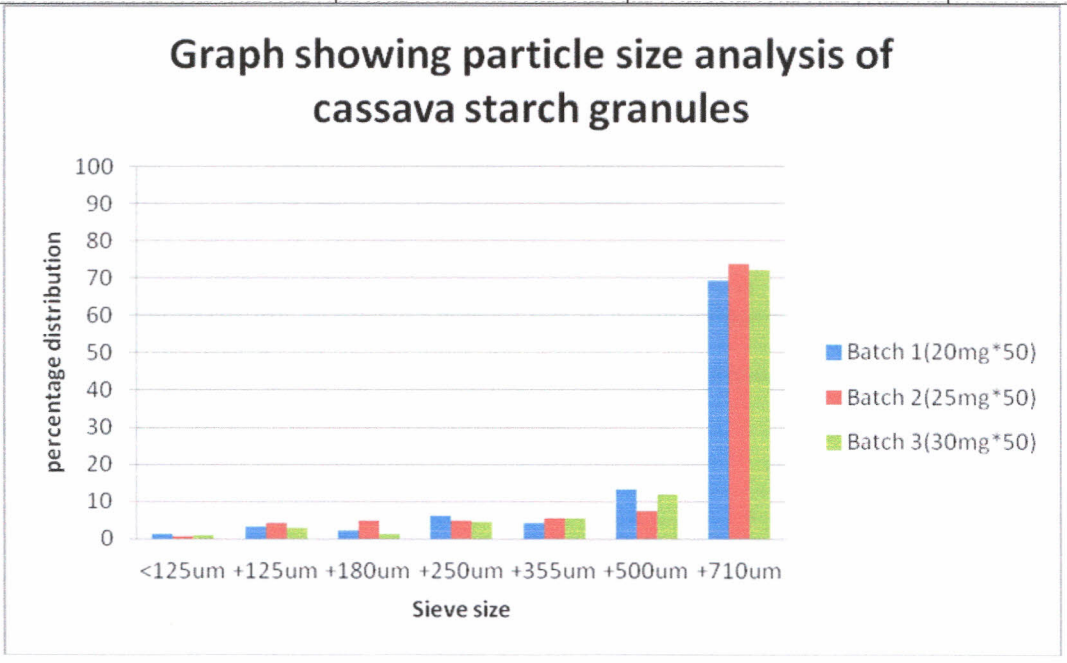

Figure 4-3: Graph presenting particle size distributions of granules prepared using cassava starch

Most granules were retained in the sieve 710um.There was no general trend that had any conclusive effect towards understanding the impact of increasing the concentration of cassava starch intragranularly.

ii) Angle of Repose

The angle of repose was obtained by using the diameter and height of cone-shaped heap of granules. The angle of repose predicts the flowability of the granules.

Table 4.3: Angle of repose of granules prepared using maize starch

Batch number	Radius of cone	Height of cone	Angle of Repose (°)
Batch 1G	7cm	7.0cm	45
Batch 2G	8cm	7.2cm	42
Batch 3G	7cm	7.4cm	46.6

Table 4.4: Angle of repose of granules prepared using cassava starch

Batch number	Radius of cone	Height of cone	Angle of Repose (°)
Batch 4G	7cm	7cm	45
Batch 5G	7cm	7.3cm	46.2
Batch 6G	7.1cm	7.5cm	46.6

According to these results, increasing concentration of starch used to prepare the granules did not affect the angle of repose significantly. However all the prepared granules had an angle of repose above 40°, predicting poor flow properties.

iii) Bulk density

Table 4.5 presents bulk densities of granules comprising maize and cassava starches at different concentrations.

Table 4.5: Bulk densities of granules prepared using maize and cassava starches

Maize Starch								
Batch 1G			Batch 2G			Batch 3G		
Mass (g)	Volume (mL)	Density (g/mL)	Mass (g)	Volume (mL)	Density (g/mL)	Mass (g)	Volume (mL)	Density (g/mL)
11.2	25	0.448	12.2	30	0.407	14.1	40	0.352
Cassava Starch								
Batch 4G			Batch 5G			Batch 6G		
Mass (g)	Volume (mL)	Density (g/mL)	Mass (g)	Volume (mL)	Density (g/mL)	Mass (g)	Volume (mL)	Density (g/mL)
12.9	30	0.43	16.14	44	0.367	13.2	40	0.33

The bulk densities of the prepared granules were between 0.3-0.45 g/mL. Interestingly an increase in the concentration of starch used to prepare the granules, showed a reduction in the granule bulk densities.

4.4. PREPARATION AND TESTING OF TABLETS

Paracetamol tablets were successfully prepared. The tablets were circular in shape and white in colour.

The following key is used in presentation of results;

Batch 1T - Tablets prepared using granules containing 1g of maize starch intragranularly
Batch 2T - Tablets prepared using granules containing 1.25g of maize starch intragranularly
Batch 3T - Tablets prepared using granules containing 1.5g of maize starch intragranularly
Batch 4T - Tablets prepared using granules containing 1g of cassava starch intragranularly
Batch 5T - Tablets prepared using granules containing 1.25g of cassava starch intragranularly
Batch 6T - Tablets prepared using granules containing 1.5g of cassava starch intragranularly

i) Uniformity of weight

Table 4.6 presents tablet uniformity of weight results. Only two batches, namely batches 1T and 6T, passed the uniformity of weight test.

Table 4.6: Uniformity of weight of the paracetamol tablets

Tablet No.	Batch 1T	Batch 2T	Batch 3T	Batch 4T	Batch 5T	Batch 6T
1	183.6mg(6.2%)	182.4mg (2.6%)	201.8mg(7.3%)	225.0mg(-13.8%)	206.5mg(-3.9%)	213.9mg(-1.9%)
2	198.3mg(-1.2%)	203.3mg (-8.5%)	229.1mg(-5.1%)	209.0mg(-5.7%)	211.3mg(-6.3%)	208.2mg(-0.8%)
3	193.4mg(1.2%)	190.7mg(-1.8g)	233.4mg(-7.1%)	187.4mg(5.2%)	215.7mg(-8.5%)	205.2mg(-2.2%)
4	193.0mg(1.4%)	193.4mg (-3.2%)	194.5mg(10.7%)	192.5mg(2.62%)	190.3mg(-0.6%)	211.8mg(-0.9%)
5	199.2mg(1.7%)	216.2mg (-15.4%)	211.7mg(2.8%)	0.187.8mg(5.0%)	200.0mg(-0.6%)	213.9mg(-1.9%)
6	195.7mg(0%)	211.2mg(-12.7%)	238.1mg(-9.2%)	191.3mg(3.2%)	196.9mg(0.9%)	207.0mg(1.4%)
7	195.0mg(0.3%)	182.4mg (2.6%)	215.7mg(0.9%)	164.9mg(16.5%)	198.0mg(3.7%)	196.7mg(6.3%)
8	195.4mg(0.1%)	177.4mg (5.2%)	236.3mg(-8.4%)	192.4mg(2.6%)	147.4mg(25.8%)	202.2mg(3.7%)
9	192.3mg(1.7)	180.1mg (3.8%)	230.6mg(-5.8%)	201.8mg(-2.1%)	196.7mg(1.0%)	216.8mg(-3.3%)
10	.197.4mg(-0.8%)	187.5mg (-0.1%)	226.5mg(-3.9%)	173.0mg(12.5%)	194.4mg(21.9%)	209.3mg(0.3%)
11	193.3mg(1.2%)	178.5mg(4.6%)	180.6mg(17.1%)	220.6mg(-11.6%)	208.0mg(-4.6%)	204.8mg(2.5%)
12	196.5mg(-0.3%)	184.7mg(1.4%)	225.7mg(-3.6%)	201.5mg(-1.9%)	202.1mg(-1.7%)	202.9mg(3.4%)
13	191.8mg(2.0%)	181.3mg(3.2%)	233.6mg(-7.2%)	205.9mg(-4.2%)	188.8mg(5.0%)	213.1mg(-1.5%)
14	183.9mg(6.0%)	179.6mg(4.1%)	230.6mg(-5.8%)	232.4mg(-17.6%)	200.0mg(-0.6%)	214.7mg(-2.3%)
15	210.0mg(-7.2%)	180.0mg(3.9%)	220.5mg(-1.2%)	205.2mg(-3.8%)	202.8mg(-2.0%)	213.3mg(-1.6%)
16	200.0mg(-0.2%)	183.1mg(2.2%)	202.1mg(7.2%)	179.5mg(9.2%)	201.2mg(-1.2%)	219.3mg(-4.4%)
17	191.0mg(2.4%)	179.1mg(4.4%)	208.1mg(4.4%)	205.8mg(-4.1%)	192.8mg(2.9%)	205.9mg(1.9%)
18	210.8mg(-7.6%)	184.9mg(1.3%)	224.6g(-3.1%)	195.5mg(1.1%)	218.1mg(-9.7%)	207.0mg(1.4%)
19	198.1mg(-1.1%)	187.1mg(0.1%)	188.0g(13.7%)	161.2mg(18.4%)	201.2mg(-1.2%)	212.6mg(-5.9%)
20	192.1mg(1.8%)	183.2mg(2.1%)	229.2g(-5.2%)	197.4mg(-0.1%)	207.2mg(4.3%)	213.3mg(-1.6%)
Weight of 20tablets	3915.6mg	3745.5mg	4357.0mg	3953.9mg	3975.0mg	4199.4mg

N.B: The deviation of individual tablet weights from the average tablet weight is given in brackets

Batch 2T failed the uniformity of weight test with the tablets 2, 5 and 6 deviating from average tablet weight by 8.5%, 15.45% and 12.7% respectively. Batch 3T also failed the test with tablets 4, 6, 8 and 11 having deviations of 10.72%, 9.92%, 8.4% and 17.098% respectively. Batch 4T failed the test with tablets 1, 7, 10, 11, 14 and 19 deviating from average tablet weight with values of 13.81%, 16.58%, 12.49%, 11.58%, 17.55% and 18.46% respectively. Batch 5T also failed with tablets 3, 8 and 10 deviating from the average tablet weight with values of 8.52%, 25.84% and 21.88%. The observed tablet weight variation could be due to a variety of factors including poor flow properties of granules leading to differences in die filling as well as equipment related problems e.g. defective punches and dies. The tablets were of approximate weight of 200mg as compared to the normal 400mg.This is because the tablet punches and dyes were not adjustable and thus the only tablets formed would be of the stipulated weights only.

ii) Disintegration

Table 4.7 presents the disintegration times of the slowest disintegrating tablet among the six tablets tested in each batch.

Table 4.7: Disintegration times of the paracetamol tablets

Starch type	Batch 1T	Batch 2T	Batch 3T
Maize	48 seconds	30seconds	16seconds
	Batch 4T	Batch 5T	Batch 6T
Cassava	56seconds	40seconds	25seconds

It was evident that the maize was the better disintegrant as it took the tablets shorter time to disintegrate at 37.0 degrees as compared to the cassava tablets which took longer. However all tablets disintegrated within specified time of 15 minutes for uncoated tablets.

iii) Tablet dimensions and hardness

The tablets seemed to have similarity of diameter and thickness as the die dimensions were constant and only varied infitismally due to the different compression forces (Tables 4.8). All tablets seemed to have a mean hardness value of 5.5kg/cm2 according to the Monsanto

tester which made them pass the test in both the maize and cassava starch containing tablets .i.e. the mean value was within 4-6kg/cm^2.

Table 4.8: Diameter, thickness and hardness of the paracetamol tablets

	1T			2T			3T		
Tablet No.	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)
1	0.2	0.9	5	0.2	0.9	5	0.3	0.9	5
2	0.2	0.9	6	0.3	0.9	5	0.2	0.9	5
3	0.2	0.9	5	0.2	0.9	5.5	0.2	0.9	6
4	0.2	0.9	6.5	0.2	0.9	6.0	0.3	0.9	7
5	0.2	0.9	5	0.2	0.9	5.0	0.2	0.9	6

	4T			5T			6T		
Tablet No.	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)	Thickness (cm)	Diameter (cm)	Hardness (kg/cm2)
1	0.2	0.9	5	0.2	0.9	4	0.2	0.9	6.5
2	0.2	0.9	5	0.2	0.9	4	0.2	0.9	6
3	0.2	0.9	5	0.2	0.9	4	0.3	0.9	6
4	0.2	0.9	5	0.2	0.9	4	0.2	0.9	6
5	0.2	0.9	7	0.2	0.9	5	0.2	0.9	6

iv) Friability

Table 4.9 presents the results of friability tests carried out on the different tablet batches.

Table 4.9: Friability of the paracetamol tablets

Batch No.	Weight of tablets before test	Weight of tablets after test	Weight lost
1T	3.9156g	3.2699g	0.6457g (16.49%)
2T	3.7455g	2.7287g	1.0168g (27.15%)
3T	4.3570g	3.7214g	0.6356g (15.73%)
4T	3.9539g	3.5600g	0.3939g (9.96%)
5T	3.9750g	3.6000g	0.375g (9.43%)
6T	4.1994g	3.7500g	0.4494g (10.70%)

In all batches, the tablets the loss on friability was more than 1% thus making them fail as the B.P Specifications 2010. Friability test is done to check on how well the tablets can withstand breaking due to transport or handling by the end user. It helps to predict the conditions of such tablets at time of administration to the patient. Failure of the friability test may be due to inappropriate binder and/or lubricant concentrations, inadequate compression force, defective equipment among other factors.

CHAPTER 5

5. CONCLUSION AND RECOMMENDATIONS

5.1. CONCLUSION

The objectives to the study were met but limitations were a clear obstacle to further research. It was evident that most tablets did not pass the friability test possibly due to the low compression forces exerted by the alternative tablet press used in the study after the breakdown of the designated tablet press.

The extracted cassava starch was successfully used as a disintegrant in paracetamol tablets. The disintegration profiles of paracetamol tablets prepared using the extracted cassava starch were comparable to those prepared using maize starch.

5.2. RECOMMENDATIONS

a) Further investigations should be carried out to determine causes of tablet friability and weight variations.

b) Evaluation of the properties of tablets prepared using a different tablet press at controlled compression force to determine any machine related errors.

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