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COMPARATIVE EVALUATION OF THE PHYSICOCHEMICAL AND DISINTEGRANT PROPERTIES OF STARCH FROM FIVE IMPROVED VARIETIES OF CASSAVA IN PARACETAMOL TABLET FORMULATIONS

A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

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By

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DECLARATION

"I, Frank Kumah Adjei, declare that I have fully undertaken the study reported herein under the supervision of Prof. K. Ofori-Kwakye and that except portions where references have been duly cited, this dissertation is the result of my research".

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DEDICATION

This work is dedicated to my lovely mother, Cecilia Esi Takyiakwaa and my lovely sister, Eunice Aboagye.

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ABSTRACT

Starch has been employed in pharmaceutical industries extensively as diluents, binding agents and disintegrants in tablet formulations and various studies have been conducted to develop novel starches from local sources for use as excipients. The objective of this study was to determine the physicochemical and tablet disintegrant properties of starches obtained from five improved cassava varieties to assess their potential as disintegrants substitute for the pharmaceutical manufacturing industry. The cassava varieties used were Sika Bankye, Ampong, AW/ 10 / 008, 12/

0245 and 12/0197 and were assigned with codes V10, V20, V30, V40 and V50, respectively. The cassava starches were obtained by wet separation techniques and the organoleptic properties of the starches were determined to be fine texture, odourless, bland taste and white in colour. The physicochemical properties of the starches namely: pH, moisture content, angle of repose, solubility, bulk and tapped densities, Hausner‟s ratio and Carr‟s index were determined to assess their suitability for pharmaceutical use. The percentage yield of the starches ranged from 7.97 – 26.82 % with V50 and V20 having the lowest and highest starch yield, respectively. The particle density, bulk density and tapped density of the starches followed the same pattern of V20 > V30 > V50 > V40 > V10. All the starches had particle size distributed from 162.2µm – 177.5µm. All the starches showed good swelling and water retention capacities with an order of swelling power of V30 > V20 > V40 > V10 > V50. The toxic metal analysis showed an insignificant amount of arsenic, lead, cadmium and mercury, suggesting the safety of the cassava starches for use as pharmaceutical excipient. FTIR study confirmed there was no interaction of the starches with the pure paracetamol powder. The uniformity of weight, tensile strength, hardness and friability of the paracetamol tablets containing different concentrations of the cassava starches as disintegrant were not significantly different ($p > 0.05$) from compacts containing the commercial disintegrant, maize starch. The cassava starches caused faster tablet disintegration and the release of paracetamol from the cassava starches showed comparative effectiveness as disintegrants to compacts containing maize starch at the same concentration. The

Crushing strength-friability (CSFR) and Crushing strength-friability/ disintegration time (CSFR/DT) values of tablets containing cassava starches were high (formed strong tablets) and were comparable to compacts containing maize starch at the same concentration. All tablets containing different concentrations of starch passed the dissolution and assay tests for immediate

release dosage forms. The results obtained establish the suitability for pharmaceutical use of the cassava starches as disintegrants with comparable properties to the commercially available maize starch.

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Chapter one

INTRODUCTION

1.1General Introduction

The modern shift from synthetic use of excipients to renewable resources, non-polluting and green technology is as a result of the use of natural sources as pharmaceutical excipients which includes plants, animals and agricultural waste. Excipients are defined by the International Pharmaceutical Excipients Council as substances with the exception of the active pharmaceutical ingredient or pro-drug which has been demonstrated to be safe and is included in a drug formulation to enhance processing during manufacturing, protect, support and also aid in stability (Robertson, 1999). Excipients are very essential in obtaining finished drug product of desired properties and also facilitate formulation design. Excipients aid in bioavailability of the active drug, patient compliance, useful in the identification of a product, other attributes may be improved and also during storage and use, the safety, effective and quality of the product may be enhanced (Robertson, 1999).

It is important to consider the coherent structure of the excipients during tablet formulation and ingenuity is often required to enhance the breakdown of the structure into its primary particles after administration (Pharmaceutical Codex, 1994). Novel and improved disintegrants are developed continually for meeting the needs of conventional drug delivery systems especially tablets manufacturing (Whistler and BeMiller, 1992). An immediate release tablet formulation of a drug is only useful until its active drug is available for absorption, hence disintegrants become the most useful excipient in a tablet to facilitate immediate drug release. Disintegrants in pharmaceuticals are excipients that are essentially employed components in tablet manufacturing to break down tablets into individual smaller primary particles, a process known as disintegration

(Nattawat *et al*., 2008). The first disintegrating agents to be used in tablet formulations were starches from corn, potato, and wheat (Orelli and Leuenberger, 2004). Disintegration test is useful in determining if tablets will disintegrate within a specified time when placed in liquid medium condition thereby presenting a greater surface area of the tablet at specific experimental conditions thereby enhancing an effective and rapid release of the active drug for adsorption in the gastrointestinal tract. Influence on the tablet properties such as compressibility, hardness or friability may be avoided or reduced at low concentrations of disintegrants (Uwaezuoke *et al*., 2014).

Botanical plants without woody stems are non- polluting and renewable which can be a constant source of raw materials if they are maintained and harvested in a sustainable manner (Beneke *et al.* 2009). Starches have been employed in the pharmaceutical industries extensively as diluents, binding agents and disintegrants in tablet formulations and investigations have been expended on novel starches development to be used as excipients from the local sources (Olufunke *et al*., 2005). Starches can prolong their disintegrating property by moisture absorption and swelling of the grain leading to rupture of tablet core (Arun, 2013).

After rice and maize, cassava plant (*Manihot esculenta*) is the third most essential source of calorie for human and livestock consumption in the world (FAO, 2008; Fauquet and Tohme, 2008). The most important and economical staple foods produced and consumed in the world is cassava and in the tropic, it is also the leading food and feed plant (Arun, 2013). In recent years, the production of cassava as subsistent crop has also been transformed to industrial cash crop. The production of cassava is marketed as a food product with promising new market opportunities in Ghana. Therefore, the government of Ghana is encouraging cassava production for industrial use which is

a positive step. Therefore, this project seeks to explore the potential use of starches from five improved cassava varieties as a pharmaceutical excipient.

1.2 Justification

In the pharmaceutical and food industries, one of the most used excipients is starch where they are used as disintegrants, fillers, glidants, binders and thickeners. Starches are applied in the gelling, bulking, wood, textile, paper, petrochemical, food and beverage industries for various end uses (Singh *et al*., 2003; Graffham *et al*., 1998).

With the versatility of starches in various pharmaceutical dosage forms, it is essential to continue the development of novel starch excipients with desirable, suitable and appealing properties to meet the needs of pharmaceutical formulators. Pharmaceutical researchers have tried to develop botanical starches to be used as tablet excipients although starch is mostly and frequently used as excipient in tableting. Unofficial and official protocols prove that starch possesses some pharmaceutically desirable features of good excipients when they were preliminarily evaluated (Adebayo and Itiola, 1998).

The Crop Research Institute of Ghana (CRIG), Fumesua, is developing new varieties of cassava with high starch, food, nutrient content and other functional properties to get rid of some of the undesirable properties which make them suitable for specific uses through genetic techniques. Starch crops modified genetically have led to improved and targeted functionality in the development of most starches (Jobling, 2004).

Genetic, physical and chemical modifications change the starch granular structure which would influence their properties when functioning as a pharmaceutical diluent, binder or disintegrant.

No study on the pharmaceutical application of these improved varieties of cassava starches has been reported, therefore, these starches are currently not used in the pharmaceutical industry.

In the present study, the suitability of the improved varieties of cassava (*Manihot esculenta*) starch as a tablet disintegrant will be investigated for possible pharmaceutical industry use. Due to poor compressibility and flow, high capping and lamination tendencies as well as lack of inherent disintegrant capacity, paracetamol was chosen as a model active drug for the study.

1.3 Aim of study

Comparative evaluation of the physicochemical and disintegrant properties of starch from five improved varieties of cassava in paracetamol tablet formulations.

1.4 Specific objectives

- To extract and identify starch from the five cassava varieties.
- To determine the physicochemical properties of the extracted cassava starches namely: swelling indices, pH, solubility, bulk properties, flow properties, toxicity content and ash values.
- To determine the optimum disintegrant concentration of the cassava starches in paracetamol tablet formulations.
- To determine the influence of the starch disintegrants on in-vitro drug release of the paracetamol tablet formulations.
- To evaluate the physico-mechanical properties of the formulated paracetamol tablets.

Chapter Two

LITERATURE REVIEW

2.1 The cassava plant

2.1.1 Taxonomy

Cassava (*Manihot esculenta*) is a woody perennial shrub native to South America which belongs to Euphorbiaceae, the spurge family. The cassava plant is sometimes known as manioc, yucca, tapioca or mandioca (Allem, 1994). The cassava plant has a fibrous root system and its edible portions are enlarged with starch-filled roots. The cassava plant is monoecious species that is cross-pollinated by wind and insects. Cassava can be artificially self-pollinated which suffers from inbreeding depression. The cassava plant flowers are in clusters that are either male or female and the cluster of the female flowers produces one to six fruit. Flowering of the cassava plant is influenced by parameters such as aridity, temperature, genotype and photoperiod with most cultivars as diploid with 2n = 36 chromosomes. Natural polyploids have a distinct morphological characteristics as well as triploids, which tends to occur as the highest yield (Richardson, 2013).

2.1.2 Description

The cassava root, which is long and tapered has a firm homogeneous flesh which is encased in a detachable ring which is about 1 mm thick, rough and brown on the outside. Most commercial varieties of cassava are about 15 to 30 cm long, 5 - 10 cm in diameter at the top and the root's axis is composed of a woody vascular bundle. Peeled cassava tuber can be chalkwhite or yellowish colour (Allem, 1994).

Figure 1. 1 Pictures of the cassava root

2.1.3 Origin and distribution

The cassava plant is widely accepted to have originated in Paraguay and Brazil which has spread throughout the tropical areas of South and Central America. Though in western countries cassava is little known or used, it is ranked as the 6th most important food crop worldwide and it is now considered as one of the most important and useful food crops in tropical countries throughout the world (FAOSTAT, 2012). The cassava plant is cultivated in southern peninsular region in India, particularly Tamil Nadu, Kerala and Andhra Pradesh which accounts for 98% of production and 93% of area in India. Kerala contributes nearly 50% of total area under cassava in India. In the 16th century, Portuguese traders introduced cassava plant to Africa from Brazil (Olsen *et al., 1999).* According to Food and Agriculture Organization Corporate Statistical Database (FAOSTAT) in 2012, Nigeria was ranked as the major growing nation in the world accounting for 50% of area and production and Ghana as the fifth producing country.

2.1.4 Cultivation

Cassava is mostly an essential food crop in the humid tropics which is able to withstand drought and mostly found at conditions of low nutrient availability (Burrell, 2003). The cassava plant can grow to a height of 1 - 3 m and many roots are mostly found on each plant. The leaves of the plant are sometimes consumed but the major harvested organ is the root tuber which is actually a swollen root. Propagation of cassava plant is mostly from stem cuttings. Usually, the rapid postharvest deterioration of the cassava root prevents the storage of the plant in the fresh state for more than a few days is a major drawback of the production cassava. The cassava roots are ready for harvest after 8 to 12 month. The starch yield of the cassava root at maturity is about 20% to 32%. (Okezie and Kosikowski, 1982).

Cassava is considered higher among crops which convert higher amount of sun energy into soluble carbohydrates per unit of area. Among the starchy food, the cassava root contains carbohydrate which is higher than rice about 40% and higher than maize about 25%. Cassava provides the cheapest energy source for animal feeding as well as human nutrition. Basically, cassava root is composed of moisture (70%), starch (24%), fiber (2%), 1% protein and other substances like minerals (3%) (Nyerhovwo, 2004).

2.1.5 Nutritional value

Cassava root is essential with nutrients such as carbohydrates, dietary fiber, vitamins and minerals as shown in Table 2.1. The cassava root is composed of 60 to 65% of moisture, 20 to 31% carbohydrate, 1 to 2% of crude protein and has high amounts of calcium (Ca) and vitamin C with a comparable low amount of vitamins and minerals. The cassava root has a significant amount of thiamine, nicotinic acid and riboflavin. It is a poor source of protein with a fairly good quantity of essential amino acids with limiting amino acids methionine, cysteine and cystine. Cassava is mostly used as nutritional source in most ecosystems because cassava is one of the most drought-tolerant root crops that are successfully grown on marginal soils which gives a reasonable yield where most staple crops do not grow well (Olumide, 2004).

Table 2. 1: Nutritional composition of raw cassava root tuber (*Manihot esculenta Crantz*)

Nutritional value of raw cassava root tuber (*Manihot esculenta Crantz*) per 100 grams		
Principle	**Nutrient value**	**Percentage of RDA**
Energy	160 kcal	8%
Carbohydrates	38.06 g	29%
Proteins	1.36 g	2.5%
Total fats	0.28 g	1%
Cholesterol	0 mg	0%
Dietary Fiber	1.8 g	4%
Vitamins		
Folates	27 µg	7%
Niacin	0.854 mg	5%
Pyridoxine	0.088 mg	7%
Riboflavin	0.048 mg	4%
Thiamin	0.087 mg	7%
Vitamin A	13 IU	<1%
Vitamin C	20.6 mg	34%
Vitamin E	0.19 mg	1%
Vitamin K	1.9 µg	1.5%
Electrolytes		
Sodium	14 mg	1%
Potassium	271 mg	6%
Minerals		
Calcium	16 mg	1.6%
Iron	0.27 mg	3%
Magnesium	21 mg	5%
Manganese	0.383 mg	1.5%
Phosphorus	27 µg	4%
Zinc	0.34 mg	3%

Source: USDA, 2010 RDA represents Recommended Dietary Allowance

Table 2. 2: Typical Composition of matured cassava roots

Composition	Percentage (%)
Moisture	69-8
Starch	22-0
Sugars	5-1
Proteins	1-1
Fats	0-4
Fibres	1-1
Ash	0-5

Source: International Starch Institute, 2014

2.1.6 Health benefits, applications and uses

Cassava roots have high starch content and contain significant amount of phosphorus (40 mg/100g), vitamin C (25 mg/100g) and calcium (50 mg/100g). It is poor in fats and protein and other nutrients compared to cereals and pulses. However, the protein content of cassava is higher compared to the other tropical food sources like potato, plantains and yam and gluten free compared to the other roots and tubers. The gluten-free nature of starch makes it very useful in preparing special foods for celiac disease patients. The cassava plant can be used as a source of providing essential B-complex vitamin group such as folates, thiamin, pantothenic acid and riboflavin. Cassava provides almost twice the energy than potatoes and the highest value calorie foods source for any tubers and roots in the tropical zone. A hundred gram cassava roots provide

160 calories which mainly comes from sucrose accounting for more than 69 percent of the total sugar content (Enidiok *et al*., 2008).

The cassava leaves are deficient in amino acid (tryptophan, methionine) but are important source of the protein lysine. Vitamin K and proteins can be sourced from dietary rich tender cassava leaves. Vitamin-K has an important role to play in the formation of bone by promoting osteotrophic activity and also by limiting neuronal damage in the brain during the treatment of Alzheimer's disease patients. For many inhabitants found in the tropical belts, the cassava plant is dependent as the main source of some essential minerals such as zinc, copper, iron, magnesium and manganese. The root tuber has sufficient amounts of potassium (271 mg per 100g or 6% of RDA) an important component of the cell and in the body fluids that helps in regulating the heart rate and blood pressure (Ravindran, 1992).

Alcoholic beverages such as Cauim and tiquira (Brazil) are made from cassava and cassava as culinary is widely consumed which has regional, national and ethnic importance wherever the plant is cultivated (Opie and Hominy, 2008).

Significant research about cassava in many countries has led to evaluating the usefulness of cassava root tuber as an ethanol biofuel feedstock. Cassava root tubers and hay are used as animal feed which is a valued good roughage source for ruminants such as goats and sheep by feeding directly or as a source of protein in concentrate mixtures. Cassava is very useful in many available commercial laundry products, mostly as starch for garments and shirts and also has been used for the treatment for prostate cancer and bladder *(*Abeygunasekera and Palliyaguruge, 2013).

2.1.7 Cassava as an industrial base

Cassava is very useful in the production of starch for industrial use and other products employed in processed food. The industrial use of starch is finding much application because of it is a

multibillion dollar business worldwide. Industries which require the use of rice, maize and wheat starches, cassava starch can be used to perform most of their functions. Starches are mostly employed in dyeing and sizing in textile production to increase the weight and brightness of the cloth. Roble *et al*., (2003) produced L-Lactic acid from raw cassava starch in a bioreactor from *Aspergillus awamori* (fungus) and *Lactococcus lactis* spp. *lactis* (bacteria). After the addition of mineral salts and nitrogen source, cassava dregs can be used for phytase production (Hong and Li, 2001). Furthermore, activated carbons from cassava peel are employed as adsorbents for metal ions and dyes (Rajeshwarisivaraj *et al*. 2001).

Cassava starch are used in many cement production to enhance the setting time and also used in oil wells to improve the viscosity of drilling muds. Cassava starch is very useful in the prevention of fluid loss in bole wholes as well as sealing the walls. Glue, adhesive and cosmetics industries use cassava starch as their main source of raw material. In paper production, cassava starch is employed as glue to achieve brightness and provide strength to products. For better recovery and to improve the shelf life of detergents in the detergent soap production, starch is mostly employed. Also, cassava starch can be used to better foaming and color in the rubber and foam productions (Nyerhovwo, 2004).

In the pharmaceutical industries, starch is used as a diluent, disintegrating agent and bonding agent in tablet production (Nyerhovwo, 2004). Again, starch from cassava in the pharmaceutical industries is employed in fructose syrups (Vuilleumier, 1993) and also it is used in the formulation of gelatin capsules (Nduele *et al*. 1993).

2.1.8 Future of cassava production

There is the need to address increased productivity, profitability and marketing opportunities of cassava production. Cassava is a staple root tuber consumed in most parts of Ghana, both rural and

urban areas. In recent years, it has also moved from being subsistent crop farming to industrial cash crop. Cassava is one of the most actively food products marketed and also the promising crop in terms of new market opportunities and growth. Sub-Saharan Africa is experiencing the faster growth in food demand tubers and roots that average from 2.6 % in a year through 2020. Cassava growth accounts for about 122 million metric tons with cassava being the most increasing root with 80 million metric tons and 66 percent of the total. The demand of cassava is estimated to grow at 2% yearly for food and 1.6% per year for feed in developing countries while the total cassava production reach 168 million tons estimated by 2020 based on the current production rate. However, this amount of cassava can be far surpassed in the developing countries with the proper incentives and policies. Most of the Africa countries have capacities large enough for cassava farming, hence governments have taken positive steps to encourage industrial use of cassava since (Scott *et al*. 2000). The starch production will increase beyond the estimated figures with increasing establishment of starch industries that utilize starch in developing Africa countries. Increased cassava production may be influenced in the establishment of starch industries. Countries with high unused land and availability of labor enhancing cassava processing and production may lead to high income for farmers as industry demand starch increases. These policies should however encourage the establishment of starch industries so that produced cassava is used in the country for local market which will stimulate real economic growth and job creation (Nyerhovwo, 2004).

2.1.9 Risks and challenges of cassava plant farming

Cassava remains easy to be produced, adaptable to many unfavorable environmental conditions with minimal labor requirements and also less susceptible to diseases and pests compared to other

crops like maize for adding value. However, poor postharvest handling is a challenge which promotes uneven good quality of the processed cassava which may result in

contamination by fungi. Inadequate and poor facilities for milling cassava, storage condition and poor access to roads which are essential for adding value increase the challenges associated to postharvest handling. Although cassava is an important crop with multiple uses, much attention needed during its production is not received which leads to low productivity of the cassava root tubers because they are normally planted on very poor soils where other crops like maize do not grow well. Cassava is mostly grown as an insurance intercrop together with other crops which are nutrient-demanding like sorghum or maize in case the main crop fails. The predominant root crop for small-holder farmers is cassava that basically grows as subsistent farming utilizing rudimentary tools and operating on small and fragmented plots. Yields from cassava production are also reduced by pests and diseases such as the brown streak disease and cassava leaf mosaic disease as the major challenge of cassava plant farming. Another vital identified challenge is also the acquisition of land located within a reasonable radius of a cassava buying company (Herren, 1995).

2.2 Starch market and production in Ghana

In Ghana, starch is gaining demand and marketing opportunities by the industries as shown in Table 2.4.The main starch sources utilized by the industries include maize, cassava and sweet potato. Most of these starches for pharmaceutical industrial use are imported because these industries rely on mostly cheaper imported maize starch. The prices of maize and cassava starches produced in Ghana are uncompetitive compared to imported starch although these starches can be produced in Ghana. This is due to the high per capita consumption of these staples which affect raw material supplies and starch production cost (Graffham *et al*., 1998).

Table 2. 3: Starch market and consumption in Ghana

Sector	Market share (%)	Estimated quantity (tonnes / annum)
Textiles	40	1680
Pharmaceuticals	20	840
Paper	10	420
Food	3	126
Plywood	27	1134
Total	100	4200

Source: Graffham *et al*., 1998

2.3 Pharmaceutical applications of starch

The unique physicochemical and functional characteristics of starch makes it a new potential biomaterial for pharmaceutical applications (Freire *et al.,* 2009). Native starches were well explored as binder and disintegrant in solid dosage forms but its utilization is restricted due to poor flowability. Pre-gelatinized starch is the commonest marketed form of modified starch and it is the most preferred directly compressible excipients in pharmaceutical industry. Modified acetate starch, rice starch and acid hydrolyzed dioscorea starch are established as multifunctional excipient in the pharmaceutical industry. Starch is rated among the top ten pharmaceutical ingredients by the International Joint Conference on Excipients (Shangraw, 1992).

2.3.1 Starch as tablet disintegrant

Starches are generally employed as disintegrant for immediate release tablet formulations which breakdown the tablet to enhance the availability of active drug(s) within a short time for absorption.

Sodium starch glycolate is generally used for immediate release tablet formulations (Aulton and Taylor, 2013).

Swelling is the most widely used and accepted mechanism of action for tablet disintegration. Swelling of starches is believed to be the mechanism in which the starches impart their disintegrating effect. When starch comes in contact with water, by swelling the adhesive force of the other ingredients in the dosage form is overcome which causes it to fall apart. Starches with high porosity lack adequate swelling force which shows poor disintegration. Hence, sufficient swelling capability is exerted in dosage forms having low porosity. Moreover, high packing fraction of the starch results in fluid being unable to penetrate in the dosage form leading to slow disintegration (Carter, 2002).

Starches with poor swelling capacity may impart their disintegrating action through porosity and capillary action or wicking when the dosage form is placed in a suitable aqueous medium. The medium replaces the air adsorbed on the particles which weakens the intermolecular force leading to the breakdown into its primary particles. The porosity of a tablet provides the pathway for the penetration of the liquid into tablets. Starch granules having low cohesiveness and compressibility enhance porosity and provide these pathways into the dosage form. Maintenance of porous structure of starches and low interfacial tension towards aqueous fluid enhances disintegration by creating a hydrophilic network around the drug particles (Aulton and Taylor, 2013).

2.3.2 Starch as controlled/sustained release polymer for drugs and hormones

Phosphate ester derivative, grafted and acetylated are modified starches which have been extensively evaluated to be used for sustained drug release to enhance patient compliance.

Polymers which are starch-based and biodegradable in the form of hydrogel or microsphere are used as a means of delivering drugs (Balmayor *et al*., 2008). An example is corn starch with high amylose which has good sustained release properties because its gel-forming capacity is excellent (Rahmouni *et al*., 2003).

2.3.3 Starch as plasma volume expander

Plasma volume expanders such as acetylated and hydroxyethyl starch are now mostly used in treating patients suffering from trauma, heavy blood loss and cancer (Gomes *et al*., 2003).

2.3.4 Starch in nanotechnology

In the production of nanoscale tissues, drug delivery applications, sensor and mechanical devices, starch nanogels, starch nanoparticles and starch nanospheres have been used successfully (Le Corre *et al*., 2010). Starch is one of the essential polymers which is appropriate for the production of biodegradable microparticles, most importantly as a means of delivering proteins such as vaccines. Microparticles which have lower dose frequency as well as low magnitude which gives it an advantage for maintaining drug concentrations and also improves the compliance of patients which is the main reason it is an attractive pulmonary drug delivery system (Le Corre *et al*., 2010).

2.4 Starch extraction and purity

All the different extraction protocols affect the physical characteristics and chemical composition of the starch. The changes of the starch characteristics in the starch granular structure results from the extraction method as a reflection of the non-rigid organization of starch granules (Singh *et al.,* 1997). Most extraction techniques follow a general methodology on either of the following two methods for isolating starch: 1.dough making, dough washing and starch recovery or 2. grain steeping, wet grinding and starch recovery (Wolf, 1964). The procedures involve sample

preparation (sieving, drying, or soaking) to break up hard materials like grains into single particles and removal of undesired particles (sands, silts, minerals, organics) and sometimes chemical preservation of the starch granules. Starch extraction protocols damage starch granules which ultimately influences physicochemical properties. An ideal representative sample should not be less than 96 % (w/w) starch and there must be absent of other plant components, soluble and insoluble, which may include protein, soluble gums, lipids and fibre and may influence the starch properties leading to false characterization (Vasanthan, 2001).

2.5 Physicochemical Properties of starches

Starches may also be distinguished on the basis of their physicochemical features and these features are characteristic for each starch and are important identification tools. These features include colour, odour, form, taste, texture, solubility in different solvents, pH, swelling index, moisture content, bulk density, particle density and angle of repose.

2.5.1 Particle density

The particle density or true density is a relatively well-defined quantity which is not dependent on the solid material‟s degree of compaction. The particle density of a starch powder or particulate solid is defined as the density of the particles that make up the powder and is obtained when the volume determined excludes the voids spaces and the pores that exist between particles within the bulk solid material. It differs from bulk density because the volume used does not include pore spaces. True density is determined using a liquid in which the sample is insoluble and the liquid is expected to fill the pores and void spaces in the bulk sample. Entrapped gases and surface tension resistance, affects the filling of very small pores. These measurements are important in

pharmaceutical formulations as they guide formulation procedure and influence the overall quality of manufactured products such as the drug dissolution and uniformity of content of solid dosage forms (Sun, 2004).

2.5.2 Bulk density

The bulk density of a solid sample depends on the ratio of the weight of an untapped powder sample which includes interparticulate void volume. Bulk density therefore is dependent on both the spatial arrangement and the density of powder particles in the solid material. The bulk properties of a powder are dependent on how they are handled, that is, the preparation of the sample, sample treatment and storage. The powder particles can be packed to have different range of bulk densities and the bulk density may change by the slightest disturbance of the powder bed. Hence, the determination of bulk density of a powder is often very difficult to give better reproducibility in reporting the results. The bulk density of a solid sample is measured in grams per cubic centimetre or grams per millilitre. However, it is essential to specify the determination procedure (Arun, 2013).

2.5.3 Tapped density

The tapped density is an increased bulk density which is mostly determined by mechanically tapping a vessel or a graduated measuring cylinder containing the solid sample. After the measuring cylinder is mechanically tapped, the initial powder volume or mass of the sample is observed and when the volume or mass change is noted, its readings are recorded. The mechanical tapping is determined by raising the vessel at a defined distance and allowing it to drop under its

own mass. During tapping down of a sample, devices that minimize any possible separation of the powder mass are preferred. That is, devices that rotate the cylinder during tapping (Arun, 2013).

2.5.4 Particle size distribution

The size of particulates is important in achieving optimum formulation and production of efficacious medicines. The manufacturer may not necessarily need to know the precise size of particles intended for the formulation, but a ranges of sizes may be specified and consequent powders are frequently graded based on the size of the particles they are composed. Majority of particles are greater than 350 µm for coarse powders while medium fine powders are between 100 to 350 µm. Fine powders from 50 to100 µm and very fine powders (10–50 µm) are cohesive, poor flowing and easily adheres to surfaces while particles greater than 250 µm usually flow freely. Air entrapment in the powder results in weight uniformity problems which with associated uneven powder flow causes capping and lamination of tablets. Particle size influences content uniformity of potent drugs and is higher with smaller powder particles because of the greater amount of the powder particles constituting the dose. Smooth and regular shaped particles with a narrow size distribution enhance flow properties. When powders and granules are more than 30 % fines, it virtually turns the product into dust which affects product yield. Large surface area exposed to solvent action enhances the high solubility and dissolution rate of smaller particles (Gilbert and Christopher, 2002).

2.5.5 Moisture content

Most natural products contain moisture and the water or moisture content of a starch -powder is a key property and their behavior is critical to efficient and successful manufacturing in pharmaceuticals. Hence, knowledge of the moisture content or losses has enormous economic

value in the manufacture and processing of materials. The information is useful for determining the value of the raw materials storability, concentration or purity, nutritional value of the product, agglomeration (in the case of powders), viscosity, dry substance content, commercial grade (compliance with quality agreements), flow properties, legal conformity (statutory regulations governing food), microbiological stability and for output quality control. Powders containing water can be in different physical states those that are adsorbed monolayer (or multilayers) on the surfaces of the particle, those that condense water on the particle surface and those that physically absorb water within the particle and those that chemisorb water. The state and distribution of the water is influenced by the amount of water taken up and the type of powder through exposure to humid air which affects many properties of the powder. Moisture content is mostly determined traditionally by analyzing the loss of weight of a sample during drying which is labor intensive and time consuming (Crouter and Briens, 2014).

2.5.6 Solubility

Solubility is the property whereby chemical substance (solid, liquid or gases) called *solute* dissolve in a solvent (solid, liquid, or gas) to form a homogeneous solution. The solubility of a substance fundamentally is dependent on the solvent used, temperature and pressure. Starch (amylum) is a polysaccharide consisting of glucose monomers which makes it poorly soluble in most solvents. The hydroxyl groups involved in the polysaccharide chain of some starches makes them water soluble whereas the branched form amylopectin are more insoluble. Starch granules are not soluble in cold water but swell and burst only when heated which becomes soluble in water. The semi-crystalline structure of the granules is lost and the smaller amylose molecules leach out of the granule which forms a network that holds water and also increases the viscosity of the mixture in

a process called starch gelatinization. Starch is not soluble in organic solvents in which the polarity index is within 3.9-4 (Lachman *et al*., 1986).

2.5.7 Swelling capacity

The starch swelling power is used for predicting the swelling and solubility index and provides the evidence of interactions between the molecules of water and the starch chains in the crystalline and amorphous regions. The investigation into the swelling ability of starch is carried out with aqueous water. The starch is initially weighed and put into water of known volume. A change in volume of the starch sample as a result of absorption of the medium is determined at definite time intervals (Kusumayanti *et al*., 2015).

2.5.8 pH

pH is a numeric scale used to identify the acidity or alkalinity of an aqueous solution. It is the negative logarithm of the hydrogen (H^+) or hydroxonium ion (OH^{-1}) concentration. Solutions with pH less than 7 are acidic and those with pH greater than 7 are alkaline or basic. Starches are mostly slightly basic with a few being neutral to acidic. The pH of cassava slurry in water is neutral. The basicity of starch is due to the unexchangable protons (hydrogen ions) which makes it difficult to define a concentration of H+ ions (much less the activity of H+ ions)
(Kusumayanti, 2015).

2.5.9 Granular shape, identification and organoleptic tests of starch

Starch granules are identified by morphological, dimensional and optically under different microscope lighting conditions give features such as size, shape (round or spherical, round or lenticular, ovate, ovoid, hemispherical), hilum position (centric or eccentric) and form (closed or

open). The iodine or chemical test for starch is used to test for the presence of starch. Iodine is mostly used as an indicator to follow the changes of iodide ion. When treated with KI solution, thus iodine dissolved in an aqueous potassium iodide solution, the triiodide anion (I_3^-) complexes with starch, producing an intense blue/black colour. However, the color intensity decreases with the presence of water-miscible organic solvents such as ethanol and with increasing temperature. The amylose in starch is responsible for the formation of a deep blue color in the presence of iodine. If starch amylose is not present, then the color will stay orange or yellow. Starch amylopectin, cellulose or disaccharides such as sucrose in sugar does not give the color. The chemical test cannot be performed at very low pH due to the hydrolysis of the starch under these conditions (Vorwerg *et al*., 2002).

2.6 Powder flow properties of starches

2.6.1 Angle of Repose

The angle of repose of a powder gives a steepest angle of descent or dip relative to the horizontal plane to which a powder can be piled without slumping. The bulk powder assumes a cone-like pile giving it a constant three dimensional angle when poured onto a horizontal surface. The internal angle between the horizontal surface and the surface of the pile powder is defined as the angle of repose. The angle of repose is influenced by parameters such as the coefficient of friction of the powder, density of the powder, surface area, shapes of the particles and gravitydependent (Kleinhans *et al*., 2011). Starch powders having low angle of repose gives flatter piles compared to those having high angle of repose. There are numerous methods for determining angle of repose and each produces slightly different results. Examples include tilting box, fixed funnel and revolving cylinder method. Although there are variations in a number of qualitative description of

the flow of a powder, formulations with angle of repose ranging from 40 - 50° are satisfactorily. An angle of repose exceeding 50° gives poor flow and is rarely acceptable for manufacturing purposes (BP, 2013).

2.6.2 Hausner's ratio and Compressibility Index

Compressibility index and Hausner‟s ratio determines the propensity of a product ability to settle and also for assessing the interparticulate interactions of the powder to be compressed. Interparticulate interactions that influence the flow properties of a powder also influence its bulking properties (Beddow, 1995). In a free flowing powder, interparticulate interactions are less significant and the bulk and tapped densities are closer in value. Powders flowing poorly have frequently greater interparticulate interactions indicating greater difference between the bulk density and tapped density which are seen in both the Compressibility Index and Hausner‟s ratio. Interactions of a powder by comparing the bulk and tapped densities can be used to index the ability of the powder to flow (WHO, 2012).

Table 2. 4: Scale of powder flowability

Angle of repose (degrees)	**Compressibility index (%)**	**Hausner's ratio**	**Flow Character**
25-30	1-10	1.00-1.11	Excellent
31-35	11-15	1.12-1.18	Good

36-40	16-20	1.19-1.25	Fair-aid not needed
41-45	21-25	1.26-1.34	Passable- may hang up
46-55	26-31	1.35-1.45	Poor – must agitate, vibrate
56-65	32-37	1.46-1.59	Very poor
>66	>38	>1.60	Extremely poor

Source: Copley, 2008

2.7 Elemental content and ash values of starches

Toxic heavy metal present in starches include Pb, Cd, Cu, Ni and Zn with their critical concentrations of 35-180 $mgkg^{-1}$, 12-70 $mgkg^{-1}$, 50-250 $mgkg^{-1}$, 20-70 mg kg-1 and 10-100 $mgkg^{-1}$ respectively. Excess in toxic heavy metals or metal concentration may lead to cancer, cardiovascular disease, obesity and stroke (Igbozuruike *et al*., 2011). Increase of toxic heavy metal content of the soil may increase plants uptake of the toxic metal which may be hazardous for human use. This suggests that farming on dump lands or area which can contribute to toxic heavy metals concentration should be discouraged (Brathwaite and Rabone 1985).

Ash values mostly designate the inorganic remnants present in natural products and other pharmaceutical substances. Ashing is the process of mineralization for preconcentration of trace substances before chemical analysis (Ashutosh, 2005). The inorganic residue remaining after water and organic matter portions are removed in the presence of oxidizing agents by heat which gives a measure of the total content of minerals present within the starch is termed as ash. Total ash typically represents metal salts which are essential for processes requiring ions such as sodium, potassium, calcium, calcium oxalate, carbonates, silicates, phosphates and other inorganic

materials from external sources. Dry ashing, wet ashing and low temperature plasma dry ashing are the main types of analytical methods for determination of ash content of natural products. These methods are based on the principle that, through heating, minerals cannot be destroyed and they are not volatile when compared to other components in food. Ash contents of fresh natural products rarely exceed 5% (Shannon *et al*., 2009).

2.8 Pharmaceutical dosage forms

Pharmaceutical dosage forms are means by which drug substance(s) are delivered to targeted sites of action in the body to exert local or systemic effect. Dosage forms are needed to ensure accurate dose, maximum drug action, sustained and controlled release medications, protection against gastric juice and masking unpleasant taste and odour. They are also needed to ensure proper drug insertion into body orifices, the usage of desired solvent for insoluble drugs and protection such as coated tablets, sealed ampules. Dosage forms may be classified depending on the route of administration (oral, topical, parenteral, inhaled, vaginal, ophthalmic, rectal, otic etc) and physical form (solid, semisolid, liquid and gases). Solid dosage forms are the largest and the oldest segment of the total drug delivery market dominated mainly by tablets (Aulton and Taylor, 2013).

2.9 Tablet dosage forms

Tablets are pharmaceutical solid dosage forms usually formulated with the aid of suitable excipients and manufactured either by molding or compression methods**.** Tablets are compacted or pressed usually from a powder mass into a solid dose made up of mixture of excipient(s) and active drug(s). Depending on the intended use and the method of preparation, tablets characteristics may be different in thickness, size, shape, hardness, disintegration, weight and dissolution and in other

properties. Primarily, tablets are manufactured by the compression method while the molding method of preparation is limited. Compressed tablets are manufactured using tabletting machines that are capable to exert great pressure on granules or powder. Molding method is mostly employed in small scale productions and laboratories while commercial production is done solely by compression. Most tablets are administered orally and they are manufactured with either colorants or different coatings. Other tablets are manufactured to have qualities most applicable to their desired route of administration such as sublingual use, buccal or vaginal application. Tablets have numerous advantages to the manufacturer and the patient such as simplicity, shipping, economy of preparation, convenience in packaging, dispensing, compactness, portability, stability, ease of administration and accuracy of dosage. However, some drugs such as protein drugs (insulin) may be unsuitable for oral administration.

Drugs that are denatured by the liver are unsuitable for oral use (Allen *et al*., 2004).

2.10 Types and classes of compressed tablets

Most tablets such as oral, buccal and sublingual are prepared by compression and may be coated with various materials after compression (Aulton and Taylor, 2013).

2.10

.1 Modified-release tablets

The three (3) types of modified-release tablets are prolonged release, pulsatile release and delayed release. The formulation and the type of excipients employed in modified-release tablets maybe different from those used in immediate-release tablets (Qiu and Zhou, 2011). A pulsatile release tablet releases their medication at an increasing time period for drug absorption after a single administration and is also accomplished by releasing the drug in two or more pulses. Prolonged-release tablets release their medication slowly at a nearly constant rate. Delayedrelease tablets are also another type in which they are intended to resist gastric fluid but disintegrate in the intestinal fluid. They are sometimes necessary to apply more than one layer. The most common type of delayed-release tablet is a gastro-resistant also known as enteric coated tablet, where the drug is released in the small intestine uppermost part after the preparation passes the stomach. Prolonged-release may combine with a delayed drug-release to exert local effect in the lower part of the intestine or colon (Aulton and Taylor, 2013).

2.10.2 Conventional or immediate-release tablets

Conventional or immediate-release dosage forms such as capsules and tablets are formulated without any special rate-controlling features such as enteric coatings or other techniques and are intended to disintegrate and release the active drug immediately after administration (Aulton and Taylor, 2013). Conventional or immediate-release tablets can also be dissolved in liquid before intake and thus administered as a solution. Immediate-release tablets are the commonest tablet type which includes chewable tablets, sublingual tablets, effervescent and buccal tablets. These tablets result in rapid drug release and absorption leading to the onset of pharmacodynamic effects. Absorption of conventional tablets of poorly soluble or lipophilic drugs may be gradual because

of slow dissolution rate or due to selective absorption across the gastrointestinal tract (Sandeep and Gupta, 2013).

2.10.3 Multiple compressed tablets

In the preparation of multiple compressed tablets, filled material is subjected to many compressions which form multiple-layer tablet. A tablet within a tablet may also form where the outer layer is the shell and the inner tablet being the core. Layered tablets are made by the compaction of part of the filled material in a die followed by additional fill material and compression which form a two-layered or three- layered tablets, depending on the number of separate fills. Layered tablets containing different active drugs are separated to avoid incompatibility and sometimes for the unique appearance of the layered tablet (Aulton and Taylor, 2013).

2.10.4 Sugar-coated tablets

Compressed tablets coated with sugar are known as sugarcoated tablets. The coated sugar layer is water soluble which may be colored or uncolored and dissolves quickly after administration. The sugar coating process involves sealing (waterproofing), coating (for smoothing and coloring), sub-coating, smoothing, colour coating, polishing and sometimes printing. Sugarcoated tablets are mostly heavier and larger than uncoated tablets by 50%. The sugar coat masks the unpleasant taste, enhances the appearance of the compressed tablets and also protects the enclosed active drug from the environment. The coating process is time consuming and require expertise. The coating of compressed tablets increases the size, shipping costs and weight of the tablet (Aulton and Taylor, 2013).

2.10

.5 Film-coated tablets

Film-coated tablets are compressed tablets coated with a polymer of a thin layer which form a skin-like film usually colored. Film-coated tablets compared to sugar coatings are more durable, less time- consuming and less bulky. The coating is designed in a way to expose the inner tablet at its targeted site in the gastrointestinal tract (Sharma *et al*., 2013).

2.10.6 Enteric-coated tablets

Enteric-coated tablets are designed to exhibit delayed-release features which enable them to get to the small intestines by passing through the stomach unchanged. The tablets then disintegrate to allow drug dissolution and absorption effects. Drug substances destroyed by gastric mucosa or gastric acid are enteric-coated to enable them bypass the stomach to the intestines (Aulton and Taylor, 2013).

2.10.7 Buccal and sublingual tablets

These tablets are mostly porous, flat, small and are used to dissolve in the buccal pouch for (buccal tablets) and those beneath the tongue (sublingual tablets) for drug release in the mouth to enhance systemic uptake of the drug. Sublingual and buccal tablets facilitate fast disintegration and drug release. They are usually intended for drugs that are destroyed by the gastric juice or drugs that are absorbed poorly in the gastrointestinal tract (GIT). Sublingual tablets such as nitroglycerin dissolve promptly and provide immediate drug effects whereas those for buccal use are designed to erode slowly (Kraan *et al.,* 2014).

2.10

.8 Chewable tablets

Chewable tablets are used basically to achieve complete and quick disintegration of the tablet. They are chewed and the tablet mechanically disintegrates in the mouth but the active drug is normally dissolved in the stomach or intestine when swallowed and a rapid drug effect is achieved. For patients with difficulty in swallowing, chewable tablets are mainly used for administration (Aulton and Taylor, 2013).

2.10.9 Effervescent tablets

Effervescent tablets release carbon dioxide when dropped into a glass of water before administration and they are prepared by granular compressing of effervescent salts. The carbon dioxide released is as a result of the bicarbonate or carbonate and the weak acid reaction. When added to water, it enhances tablet disintegration which facilitates the dissolution of the drug and the dissolution is completed within few minutes. Effervescent tablets enhance the intake of the drug, example vitamins, and also used to obtain rapid drug action such as for analgesic drugs (Srinath *et al.,* 2011).

2.10.10 Compressed lozenges

Compressed lozenges or troches are pharmaceutical solid dosage forms which are intended to dissolve slowly in the oral cavity intended to exert local or systemic effect. Examples include local anaesthetic, antiseptic and antibiotic drugs. Disintegrants are not included in the formulation but they are often coloured and include a flavor (Aulton and Taylor, 2013).

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2.10

.11 Molded tablets

Certain tablets such as tablet triturates, are mostly manufactured by the molding method rather than the compression method. The resultant tablets are usually soluble and soft and are designed to exert rapid dissolution (Aulton and Taylor, 2013).

2.10.12 Tablet triturates

Tablet triturates are molded or compressed and they are usually small and cylindrical in shape and mostly contain low amounts of potent drug(s). Low amount of pressure is required during their manufacture since triturated tablets must be completely and readily soluble in water. Sucrose and lactose is usually combined as the diluent. Tablet triturates are employed in compounding, some are inserted in capsules and few such as nitroglycerin tablets are used sublingually. For potent drug substances to give an accurate dose, the triturate tablets maybe dissolved in a liquid medium (Aulton and Taylor, 2013).

2.11 Methods of tablet preparation

The three (3) main methods of preparing tablets are dry granulation, wet granulation and direct compression (Allen *et al*., 2004).

2.11.1 Wet Granulation method

This is the most widely employed method of tablet production because the desired requirements for the compressed tablets are usually met. The separate steps involved are weighing and blending of materials, the preparation of a damp mass or dampened powder, screening the dampened powder

mass into granules or pellets, sizing the granules (dry screening), drying the granules, lubricant addition and blending and producing tablets by compression (Keleb *et al*., (2004).

2.11.2 Dry Granulation Method

Dry granulation is also known as the double-compression method or precompression method. It is mostly employed when the ingredients involved in the tablet production are influenced by elevated temperature and moisture as a result of the cohesive properties or high inherent binding of the ingredients. Dry granulation is especially used to ingredients that cannot be undertaken by wet granulation method because these ingredients are degraded by elevated temperatures required for drying the granules or in moisture. In dry granulation method, the steps employed may include weighing and mixing of ingredients, slugging, dry screening followed by lubrication and compression (Allen *et al*., 2004).

2.11.3 Direct compression

Granules which are free-flowing and possess cohesive properties can be compressed directly using a tabletting machine without granulation. Granules which are not free-flowing and lack cohesive properties, special pharmaceutical adjuncts may be added to impart the desired features for the production of tablets by direct compression method. Air entrapment during direct compression causes capping, splitting, or laminating (Thoorens *et al*., 2014).

2.12 Excipients for tablet formulation

To achieve the desired characteristics in tablet manufacture, most preparations require addition of excipients which may include disintegrants, binders, lubricants and diluents.

2.12.1 Binders

Binders, also known as adhesives, are added to powdered material to form granules of desired mechanical strength and also to impart cohesiveness to the powdered material after compression (Stanley-Wood and Shubair, 1978). Binders also enhance the free-flowing of granules of required size and hardness. Binder in a dried form can be added to a powder with the other ingredients before compression (slugging or tableting) which is often referred to as a dry binder.

The most effective and common way to incorporate a binder into granules is as a solution binder. In wet agglomeration, solution binder is mostly employed as the agglomeration liquid. Binding capacity increases the disintegrating time of tablets and this counteracts rapid disintegration.

Examples of binders include starch, gelatin, sucrose, lactose, acacia and polyvinylpyrrolidone (Mukesh, 2009).

2.12.2 Glidants

Glidants are used in tablet formulations for direct compaction and also added to granules before tableting to achieve sufficient flowability of the granules. Examples may include boric acid, talc, starch, calcium and sugar (Aulton and Taylor, 2013).

2.12.3 Lubricants

Lubricants improve tablet formation by improving the rate of flow of granules and the ejection of tablets from the die cavity. Lubricants also reduce the interparticle friction and prevent adhesion of granules to the die punches surfaces. Examples of lubricants include talc, stearic acid and magnesium stearate (Carter, 2002).

2.12.4 Diluents or Fillers

Potent drug with low dose concentration requires addition of an ingredient into the formulation to increase its size. Diluents or fillers are included in preparations to increase the bulk size of the powder to produce a practical size for compression and also to form tablets of suitable size for handling. Diluents or fillers should be non-hygroscopic, compatible with other excipients and the active drug, chemically inert, should possess good biopharmaceutical properties, should possess an acceptable taste and smell and should be cheap. Examples may include lactose, mannitol, dry starch and powdered sugar (Aulton and Taylor, 2013).

2.12.5 Disintegrants

Disintegrants are substances or mixture of substances, which ensures that when a tablet comes in contact with a liquid disintegrates or breaks up after the tablet is administered to promote rapid drug dissolution. Disintegrating substances breakup tablets into its primary particles in order to achieve the largest effective surface area for dissolution. The disintegration of a tablet is important for the drug to become fully available for absorption since the tablet must disintegrate first to discharge the drug for local or systematic absorption. Disintegrants employed in plain tablets are grouped into two classes; disintegrants that facilitate the uptake of water and disintegrants that aid in tablet rupture. Examples of -00ts may include methylcellulose, bentonite, cellulose, guar gum and carboxymethlycellulose (Carter, 2002).

2.13 Consideration of excipients selection for a formulation

Considerations for the selection of excipients for formulation include the influence of the excipients on the stability, quality and effectiveness of the drug substance. Packaging system of

excipient, compatibility of drug and excipient and the manufacturing procedure is also considered. Depending on the active drug, certain excipients may be selected due to their effectiveness on enhancing or retarding the release of the active drug to give the desired profile of the in-vitro dissolution release. The amount of excipients to be added to the drug product is also considered. With two excipients with equivalent function, the cheaper of the two may be selected for the formulation process. Manufacturers usually consider excipients with which they have the most experience even though there may be excipients to perform the same function (Carter, 2002).

2.14 Quality control tests

2.14.1 Tablet crushing strength

Tablet crushing strength, also called tablet hardness, indicates how hard tablets should resist handling, chipping, breakage (or abrasion) during storage and transportation. Hardness is important since it can affect disintegration and dissolution. There are a variety of presentations such as rapidly chewable, disintegrating, slowly disintegrating, eroding and lozenge for tablets as delivery systems (BP, 2013). Each of these presentations places a certain demand on the integrity, bonding and structure of the compressed tablet. Tablets should be able to withstand handling during manufacturing activities, transportation pressure and distribution system and also to patients and consumers. Tablet hardness depends on the amount and nature of the binder used and the compression force applied. Certain tablets such as lozenges and buccal tablets releases their medication slowly which have higher hardness values compared to normal tablet hardness with hardness value ranging from 4-7 KgF (1 KgF = 9.80665 Newton) (Alfonso, 1990).

2.14.2 Tablet thickness

Tablet thickness is influenced by the granulation density, compression force, compaction properties of the granules and the amount of fill material allowed into the die which may change the tablet

thickness without any change in weight. Tablet thickness is important in maintaining the identical appearance of the tablets and enhancing patient compliance (those intended for swallowing). The same factors of fill material, pressure and die must be employed to produce tablets of uniform thickness for the same formulation. The thickness of a tablet may be determined using a vernier caliper or any other automatic equipment.

2.14.3 Uniformity of weight

The weight of a compressed tablet is dependent on the volumetric fill and the amount of the granulation material in the die cavity. Weight uniformity test is usually performed when the drug substance is the greater percentage of the tablet content, as a variation in weight uniformity indicates a variation in the drug substance. After the tablet machine is in operation, tablets weights routinely checked to ensure that the desired tablets have the specified weights. This is determined by initially weighing 20 individual tablets and the mean weight is also estimated. Tablets are said to have passed the uniformity of weight test if not more than two of the individual tablet weight differ from the average tablet weight by more than the percentage shown in Table 2.5 and no tablet differ from the average tablet weight by more than twice that percentage (BP, 2013).

Table 2. 5: Limits of weight Uniformity

Pharmaceutical form	Average weight	Deviation
Tablets	80 mg or less	10 %
	>80 mg - <250 mg	7.5 %
	250 mg or more	5 %

Source: BP, 2013.

2.14.4 Tablet content uniformity

A basic pharmaceutical analysis parameter for the quality control of tablets during tablet production is the requirement for a constant dose of drug substance between individual tablets. For drug substances administered in low amounts, the greater portion of the tablet weight is excipients and there may be poor correlation between tablet weight and the amount of drug substance. Therefore, weight variation test must be combined with the variation in content test to estimate the amount of drug substance in a tablet. Multiple tablets are selected at random and a well-defined analytical method is applied to assay the active ingredient of the tablets. A production lot fails to comply with the test if the drug substance is outside the limits of 85 to 115% (BP, 2013).

2.14.5 Friability test

Shock and frictional forces may cause breakage or tablet damage. Friability test is useful in determining the ability of a tablet to withstand pressure associated with packaging, handling and shipping which is usually expressed as a percentage. Usually, this property of the tablet is due to compression force, the nature and amount of binder used. Increasing parameters contributing to tablet hardness gradually decreases the percentage friability of the formulation. The harder the tablets, the lesser the percentage friability of the tablets, and vice versa. Tablets having a unit mass less or equal to 650 mg, the whole tablets corresponding nearly to 6.5g are selected. Tablets having a unit mass greater than 650 mg, ten (10) whole tablets are selected. The test is generally run once. If any broken, cracked or smashed tablet is present in the sample after tumbling, the tablets are considered generally to have failed the test. After the friability test, a weight loss not exceeding 1% of the initial tablets weight is generally considered acceptable (BP, 2013).

2.14.6 Tablet tensile strength

The tensile strength of a tablet is an important parameter as the tablet needs to be mechanically strong enough to withstand pressure such as handling, film–coating, packaging, transport and end-use by the patient, but must be weak enough to break apart when administered to release its contents. The tensile strength of a tablet is influenced by the crushing strength, diameter and the thickness of the tablet (Sugimoto *et al*., 2001).

2.14.7 Tablet disintegration test

Pharmaceutical drug release process from tablets often includes a step at which the tablet breaks into its smaller primary particles. Disintegration implies penetration of the tablet in the presence of an aqueous liquid and disruption of internal bonds which lead to subsequent breakdown of the tablet. The first step before dissolution occurs is usually the breakdown of the tablet into primarily particles, a process described as disintegration. It is reasonable to suppose that rapid penetration of liquid is an essential requirement for rapid disintegration of conventionally formulated tablets. The disintegration test results in a time necessary to break down a group of tablets into small particles under standard conditions. Disintegration test is helpful in the preformulation stage to the formulator in the preparation of an optimum tablet formula**,** optimization of manufacturing parameters, such as compressional force and dwell time and as an in-process control tool to ensure lot-to-lot uniformity. However, disintegration test is not a bioavailability indicator. Higher disintegration time lowers the dissolution rate which results to poor absorption. All tablets and capsules must pass a test for disintegration except for chewable tablets, troches and modified or extended release tablets. Tablets pass the test if they break and pass through the mesh screen before

the time specified in the monograph**.** Uncoated tablets have disintegration time standards as high as 15 minutes (BP, 2013).

2.14.8 Dissolution test

In vitro dissolution testing of solid dosage forms guides formulation and product development toward product optimization. The dissolution testing is performed to provide reasonable prediction or correlation with the active substance in-vivo bioavailability. The in-vitro dissolution testing system compares combinations of the active drug‟s solubility (low or high) and its intestinal permeability (low or high) as a fundamental for predicting the chance to achieve a successful in vivo–in vitro correlation (IVIVC). Dissolution is performed in-process or on the final product as a component of the overall quality assurance program. Dissolution media used in the testing may include purified water, simulated gastric fluid and simulated intestinal fluid excluding organic solvents. The British Pharmacopoeia recommends that at least 70 % of the active drug should be released in 45 minutes for conventional dosage forms tested under reasonable and justified conditions (BP, 2013).

Chapter Three

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Pharmaceutical raw materials

Maize starch (Kathwada Ahmedabad-382430, India), magnessium stearate (Anhui Sunhere Pharmaceutical Company Limited, China), talc (Haicheng Pinyang Talc Company Limited, China), polyvinyl pyrrolidone (Quzhou Jianhua Nanhang Industrial Company Limited, China), lactose (Haicheng Pinyang Talc Company Limited, China) and paracetamol powder (Changshu Huagang Pharmaceutical Company Limited, China).

The maize starch (Kathwada Ahmedabad-382430, India) used for this investigation was assigned with code **V60** and was obtained gratis from Amponsah-Effah Pharmaceutical Limited, Kumasi.

3.1.2 Reagents

Concentrated sulphuric acid (Merch KGaA, Germany), concentrated hydrochloric acid (Merch KGaA, Germany), ethanol 96% (Sasol Chemical Industry Limited, South Africa), nitric acid (Merch KGaA, Germany), potassium dihydrogen orthophosphate (Kosdaq Listed Company, South Korea) and sodium hydroxide pellets (Merch KGaA, Germany). Distilled water was freshly prepared and used.

3.1.3 Equipment and apparatus

Hot air oven (Gallenkamp Oven 300 Plus series; United Kingdom), Friabilator (TA-20, ErwekaGermany), Disintegration apparatus (ZT-4, Erweka-Germany), Tabletting machine (Cadmach CTx 26-U.S.A), Eleclab India hardness tester, FTIR spectrometer (PerkinElmer UATR two), Retsch mechanical shaker (AS-200 Basic, Retsch- Germany), Analytical balance (SN: AE 436647 Adam Equipment, UK), Powerfix electronic digital caliper (model number : z22855, UK), Eutech pH meter (pH 510, pH/mV/°C meter, SN: 2025520, Singapore), UV spectrophotometer (T90 UV/VIS spectrometer, PG Instruments Ltd, UK), Erweka Dissolution Apparatus (Type DT6, GmbH Heusenstamm, Germany) and Retch test sieves. Other apparatus and equipment used included; oven, mortar and pestle, petri dishes, general purpose glassware, hot water bath, porcelain crucibles, thermometer, desiccator, density bottle and aluminium foils.

3.2 Methods

3.2.1 Collection and Identification of the cassava root tubers

Crop Research Institute (CRI) of the Council for Scientific and Industrial Research (CSIR), Fumesua, Kumasi, Ghana, provided the matured fresh good quality root tubers of five (5) different varieties of cassava (*Manihot esculenta*). They were identified to be root tubers of Sika Bankye, Ampong, AW/ 10 / 008, 12/ 0245 and 12/0197 which were assigned with codes V10, V20, V30, V40 and V50**,** respectively, for the purpose of this investigation. This identification and authentication was carried out by Mrs. Evelyn Kwarteng, Laboratory Analyst, Cassava Department, CSIR, Fumesua-Kumasi. All the five varieties of cassava were planted in March, 2014 and harvested in October, 2015 and the starch extraction was undertaken within two days after harvesting.

3.2.2 Extraction of cassava starch

The method of Isah *et al*. (2009) was used with minor modifications. The freshly harvested varieties of cassava were thoroughly washed and all foreign materials were removed. The outer layer of the root tubers was peeled off and the tubers were cut to small pieces, washed and weighed. The edibles parts of the cassava root tubers were then milled in a grinding machine and water was added to the pulp which was then passed through a nylon fibre. The supernatant was decanted after the resulting slurry was left to stand for 12 hours. The starch which was packed tightly was then collected and spread to dry in an oven at 40 °C for 30 minutes. The dried cassava starch was size reduced to fine powder by triturating and passed through 1.6 mm sieve mesh.

3.2.2.1 Starch yield on fresh weight basis (fwb)

The ratio of the weight of starch (g) to weight of fresh edible root tubers (g) was used to calculate the cassava starch yield on fresh weight basis.

$$\text{Percent (\%) starch yield from fresh cassava root tuber} = \frac{\text{weight of dried starch}}{\text{weight of peeled tubers}} \times 100$$

3.2.3 Moisture content of the dried cassava starch

Ten (10) grams of the powdered cassava starch was weighed accurately into porcelain crucibles which had already been dried to have a constant weight. The powdered starch was placed in a hot air oven and the temperature was maintained at 105°C. After 5 hours, the cassava starch was removed and cooled after which the powder were placed in a desiccator for 30 minutes. The weight of both crucible and starch were recorded. The determination was done in triplicates. The moisture contents were expressed as a percentage of all starch samples (Shehzadi, 2014).

$$\text{Percent (\%) of moisture content} = \frac{\text{weight lost after drying}}{\text{Initial weight of sample}} \times 100$$

3.2.4 Identification and organoleptic tests for cassava starch

Starch identification and organoleptic properties were carried out using methods and procedures described in the British Pharmacopeia (BP, 2013).

3.2.4.1 Identification test

A smooth mixture was prepared by adding 1g of the cassava starch powder to 2 ml of distilled water. Boiling water of 15 ml volume was then added to the mixture and heated gently for 2 minutes.

Clarity or otherwise a jelly formed when the slurry was allowed to cool as well as any change in colour of the slurry upon addition of iodine test solution (TS), was observed and recorded.

3.2.4.2 Organoleptic properties

The organoleptic properties of the cassava starches, namely: colour, odour, taste and texture were observed and recorded.

3.2.5 Physicochemical properties of the cassava starch

3.2.5.1 Bulk and powder flow properties

The methods described in the British Pharmacopoeia, (2013) were used in the determination of the angle of repose, Hausner‟s ratio and Carr‟s compressibility index.

3.2.5.1.1 Determination of Particle Density of the cassava starch powders

The particle density was determined with a 50 ml relative density bottle using liquid paraffin as the displacement fluid at 25°C.

The weight of the empty relative density bottle was determined (W) using an analytical balance (SN: AE 436647 Adam Equipment, UK) and recorded, filled with the liquid paraffin and excess was wiped off. The filled bottle was weighed (W_1) and the difference between W_1 and W was

obtained as W_2. A 1g quantity of the cassava starch powder was weighed (W_3) and transferred into the relative density bottle. The excess solvent was wiped off after filling and the bottle weighed again (W_4) (Odeku *et al.,* 2005).

The particle density, ρt (g/cm^3) was calculated from the equation;

$$\rho t\ (g/cm^3) = [W_2 * W_3] / [50\ (W_3 - W_{4+}\ W_2 + W)]$$

3.2.5.1.2 Average diameter and Particle Size Distribution of the cassava starch powders

Particle size distribution of the starch powders was determined using the sieve method. Sieves of 250, 180 and 75 µm mesh sizes and a collecting pan were arranged in a descending order on the sieve shaker. Twenty grams (20g) of the powdered starch was placed on the top most (250 µm) sieve and then shaken at amplitude 70 for 10 min on a Retsch mechanical shaker (AS-200 Basic, Retsch- Germany). The powders retained on each sieve were collected and weighed (Isah *et al*., 2009).

The average diameter was determined as $\Sigma \frac{[(\%\ \text{retained}) \times (\text{mean aperture})]}{100}$

3.2.5.1.3 Bulk and Tapped Densities

Thirty grams (30g) of each of the cassava starch powders were weighed and poured into a 100 ml measuring cylinder and the volume occupied was noted. The bulk density was then calculated. Bulk Density (BD) = M / V, Where M is mass and V is volume.

Thirty grams (30g) of each of the cassava starch powder was weighed and poured into a 100 ml measuring cylinder and then tapped on a hard surface thirty (30) times about 2cm height and the volume was noted (Arun, 2013). Tapped Density (TD) = M/V, Where M is mass and V is volume.

3.2.5.1.4 Angle of repose

A funnel was clamped and its tip was 2cm above a hard horizontal surface. The starch powder was allowed to flow through the funnel until the apex of the powder formed just touched the funnel"s tip. The mean diameter (D) of the base of the starch powder cone was determined and the angle of repose (θ) was determined using the relation Tan $\theta = \frac{2h}{D}$, $\theta = \tan^{-1}\frac{2h}{D}$.

3.2.5.1.5 Hausner's ratio

Hausner"s ratio (H.R) was determined using the following relationship:

H.R=$Tapped\ density/Bulk\ density$

3.2.5.1.6 Carr's Compressibility Index

Compressibility index (C.I) (%) was determined using the equation below:

C.I= $\frac{Tapped\ density - bulk\ density}{Tapped\ density}$ x 100

3.2.5.2 Solubility of the cassava starch powders in various solvents

The solubility of the cassava starch powders was determined in cold distilled water, hot distilled water, chloroform and ethanol (96 %). A weight of 0.5 gram of each variety of the starch powder was added to 50 ml of solvents and was allowed to stand overnight. A volume of 25 ml of the

supernatants were placed in pre-weighed petri dishes which were evaporated to dryness over a constant water bath. Using an analytical balance (SN: AE 436647 Adam Equipment, UK), the mass of the residues with reference to the volume of the solutions were measured and expressed as the percentage solubility of each of the cassava starch in the respective solvents (Carter, 2005).

3.2.5.3 Swelling capacity of cassava starch powders

The tapped volume occupied by 10g of the powdered cassava starch in a 100 ml measuring cylinder was recorded as "Vd". The starch powder was then dispersed in 85 ml of distilled water and the volume made up to 100 ml with more water. After 18 hours of standing, the volume of the sediment, (Vw) was estimated and expressed as a percentage swelling power of the starches (Arun, 2013).

The swelling capacity (%) was computed as; swelling capacity= $\frac{(Vw - Vd)}{Vd} \times 100$

3.2.5.4 pH of the cassava starch powders

Ten (10) grams of the cassava starch powder was weighed accurately and added to 15 ml distilled water and was mixed properly. Boiling distilled water was then added to the mixture to make up 100 ml of slurry and the slurry was then allowed to cool. Using a Eutech pH meter (pH 510, pH/mV/°C meter, SN: 2025520, Singapore), the pH of the slurry was measured (BP, 2013).

3.2.6 Determination of elemental content and ash values of the cassava starch powders

3.2.6.1 Preparation and dry ash digestion of the cassava starch powders for elemental analysis

One (1.0) gram of the cassava starch powder was weighed into a clean ceramic crucible. The sample was kept in a cool muffle furnace over a period of two (2) hours at a temperature of 500°C.

This temperature was allowed to remain for an additional 2 hours. The samples were allowed to cool down in the oven. After it was sufficiently cooled, it was taken out of the furnace avoiding any external air. The ash sample was first placed into previously labelled 50 ml centrifuge tube. 10 ml of distilled water was used to rinse the crucible into the centrifuge tube. The crucible was further washed with 10 ml of aqua regia (HNO_3 and HCl, 3: 1). The sample was shaken for about 5 minutes for proper mixing on a mechanical reciprocating shaker. At 3000 rpm, the sample was then centrifuged for 10 minutes and which was then transferred into a 100 ml volumetric flask and the volume was topped up to the 100 ml mark with deionized water.

The clear supernatant digest were decanted into clean reagent bottle for the elemental analysis (Okalebo *et al*., 1993).

3.2.6.2 Determination of total ash of the cassava starch powders

A clean ash porcelain crucible was placed in an oven until it dried to a constant weight. It was then taken out of the oven and left in a desiccator to cool. The weight of the empty crucible was recorded as A. 2.0 g of cassava starch powder (B) was placed in the crucible and was then placed into a muffle furnace for 4 hours at a temperature of 550°C. It was allowed to cool below 200°C and maintained for another 20 minutes. The sample was put in a desiccator to cool completely and the weight of the ashen sample was determined as C.

The total ash was calculated using the formula below,

(A + B) − A = B (A

+ C) – A = C

% total ash = C/B × 100; where A = weight of crucible, B = weight of sample, C = weight of ash.

3.2.6.3 Determination of acid insoluble ash of the cassava starch powders

A volume of distilled water was heated to near boiling point. 2+5 HCl was prepared by mixing 2 volumes of concentrated HCl with 5 volumes of distilled water. The total ash residue was transferred from the crucible to a beaker using 25 ml of the (2+5) HCl. Using a glass rod, the contents of the beaker was stirred and then covered with a watch glass. It was then heated gently for about five minutes in a hood. The bottom of the watch glass was rinsed with hot water into the beaker. The acid solution was filtered through an ash filter paper. It was ensured that all traces of the acid and ash were completely rinsed (with hot water) from the beaker and crucible onto the filter. More washing of the filter paper was done until the washings were acid free to litmus.

The filtrate was allowed to drain and the residue was carefully transferred into a weighed crucible. It was then dried in an oven and ignited in the muffle furnace at 600°C, cooled and weighed (Okalebo *et al*., 1993).

The acid insoluble ash was evaluated using the equation below;

$$\% \text{ Acid insoluble ash} = \frac{A - B}{C - B} \times 100$$

Where A = weight of crucible and ash; B = weight of empty crucible and C = weight of crucible and original sample weight.

3.2.7 Investigation of possible drug-excipient interaction using FTIR spectroscopy

Chemical and physical characterization is an important element to be considered before a drug substance is formulated into a dosage form. Drug-excipient interaction provides the information necessary to define the nature of the active drug .It also provides an idea about the drug combination with the pharmaceutical excipient in the development of a dosage unit. A study was

carried out using Fourier transform Infra-red spectrometer (model-spectrum 2; 941333) to analyze any chemical interaction between the active drug (paracetamol) and the cassava starch. The powdered dry starch was analyzed separate and then mixed with the active drug for compatibility studies. The spectra was recorded by scanning in wavelength region 4000-400 cm^{-1} using PerkinElmer (UATR two) FTIR spectrometer after the powdered mixture was put into a diffuse reflectance sampler. The IR spectrum of paracetamol was compared with the IR spectrum of the physical mixture of the active drug and the dry cassava starch to check for any possible drug-excipients. The procedure was repeated for all the varieties of the cassava starches to investigate any interaction with the paracetamol powder (Patil and Shrivastava, 2014).

3.2.8 Formulation of paracetamol granules and tablets

Table 3.2. 1: Composition of paracetamol tablets for evaluation of the cassava starches

Ingredients	**Quantities for the different concentrations of the investigative disintegrant (cassava starch)**			**Quantities for the reference disintegrant (Maize starch)**		
	5.0%w/w	7.5%w/w	10.0%w/w	5.0%w/w	7.5% w/w	10.0%w/w
Paracetamol (Active drug), 83.3%)	500.000mg 420.000g*	500.000mg 420.000g*	500.000mg 420.000g*	500.000mg 420.000g*	500.000mg 420.000g*	500.000mg 420.000g*
Cassava Starch (Investigative disintegrant)	30.000mg 25.200g*	45.000mg 37.800g*	60.000mg 50.400g*	-	-	-
Maize Starch (Reference disintegrant)	-	-	-	30.000mg 25.200g*	45.000mg 37.800g*	60.000mg 50.400g*
Lactose (Diluent)	31.000mg 26.040g*	16.000mg 13.440g*	1.000mg 0.840g*	31.000mg 26.040g*	16.000mg 13.440g*	1.000mg 0.840g*

Polyvinylpyrrolidone, K-30 (Binder,4.5% w/v)	27.000mg 22.680g*	27.000mg 22.680g*	27.000mg 22.680g*	27.000mg 22.680g*	27.000mg 22.680g*	27.000mg 22.680g*
Talc (1.8% w/w)	10.800mg 9.0720g*	10.800mg 9.0720g*	10.800mg 9.0720g*	10.800mg 9.0720g*	10.800mg 9.0720g*	10.800mg 9.0720g*
Magnesium stearate (0.2% w/w)	1.200mg 1.0008g*	1.200mg 1.0008g*	1.200mg 1.0008g*	1.200mg 1.0008g*	1.200mg 1.0008g*	1.200mg 1.0008g*
Weight per tablet **Total weight for 840 tablets**	**600mg** **504g***	**600mg** **504g***	**600mg** **504g***	**600mg** **504g***	**600mg** **504g***	**600mg** **504g***

*Represents scaled quantities (×840)

Using the wet granulation method, paracetamol granules were prepared using the formula above. The active ingredient was dry mixed with lactose as the diluent and the disintegrant for 5 minutes using mortar and pestle. The five (5) varieties of the cassava starch powder used as disintegrant as well as the reference disintegrant (maize starch) were added at three different concentrations of 5.0, 7.5 and 10.0 % w/w to form the three batches namely, batches I, II and III respectively. Mucilage with polyvinylpyrrolidone (K-30) as binder was made and added in aliquots into the dry mixed powder and massed for 5 minutes. The damp mass of the different batches was then force screened through a 1.7mm sieve mesh and placed in hot air oven (Gallenkamp Oven 300 Plus series) maintained at 40ºC for 20 minutes. The prepared granules were then screened through a 1.6mm sieve and dried for 2hours at 40ºC. The dried granules were respectively mixed with appropriately weighed amounts of glidant and lubricant.

3.2.9 Tablet compression

Paracetamol granules was compressed at 45-50KN into tablets (600mg) using Cadmac CTx 26 tabletting machine lubricated with magnesium stearate prior to compression. After ejection, the

tablets were stored for 24 hours to allow for elastic recovery and hardening before evaluation. Fill weights of 600mg of tablets were compressed and formulations for an investigational batch of 840 tablets were made in each case.

3.2.10 Pharmaceutical evaluations of the formulated paracetamol tablets

3.2.10.1 Weight uniformity

Twenty (20) tablets from each batch were randomly selected and the individual weight of each tablet was determined and also the total weight using a digital analytical balance (SN: AE 436647 Adam Equipment, UK). The mean weight of the tablets was determined and the individual weight was subtracted from the mean weight to determine the percentage deviation of each tablet from the mean (BP, 2013).

$$\text{Percentage deviation} = \frac{[\text{Individual tablet weight} - \text{Mean tablet weight}]}{\text{Mean tablet weight}} \times 100$$

3.2.10.2 Thickness uniformity of the paracetamol tablets

Ten (10) tablets were selected at random from each batch and the thickness was determined with the help of a digital Vernier caliper (4Cr13 stainless steel digital caliper). The mean and standard deviations were calculated for each batch.

3.2.10.3 Tablet crushing strength

The crushing strength test (hardness test) is a non-compendial test which is undertaken to determine the ability of the tablets to withstand pressure during handling, packaging and transportation. The hardness of the tablets was determined individually with the Eleclab India hardness tester. Ten (10) tablets were randomly selected from each batch of tablets. The hardness

values of the paracetamol tablets were recorded on the gauge in KN and the mean crushing strength was calculated for each batch.

3.2.10.4 Tensile strength

The tensile strength (T) of the formulated paracetamol tablets was determined using the equation; $T = 2P/ \pi Dt$, where T is tensile strength, P is the tablet crushing strength, D is the diameter of tablet, t is the thickness of tablet (Sugimoto *et al*., 2001).

3.2.10.5 Tablet friability

An Erweka Friabilator (TA-20, Erweka-Germany), was used to carry out the friability test. Tablets weighing about 6.5g from each batch was taken, weighed and then placed on the friabilator, which was then operated for four (4) minutes at 100 rpm (100 revolutions). The tablets were de-dusted, reweighed and the difference in tablet weight was determined. Tablets were also observed for cracks, lamination as well as broken tablets.

Friability (%) = (W1- W2 / W1) ×100

W1 = original weight, W2 = final weight.

3.2.10.6 Determination of tablet disintegration time

The disintegration time of tablets with cassava starch as disintegrant was determined according to the disintegration test for uncoated tablets described in the British Pharmacopoeia (BP, 2013). Six tablets were taken from each batch and a tablet was placed in each of the six tubes of the disintegration testing apparatus (ZT-4, Erweka-Germany). Distilled water thermostated at 37º C ±

2° C was used as the disintegrating medium. The time taken for each tablet to break up and pass through the mesh screen was recorded.

3.2.10.7 Determination of drug content of the paracetamol tablets

3.2.10.7.1 Calibration curve of paracetamol in 0.1M NaOH

A stock solution of paracetamol of concentration 0.1 $\%^{w}/_{v}$ was prepared by dissolving 0.1 g of pure paracetamol powder in a small volume of 0.1M NaOH and then made up to 100 ml mark.

The following concentrations of paracetamol, 0.00025, 0.00050, 0.00075, 0.00100 and 0.00150 $\%^{w}/_{v}$ were then prepared from the stock solution. The absorbance of these solutions was determined spectrophotometrically at λ-max of 257nm using 0.1M NaOH as blank. A calibration curve showing the relationship between concentration and absorbance was plotted and the resultant regression equation generated from the scatter plot was subsequently used to estimate the amount of drug in the tablets.

3.2.10.7.2 Assay of Paracetamol

Procedures described in the British Pharmacopoeia (BP, 2013) were used in assaying the various batches of the paracetamol tablets.

Twenty (20) tablets were accurately weighed and the average weight of the tablets determined. The tablets were crushed to a fine powder and a quantity of the powder equivalent to 0.15g of paracetamol was accurately weighed which was then dissolved with 50 ml of 0.1 M NaOH in a 200 ml volumetric flask. The solution was diluted with 100 ml of water, shaken for 15 minutes and sufficient water was added to produce 200 ml. The resulting solution was filtered and then 10 ml was taken from the filtrate and diluted with water to produce 100 ml. The absorbance of these solutions was determined spectrophotometrically at λ-max of 257 nm using 0.1 M sodium

hydroxide (NaOH) as blank. The amount of drug released from the tablets was determined spectrophotometrically using the regression data of the calibration plot of paracetamol in 0.1 M sodium hydroxide (NaOH).

3.2.10.8 In vitro dissolution studies of the paracetamol tablets

3.2.10.8.1 Calibration curve of paracetamol in phosphate buffer (pH = 6.8)

A stock solution of paracetamol of concentration 0.1 $\%^{w}/_{v}$ was prepared by dissolving 0.1 g of pure paracetamol powder in a small volume of phosphate buffer (pH 5.8) and then made up to 100 ml mark. The following concentrations of paracetamol, 0.00025, 0.00050, 0.00075, 0.00100 and 0.00150 $\%\ ^{w}/_{v}$ were then prepared from the stock solution. Using phosphate buffer (pH 5.8) as a blank solution, the absorbance of the solutions was noted spectrophotometrically at a maximum wavelength of 257nm. A calibration curve showing the relationship between concentration and absorbance was plotted and the resultant regression equation generated from the scatter plot was subsequently used to estimate amount of drug released from the tablets.

3.2.10.8.2 Dissolution testing of tablets

In-vitro dissolution testing was carried out using methods described in the British Pharmacopoeia (BP, 2013), (paddle apparatus). Dissolution of tablets was determined in 900 ml dissolution medium. Phosphate buffer (pH of 5.8) was used as the dissolution medium for the paracetamol tablets and the temperature of dissolution medium was maintained constantly at 37ºC ± 2ºC. The agitation intensity of the paddle was 50 rpm (50 revolutions per minute). The tablets were carefully placed into each vessel to exclude air bubbles from its surface. At the midway between the surface of the dissolution medium and the top of the rotating paddle blade, a volume of 20 ml of the dissolution medium was withdrawn and filtered at 5, 10, 15, 30, 45 and 60 minutes interval. Equal

volume of fresh medium having the same temperature was replaced at each time. The samples were suitably diluted to 50 ml with 0.1 M NaOH. The absorbance of the resultant solutions were measured at 257 nm with the UV spectrophotometer and the amount of active ingredient was determined spectrophotometrically using the regression data of the calibration plot of paracetamol in phosphate buffer (pH = 5.8). A graph of percentage drug released was plotted against time to establish the dissolution profile of paracetamol.

3.2.11 Statistical analysis

GraphPad Prism (version 5.0.3.0, Software Inc., San Diego - California) was used for the statistical analysis. The results were in triplicates or otherwise stated and expressed as Mean ± SD. „P" values were obtained after performing one-way analysis of variance (ANOVA) test and the values show whether the means of the paired samples are significantly different or not. The means of paired samples were considered to be significantly different when $P < 0.05$.

Chapter Four

RESULT S

4.1 Starch extraction and yield

Industries usually require cassava root tubers with starch content higher than 30 % for economic viability. All the five cassava varieties had starch percentage yield ranging from 7.97 – 26.82 % with V50 having the lowest starch yield and V20, with the highest starch yield.

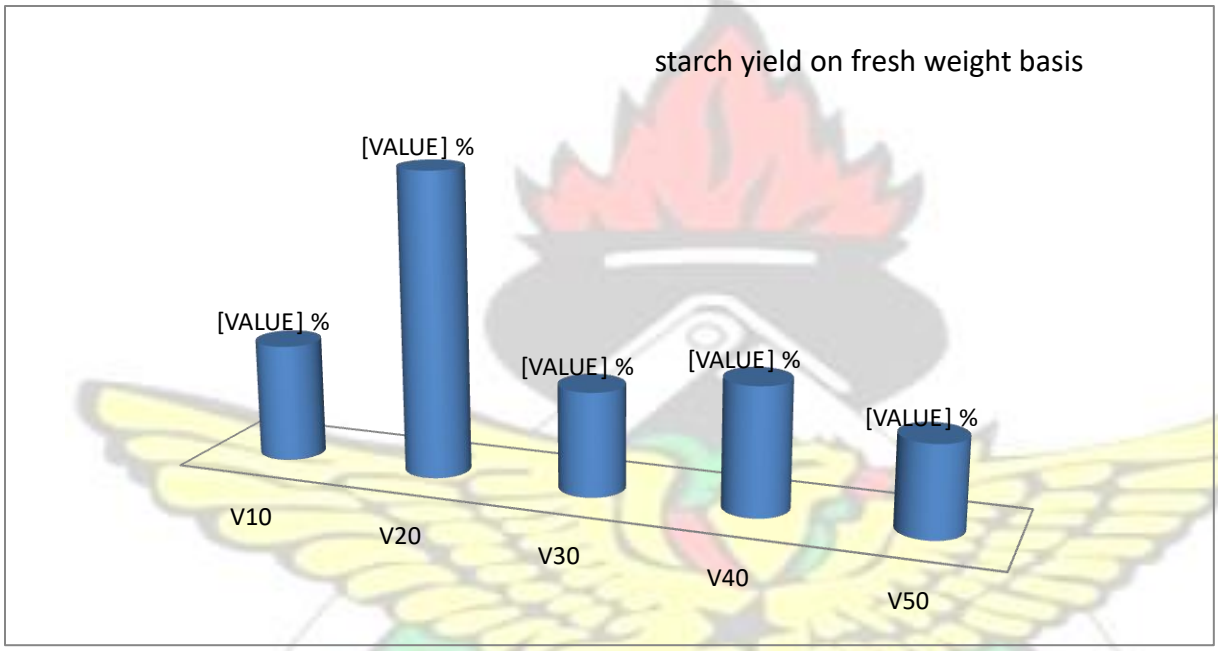

Figure 4. 1: Starch yield from the five varieties of cassava

4.1.1 Percentage of starch yield from fresh root tubers

$$\text{Percent (\%) starch yield from fresh root tubers} = \frac{\text{weight of dried starch (g)}}{\text{weight of peeled tubers (g)}} \times 100$$

For V10, percent (%) starch yield from fresh root tubers $= \frac{400.39}{3850} \times 100$

10.4 %

This was repeated for the other varieties of the cassava starches

4.2 Moisture content

Moisture content determination helps to predict the amount of water contained in a powdered sample. The moisture content in V30 was higher than the other varieties and V20 showed the lowest moisture content.

Table 4. 1: Moisture content (n= 3) and starch yield on fresh weight basis

Starch	Moisture content (%)	starch yield on fresh weight basis
V10	7.200 ± 1.217^{c}	10.400
V20	2.067 ± 0.306^{a}	26.820
V30	10.000 ± 0.000^{b}	9.150
V40	9.533 ± 0.116^{b}	11.170
V50	9.536 ± 0.306^{b}	7.970

Means followed by the same superscript in a column are not significantly different ($p > 0.05$) while means followed by a different superscript are significantly different ($p < 0.05$).

4.3 Identification and organoleptic tests for the cassava starch

The results of the identification and organoleptic tests carried out on the cassava starches are outlined in the tables below. All the starches were positive to iodine test (BP, 2013) which showed a characteristic dark blue colour indicating the presence of starch. The starch powders had characteristic parameters which complied with BP (2013) organoleptic test for starch.

Table 4. 2: Starch identification test

Starch	Test	Observation	Inference
V10	A drop of iodine solution was added to 15 ml of starch slurry	Clarity and jelly formed turned dark black	Dried powder sample complied with BP identification test for starch
V20	-	-	-
V30	-	-	-
V40	- - -	V50 - - -	

Table 4. 3: Cassava starch organoleptic test

Starch	Test	Observation	Inference
V10	Starch powder was observed for texture, odour, taste and colour	Starch powder appeared as fine, odourless, bland taste with a white colour	Dried powder sample complied with BP identification test for starch
V20	_	_	_
V30	_	_	_
V40	_	_	_
V50	_	_	_

4.4 Physicochemical properties of the cassava starch

4.4.1 Bulk properties of the cassava starch

The results of the bulk properties carried out on the starches are outlined in the table below. These parameters describe the density, consolidation, density and flow of a powder mass and also give an idea of how well the starch powders will be compressed. The cassava starches had good bulking properties for pharmaceutical use with V20 highest and V10 lowest.

Table 4. 4: Bulk properties of the cassava starch

Parameter	Starch				
Bulk properties:	**V10**	**V20**	**V30**	**V40**	**V50**
Particle density	1.833 ± 0.020^{a}	1.863 ± 0.018^{b}	1.851 ± 0.000^{b}	1.836 ± 0.022^{a}	1.848 ± 0.020^{a} (g/cm^3)
Bulk density (g/cm^3)	0.585 ± 0.013^{a}	0.693 ± 0.018^{b}	0.625 ± 0.000^{b}	0.608 ± 0.014^{a}	0.612 ± 0.000^{a}
Tapped density	0.643 ± 0.016^{a}	0.818 ± 0.025^{b}	0.703 ± 0.018^{b}	0.672 ± 0.017^{a}	0.682 ± 0.000^{a} (g/cm^3)

Means followed by the same superscript in a row are not significantly different ($p > 0.05$) while means followed by a different superscript in a row are significantly different ($p < 0.05$).

4.4.2 Average diameter and Particle Size Distribution of the cassava starch powders

Average diameter and particle size distribution influence the flow of granules and uniformity of a dosage form. The results for the starches evaluated had mean particle size ranging from 162.2µm – 177.5µm with V30 highest and V10 lowest as shown below. All the starches had good average diameter and particle size distribution for optimum pharmaceutical formulation.

Table 4. 5: Average diameter and particle size distribution of the cassava starch powders

Starch	Sieve aperture (µm)	Weight of starch retained (Mean ± SD) (%)	Mean starch particle diameter (µm)

V10	>250	53.880 ± 0.076	177.5 ± 0.212[a]
	180-250	9.800 ± 0.050	
	75-180	17. 030 ± 0.050	
	<75	0.000 ± 0.000	
V20	>250	37.52 ± 0.076	175.3 ± 0.211[a]
	180-250	19.08 ± 0.076	
	75-180	31.75 ± 0.050	
	<75	0.000 ± 0.000	
V30	>250	41.31 ± 0.076	162.2 ± 0.101[a]
	180-250	11.37 ± 0.322	
	75-180	27.05 ± 0.050	
	<75	0.000 ± 0.000	
V40	>250	33.35 ± 0.087	173.7 ± 0.220[a]
	180-250	27.00 ± 0.050	
	75-180	25.32 ± 0.076	
	<75	0.000 ± 0.000	
V50	>250	32.62 ± 0.029	162.8 ± 0.098[a]
	180-250	20.88 ± 0.029	
	75-180	28.50 ± 0.050	
	<75	0.000 ± 0.000	

Means followed by the same superscript in a column are not significantly different ($p > 0.05$)

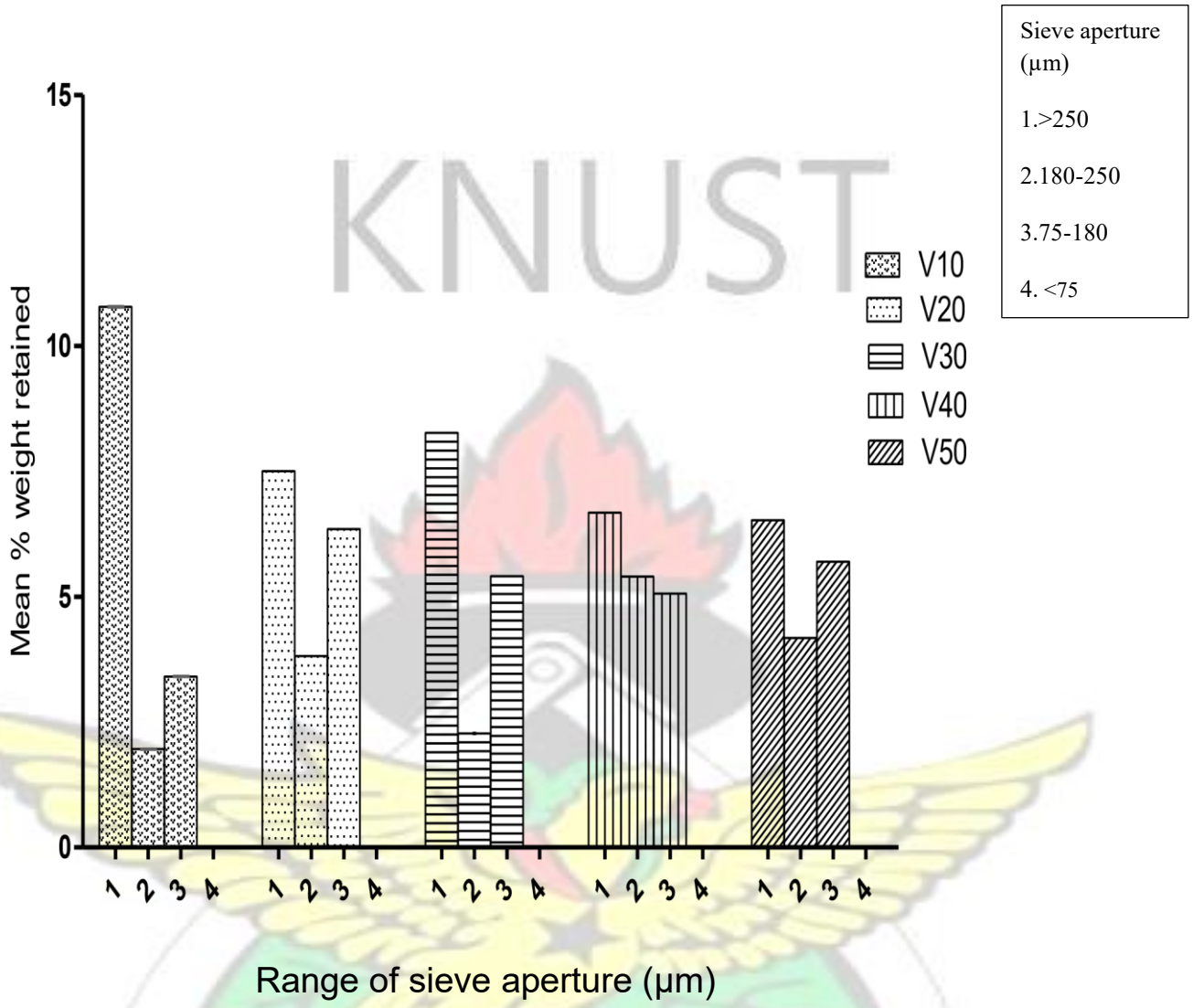

Figure 4. 2: Particle size distribution of the cassava starch powders

4.4.3 Solubility of the cassava starch powders in various solvents

Under the same conditions, the starches showed very little solubility in both 96 % ethanol and chloroform, a very insignificant solubility in cold water. All the starches showed higher solubility in warm water compared to the other solvents.

Table 4. 6: Solubility of the cassava starch powders in various solvents, n= 3

Solvent	Solubility of the cassava starch powders in various solvents (%)				
	V10	**V20**	**V30**	**V40**	**V50**
Cold water	0.0016 ± 0.000^{a}	0.0006 ± 0.001^{c}	0.0083 ± 0.001^{b}	0.0015 ± 0.001^{a}	0.0020 ± 0.000^{a}
Warm water	0.2140 ± 0.012^{b}	0.1055 ± 0.001^{a}	0.1460 ± 0.011^{a}	0.1232 ± 0.010^{b}	0.1043 ± 0.002^{a}
Ethanol	0.0035 ± 0.001^{a}	0.0003 ± 0.001^{a}	0.068 ± 0.000^{a}	0.0030 ± 0.001^{a}	0.0092 ± 0.000^{a}
Chloroform	0.0028 ± 0.004^{a}	0.0015 ± 0.001^{a}	0.0024 ± 0.001^{a}	0.0052 ± 0.001^{a}	0.0060 ± 0.001^{a}

Means followed by the same superscript in a row are not significantly different ($p > 0.05$) while means followed by a different superscript in a row are significantly different ($p < 0.05$).

4.4.4 Swelling capacity of the cassava starch powders

The swelling power gives an idea of how well the starches will absorb water and swell in an aqueous medium. V30 showed the highest swelling index and V50 also retained the lowest swelling capacity under similar conditions. The high swelling power and water retention capacities of all the starches will give good disintegrating properties.

Table 4. 7: Swelling capacity of the cassava starch powders, n= 3

	Swelling capacity of the cassava starch powders (%)				
	V10	**V20**	**V30**	**V40**	**V50**
Swelling index (%)	21.43 ± 0.000^{a}	23.72 ± 1.110^{a}	26.52 ± 1.312^{a}	21.98 ± 0.952^{a}	20.00 ± 0.000^{a}

Means followed by the same superscript in a row are not significantly different ($p > 0.05$)

4.4.5 pH of the cassava starch powders pH studies on the starches was conducted under the same conditions. All the starches had basic pH values with V10 the being highest (pH = 9.94) and V20 (pH = 8.07) the lowest.

Table 4. 8: pH of the cassava starch powders, n= 3

	pH of the cassava starch powders				
	V10	**V20**	**V30**	**V40**	**V50**
pH	9.94 ± 0.012^{a}	8.07 ± 0.031^{a}	9.03 ± 0.021^{a}	9.25 ± 0.060^{a}	9.47 ± 0.091^{a}

Means followed by the same superscript in a row are not significantly different ($p < 0.05$)

4.5 Powder flow properties of the cassava starches

Powder flow properties characterize and also tell the percentage compressibility of a starch powder. All the starches had better flow properties with V20 showing the highest and V10 the least flow properties.

Parameter	**Starch**				
Flow Properties:	**V10**	**V20**	**V30**	**V40**	**V50**

Table 4. 9: Flow properties of the cassava starches

Angle of repose (º)	35.87 ± 0.76^{a}	46.57 ± 0.06^{b}	41.97 ± 0.86^{c}	37.87 ± 0.76^{a}	42.77 ± 0.50^{c}
Hausner"s ratio	1.09 ± 0.03^{a}	1.18 ± 0.04^{b}	1.13 ± 0.03^{c}	1.10 ± 0.05^{a}	1.14 ± 0.00^{c}
Compressibility index (%)	9.05 ± 2.13^{a}	15.33 ± 2.46^{b}	11.10 ± 2.37^{c}	9.58 ± 2.12^{a}	12.02 ± 0.00^{c}

Means followed by the same superscript in a row are not significantly different ($p > 0.05$) while means followed by a different superscript in a row are significantly different ($p < 0.05$).

4.6 Toxic metal content and ash values of the cassava starch powders

In the toxic metal content analysis of the starches, all the starches showed the presence of very low amounts of toxic heavy metals like arsenic, lead and cadmium but were totally free of mercury. The figure below compares the toxic metal content of the starches.

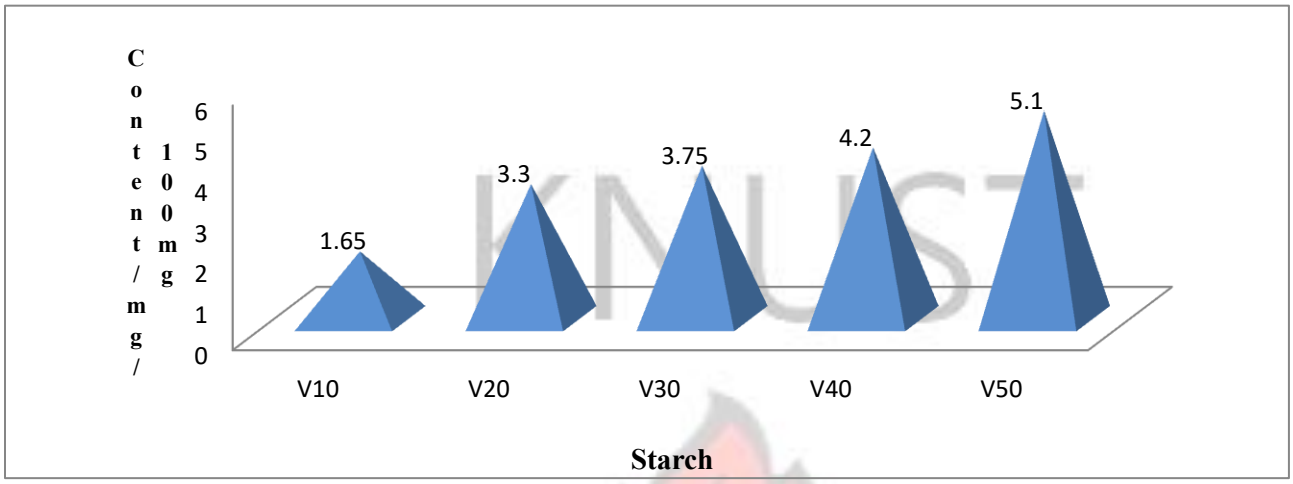

Figure 4. 3: Content of Cadmium (Cd) in the cassava starch powders

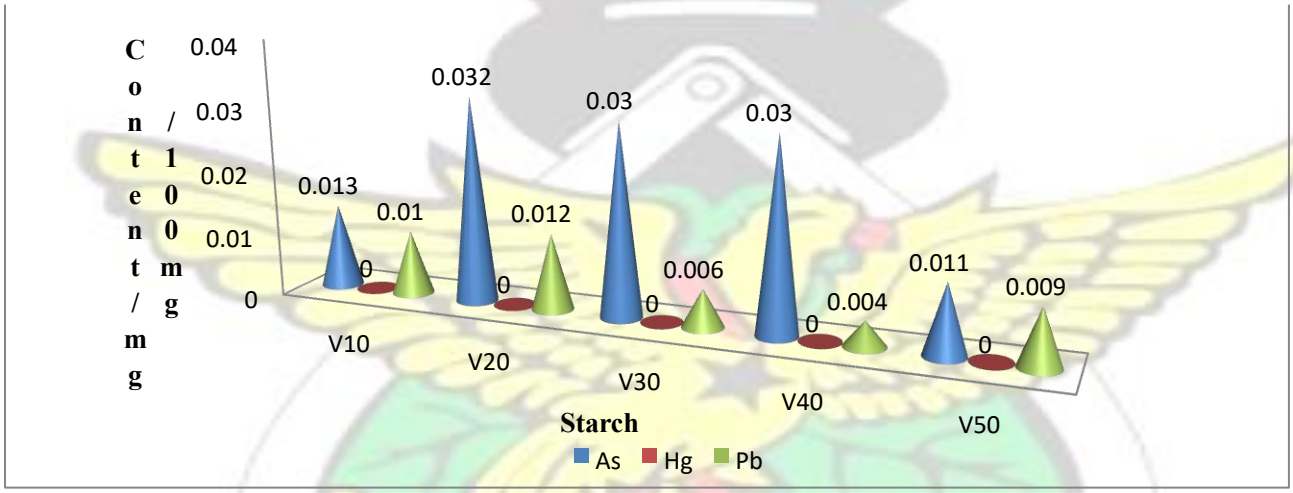

Figure 4. 4: Content of other toxic metals in the cassava starch powders. As =Arsenic, Hg= Mercury and Pb = Lead

4.6.1 Ash value of the cassava starch powders

Ash value determination is a key to checking and detecting any adulteration with extraneous materials that may be included during treatment and harvesting. Total ash ranged from 0.56 -

0.98 with V10 the lowest and V20 showing the highest total ash. Acid-insoluble ash ranged from 0.005 - 0.013 with V40 the lowest and V10 containing the highest acid-insoluble ash. V10 had the highest water soluble ash and V30 showed the least water soluble ash.

Table 4. 10: Ash values of the cassava starch powders, n= 3

Starch powders	Ash values of the cassava starch powders (%w/w)		
	Total ash	**Water soluble ash**	**Acid insoluble ash**
V10	0.56 ± 0.054^{a}	0.048 ± 0.022^{a}	0.013 ± 0.007^{b}
V20	0.98 ± 0.066^{a}	0.025 ± 0.121^{a}	0.009 ± 0.054^{a}
V30	0.68 ± 0.022^{a}	0.005 ± 0.326^{b}	0.004 ± 0.021^{a}
V40	0.70 ± 0.032^{a}	0.037 ± 0.009^{a}	0.005 ± 0.033^{a}
V50	0.69 ± 0.007^{a}	0.024 ± 0.023^{a}	0.003 ± 0.011^{a}

Means followed by the same superscript in a column are not significantly different ($p > 0.05$) while means followed by the different superscript in a column are significantly different ($p < 0.05$).

4.7 Investigation of possible drug-excipient interaction using FTIR spectroscopy

FTIR analysis revealed all the intense peaks in the spectrum of pure paracetamol and starch after their physical mixture. The FTIR study indicates the stable nature of paracetamol with the starches which confirms that the drug and the starches do not interact.

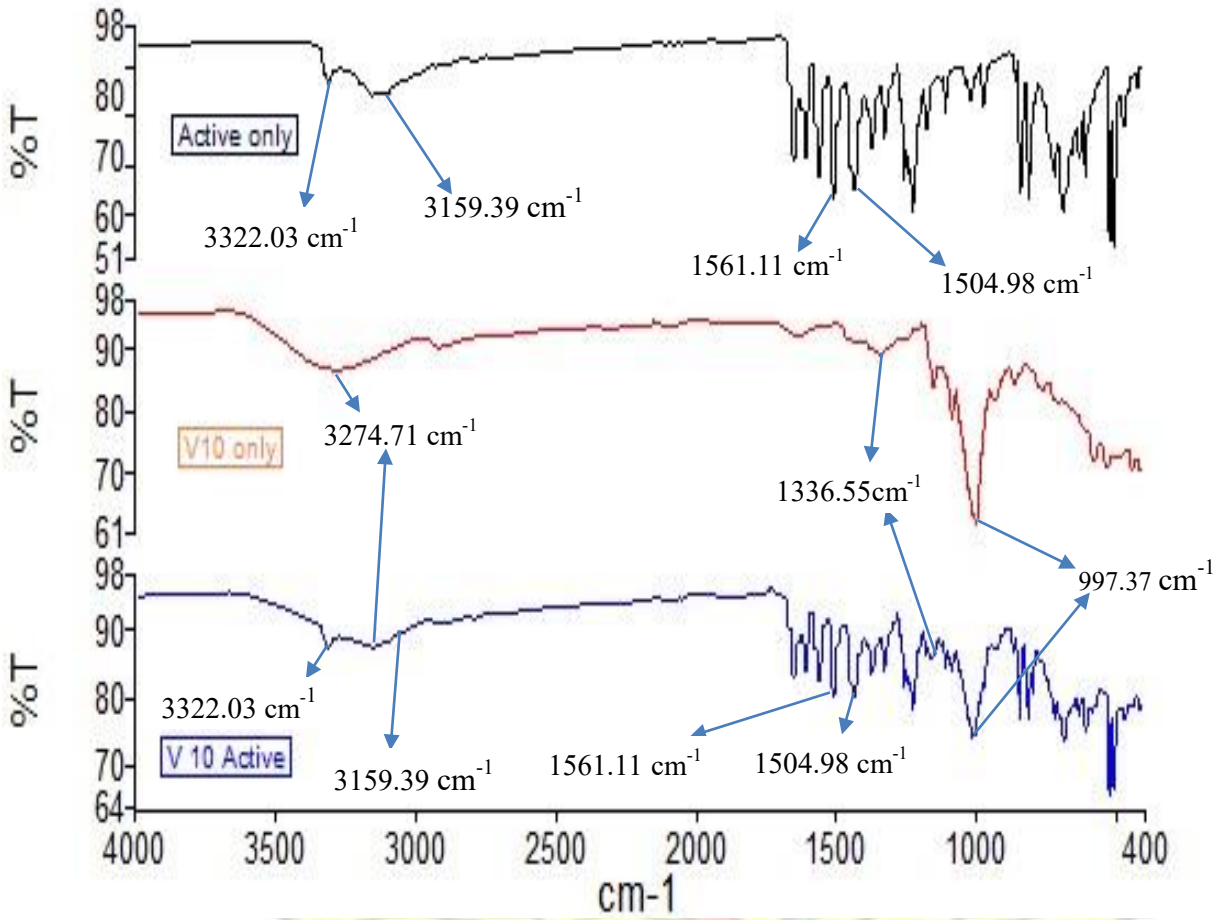

Figure 4. 5: FTIR spectra showing compatibility of V10 and paracetamol. Active only represent paracetamol powder; V10 only represents V10 and V10 active represents physical mixture of V10 and pure paracetamol powder.

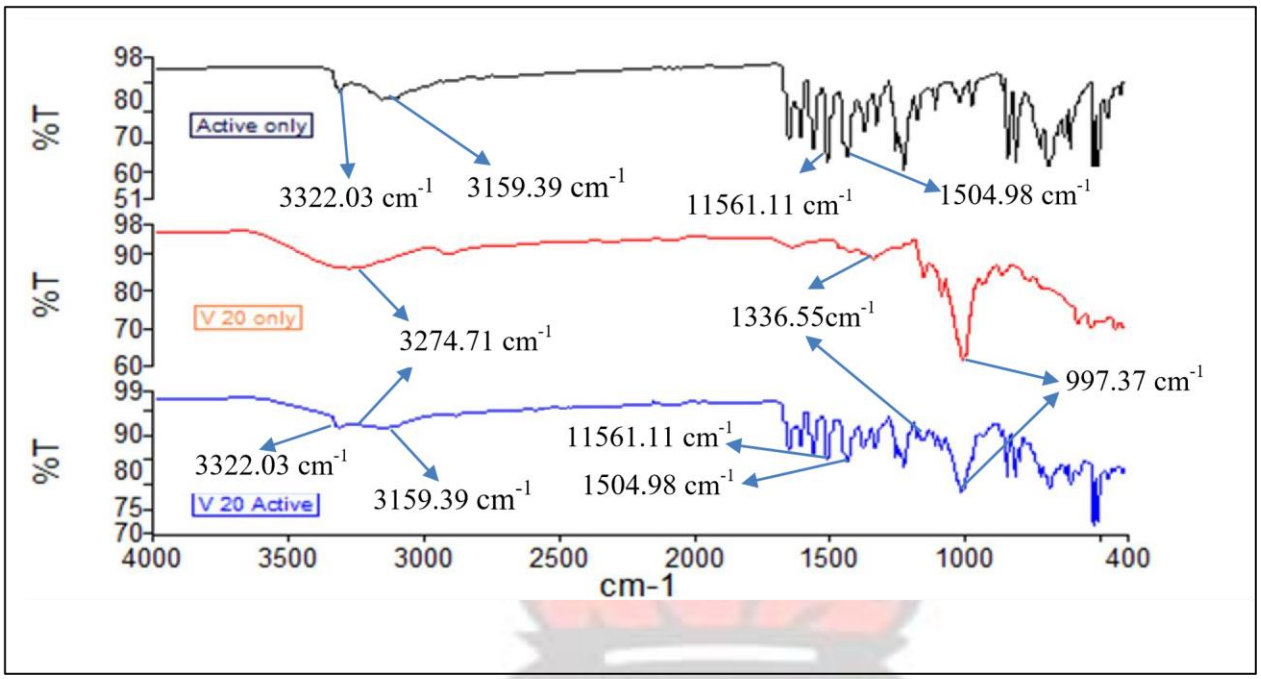

Figure 4. 6: FTIR spectra showing compatibility of V20 and paracetamol. Active only represent paracetamol powder; V20 only represents V20 and V20 active represents physical mixture of V20 and pure paracetamol powder.

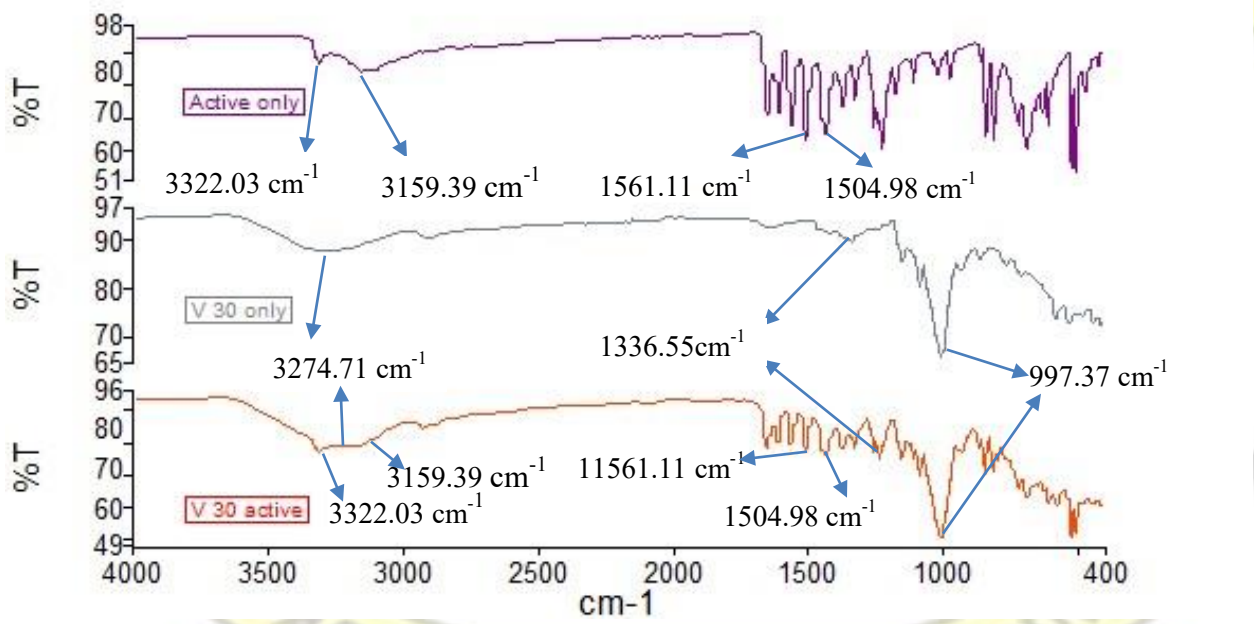

Figure 4. 7: FTIR spectra showing compatibility of V30 and paracetamol. Active only represent paracetamol powder; V30 only represents V30 and V30 active represents physical mixture of V30 and pure paracetamol powder.

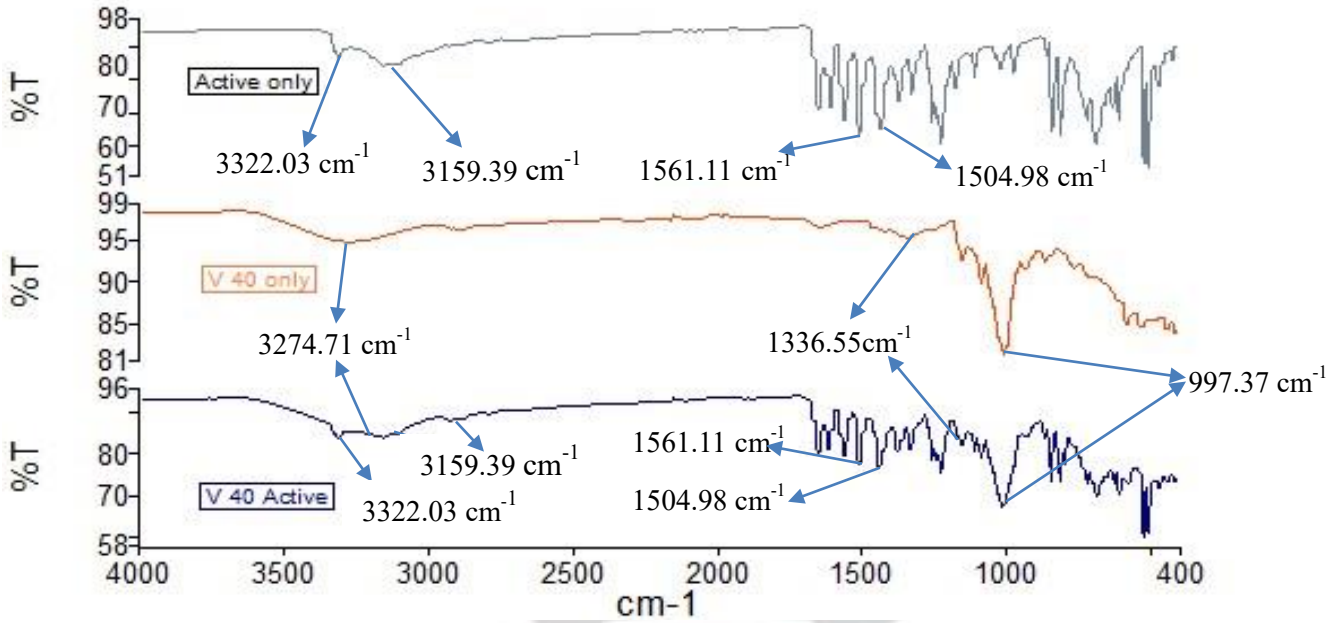

Figure 4. 8: FTIR spectra showing compatibility of V40 and paracetamol. Active only represent paracetamol powder; V40 only represents V40 and V40 active represents physical mixture of V40 and pure paracetamol powder.

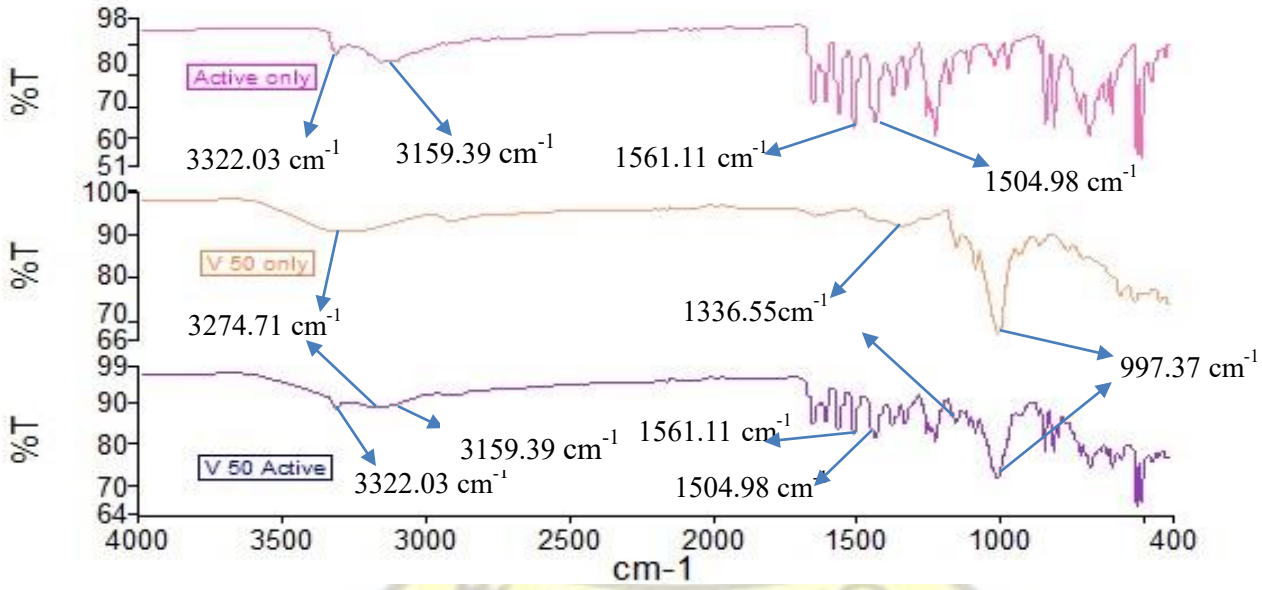

Figure 4. 9: FTIR spectra showing compatibility of V50 and paracetamol. Active only represent paracetamol powder; V50 only represents V50 and V50 active represents physical mixture of V50 and pure paracetamol powder.

4.8 Pharmaceutical evaluations of the formulated paracetamol tablets

4.8.1 Weight Uniformity

Weight uniformity is performed to determine the occurrence of overdosing or under dosing if the active drug forms a high percentage of the dosage unit and also to ensure consistent dose of different dosage units of the same batch. The weights of the formulated tablets ranged from 534 - 641mg. All the formulated tablets at different starch concentrations passed the BP (2013) uniformity of weight test except V50 at a concentration of 10 % as shown in Table 4.11.

Table 4. 11: Uniformity of weight (n= 3) of the paracetamol tablets

Starch	Starch Concentration (% w/w)	Mean weight of 20 tablets (g)	Mean weight of 1 tablet (g)	Mean minimum weight deviation (%)	Mean maximum weight deviation (%)	Inference (BP, 2013)
V10	5.0	12.27 ± 0.02	0.614 ± 0.001	-2.69 ± 0.34		Passed
	7.5	11.48 ± 0.42	0.574 ± 0.021	2.44 ± 0.84	-4.53 ± 0.74	Passed
	10.0	10.68 ± 1.20	0.534 ± 0.060	2.62 ± 1.98	-1.12 ± 1.92	"
V20	5.0	12.27 ± 2.42	0.614 ± 0.121	3.83 ± 3.63	-2.68 ± 3.61	"
	7.5	12.55 ± 1.80	0.627 ± 0.090	4.31 ± 3.53	-0.47 ± 3.6	"
	10.0	10.70 ± 0.18	0.535 ± 0.009	2.80 ± 0.36	-0.93 ± 0.38	"
V30	5.0	10.86 ± 2.44	0.543 ± 0.122	4.24 ± 5.37	-3.13 ± 5.30	"
	7.5	11.85 ± 2.24	0.593 ± 0.112	2.12 ± 4.26	-2.95 ± 4.29	"

	10.0	11.98 ± 2.06	0.599 ± 0.103	3.17 ± 3.40	-1.84 ±3.38	“
V40	5.0	12.50 ± 0.36	0.625 ± 0.018	4.00 ± 0.60	-2.40 ± 0.58	“
	7.5	11.88 ± 0.56	0.594 ± 0.028	2.36 ± 0.92	-4.38 ± 0.90	“
	10.0	11.65 ± 0.16	0.583 ± 0.008	3.86 ± 0.26	-3.00 ± 0.20	“
V50	5.0	12.62 ± 1.74	0.631 ± 0.087	3.32 ± 2.87	-1.43 ± 2.90	“
	7.5	12.00 ±2.38	0.600 ± 0.119	3.33 ± 3.93	-1.67 ± 3.81	“
	10.0	12.81 ± 0.22	0.641 ± 0.011	6.30 ± 0.45	-1.48 ± 0.35	Failed
V60	5.0	11.22 ± 1.84	0.561 ± 0.092	3.86 ± 3.04	-3.17 ± 4.11	Passed
	7.5	11.23 ± 2.02	0.562 ± 0.101	3.83 ± 3.33	-3.29 ± 3.50	Passed
	10.0	10.82 ± 1.78	0.541 ± 0.089	4.23 ± 3.56	-3.16 ± 3.42	Passed

4.8.2 Crushing strength, friability, thickness and diameter of the paracetamol tablets

The results obtained showed mean crushing strength ranging from 5.17 – 10.03 KgF with V20 at a concentration of 10 % being the lowest and V50 at a concentration of 5 % the highest. All the formulated tablets at different starch concentrations passed the friability test except V10 at a concentration of 10 % which failed the test. The mean tablet thickness ranges from 3.55 - 4.237mm with V60 at a concentration of 10 % having the least thickness while V40 at a concentration of 5 % also was showing the highest mean thickness. V30 at a concentration of 7.5 % had the least mean diameter of 3.03mm while V20 at a concentration 10 % also had the highest mean diameter.

Table 4. 12: Crushing strength (n=10), friability, thickness and diameter of the paracetamol tablets, n=3

Starch (%)	Starch thickness	Crushing diameter (w/w %)	Friability (KgF)	Tablet (mm)	Tablet Concentration strength
	5.0	6.45 ± 4.16	0.74 ± 0.01	4.072 ± 0.047	13.06 ± 0003
V10	7.5	5.71 ± 1.73	0.90 ± 0.02	3.653 ± 0.217	13.08 ± 0.052
	10.0	6.73 ± 5.29	*	3.902 ± 0.088	13.05 ± 0.017
	5.0	7.89 ± 4.16	0.88 ± 0.01	4.127 ± 0.008	13.08 ± 0.050
V20	7.5	9.93 ± 2.89	0.46 ± 0.04	4.215 ± 0.129	13.08 ± 0.016
	10.0	5.17 ± 2.89	0.43 ± 0.02	3.642 ± 0.074	13.10 ± 0.006
	5.0	7.58 ± 5.03	0.92 ± 0.01	3.758 ± 0.216	13.06 ± 0.012
V30	7.5	6.71 ± 5.13	0.89 ± 0.06	4.125 ± 0.102	13.03 ± 0.069
	10.0	6.25 ± 3.06	0.71 ± 0.05	4.085 ± 0.030	13.08 ± 0.031
	5.0	7.76 ± 5.29	0.28 ± 0.06	4.237 ± 0.071	13.09 ± 0.035
V40	7.5	9.62 ± 3.12	0.71 ± 0.01	3.853 ± 0.085	13.07 ± 0.006
	10.0	5.68 ± 5.13	0.27 ± 0.03	3.888 ± 0.027	13.08 ± 0.010
	5.0	10.03 ± 0.58	0.29 ± 0.04	4.072 ± 0.072	13.08 ± 0.010
V50	7.5	7.11 ± 3.21	0.91 ± 0.03	4.032 ± 0.152	13.05 ± 0.012

	10.0	6.40 ± 3.01	0.43 ± 0.05	4.208 ± 0.079	13.08 ± 0.010
	5.0	9.80 ± 1.73	0.45 ± 0.01	3.713 ± 0.117	13.07 ± 0.042
V60	7.5	8.06 ± 3.61	0.45 ± 0.06	3.748 ± 0.073	13.10 ± 0.046
	10.0	6.53 ±4.00	0.59 ± 0.02	3.555 ± 0.100	13.08 ± 0.021

*Represents failed tablets

4.8.3 Drug content of the paracetamol tablet formulations

The least amount of paracetamol (95.39 %) in the formulations was attained by V20 at a concentration of 5 % while V30 at a concentration of 5 % had the highest content of paracetamol with 103.42 % which complied with BP (2013) paracetamol assay test. There was no significant difference between the tablets of the same starch concentration.

Table 4. 13: Calibration of paracetamol in 0.1 M NaOH at a wavelength of 257 nm, n=4

Concentration (%w/v)	**Absorbance**
0.00025	0.172 ± 0.002
0.0005	0.334 ± 0.001
0.00075	0.511 ± 0.004
0.001	0.661 ± 0.002
0.0015	0.952 ± 0.006

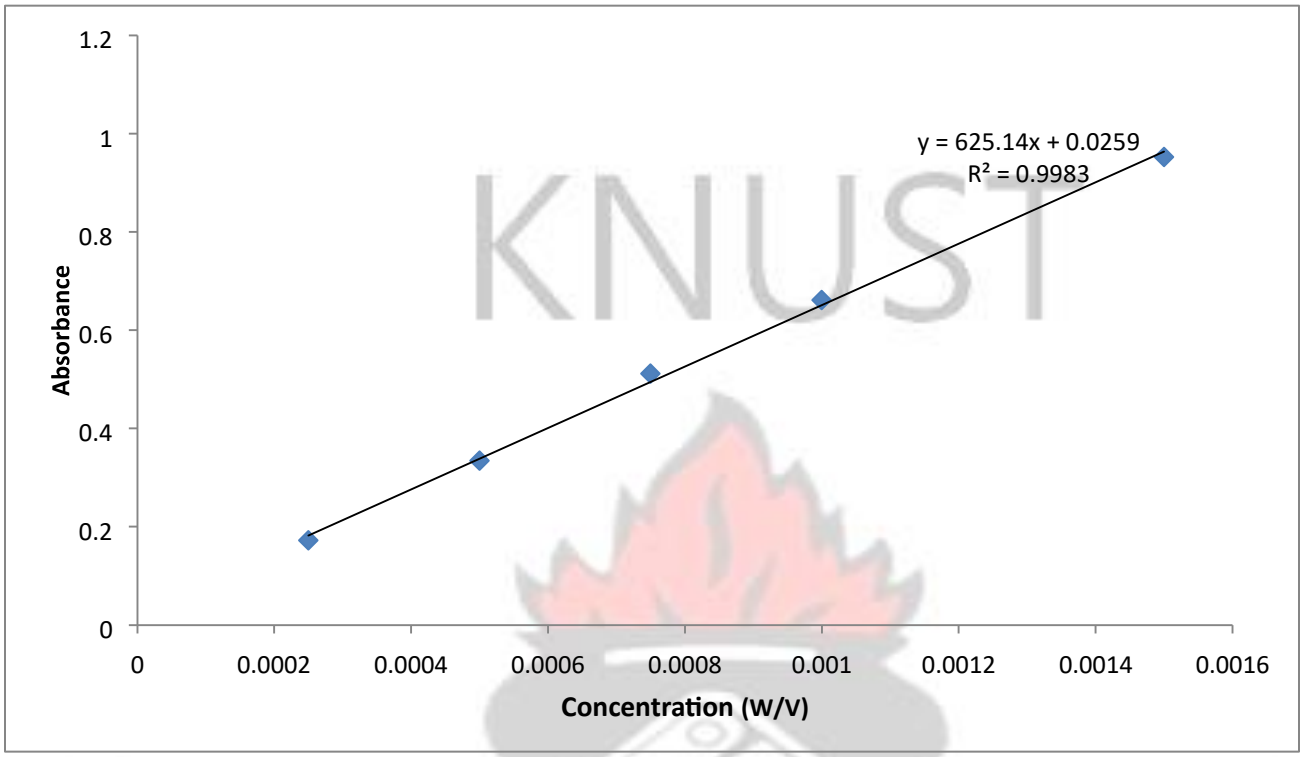

Figure 4. 10: Calibration curve of paracetamol in 0.1 M NaOH

Table 4. 14: Assay of formulations, n= 4

Starch	Assay (%) of the paracet mol tablet formulations at different starch concentrations		
	5.0 %	**7.5 %**	**10.0 %**
V10	101.72[a] ± 0.0036	100.68[a] ± 0.0027	98.67[a] ± 0.0024
V20	95.39[a] ± 0.0037	102.31[a] ± 0.0048	95.42[a] ± 0.0022
V30	103.42[a] ± 0.0039	95.53[a] ± 0.0005	96.87[a] ± 0.0012
V40	95.96[a] ± 0.0062	98.86[a] ± 0.0021	95.71[a] ± 0.0043
V50	96.35[a] ± 0.0032	95.67[a] ± 0.0038	100.86[a] ± 0.0010
V60	95.78[a] ± 0.0087	96.65[a] ± 0.0028	98.23[a] ± 0.0031

Means followed by the same superscript in a column are not significantly different ($p > 0.05$)

4.8.4 Disintegration time of the paracetamol tablet formulations

Disintegration is a crucial step at which tablets break into its smaller primary particles to release the drug(s**).**

From the results below, V10 at a concentration of 10 % had the least disintegration time of 3 minutes 20 seconds while V30 at a concentration of 5 % had the highest disintegration time (14 minutes 10 seconds). There was no significant difference between the tablets of the same starch concentration. There was no significant difference in the disintegration time between the tablets of the same starch concentration except tablets containing 10 % starch. The formulated tablets complied with BP (2013) disintegration test for immediate release tablets of not having the disintegration time exceeding 15 minutes.

Table 4. 15: Disintegration times of the paracetamol tablet formulations

starch	**Mean disintegration time (minutes) of the paracetamol tablet formulations at different starch concentrations, n= 3**		
	5.0 %	**7.5 %**	**10.0 %**
V10	$12.58^{a} \pm 0.033$	$13.10^{a} \pm 0.082$	$3.20^{a} \pm 0.010$
V20	$14.00^{a} \pm 0.062$	$12.00^{a} \pm 0.101$	$5.00^{a} \pm 0.009$
V30	$14.10^{a} \pm 0.006$	$13.06^{a} \pm 0.021$	$9.10^{b} \pm 0.019$
V40	$13.40^{a} \pm 0.012$	$10.00^{a} \pm 0.051$	$4.45^{a} \pm 0.032$
V50	$14.30^{a} \pm 0.083$	$11.36^{a} \pm 0.071$	$7.55^{a} \pm 0.108$
V60	$14.20^{a} \pm 0.029$	$13.15^{a} \pm 0.012$	$11.46^{b} \pm 0.06$

Means followed by the same superscript in a column are not significantly different ($p > 0.05$) while means followed by a different superscript in a column are significantly different ($p < 0.05$).

4.8.5 Mechanical properties of the paracetamol tablet formulations

In measuring tablet mechanical strength to eliminate all negative effects on disintegration time and weakness related to friability, crushing strength-friability ratio (CSFR) and crushing strength-friability/disintegration time (CSFR/DT) are better parameters of measuring the tablet quality. From the results below, V10 at a concentration of 7.5 % had the least CSFR of 6.349 while V50 at a concentration of 5 % had the highest CSFR of 34.589. V40 at a concentration of 10 % showed the highest CSFR/DT of 4.730 while V10 at a concentration of 7.5 % had the lowest CSFR/DT of 0.485. However, for V10 (at 10 % concentration) the CSFR and CSFR/DT were not determined due to the failure of the friability test. The tensile strength of the formulated tablets ranged from 6.902 - 12.849 Kg/cm^2 with V40 at a concentration of 10 % having the lowest and the highest attained by V60 at a concentration of 5 %.

Table 4. 16: Crushing strength-friability ratio (CSFR), Crushing strength-friability/disintegration time (CSFR/DT) and Tensile strength of the paracetamol tablets

Starch	Starch (Kg/cm^2) (w/w)	CSFR	CSFR/DT	Tensile strength concentration
V10	5.0	8.729	0.694	7.731[a]
	7.5	6.349	0.485	7.613[a]
	10.0	*	*	8.419[a]
V20	5.0	8.963	0.640	9.301[a]
	7.5	21.584	1.799	11.463[b]
	10.0	12.031	2.406	6.902[a]
V30	5.0	8.240	0.584	9.833[b]
	7.5	7.544	0.578	7.952[a]
	10.0	8.810	0.968	7.452[a]

	5.0	27.697	1.689	8.893[a]
V40	7.5	13.553	1.355	9.657[a]
	10.0	21.051	4.730	7.114[a]
	5.0	34.589	2.261	11.988[b]
V50	7.5	7.816	0.935	8.604[a]
	10.0	14.879	1.971	8.422[a]
	5.0	21.768	1.533	12.849[b]
V60	7.5	17.914	1.362	10.451
	10.0	11.069	0.966	8.940[a]

*Represents failure of the friability test.

Means followed by the same superscript in a column are not significantly different ($p > 0.05$) while means followed by a different superscript in a column are significantly different ($p < 0.05$).

4.8.6 In vitro dissolution studies for the paracetamol tablet formulations

Drug dissolution is a crucial step in drug delivery because before a drug is adsorbed, it has to be dissolved in a physiological fluid. The *in vitro* dissolution analysis was done using UV and a calibration curve was drawn for paracetamol in phosphate buffer, pH 5.8. The results obtained from the study in the Figures below showed that, at 45 minutes, the percentage of the active drug released from all the formulated tablets were above 70%. However, the differences in drug release pattern from the formulated paracetamol tablets containing different starch (cassava starch or commercial maize) were not significant ($P > 0.05$).

Table 4. 17: UV absorbance of paracetamol in phosphate buffer (pH 5.8), n= 4

Concentration (%w/v)	**Mean Absorbance**
0.00025	0.169 ± 0.0031
0.0005	0.343 ± 0.0026
0.00075	0.506 ± 0.0022
0.001	0.671 ± 0.0014
0.0015	0.949 ± 0.0025

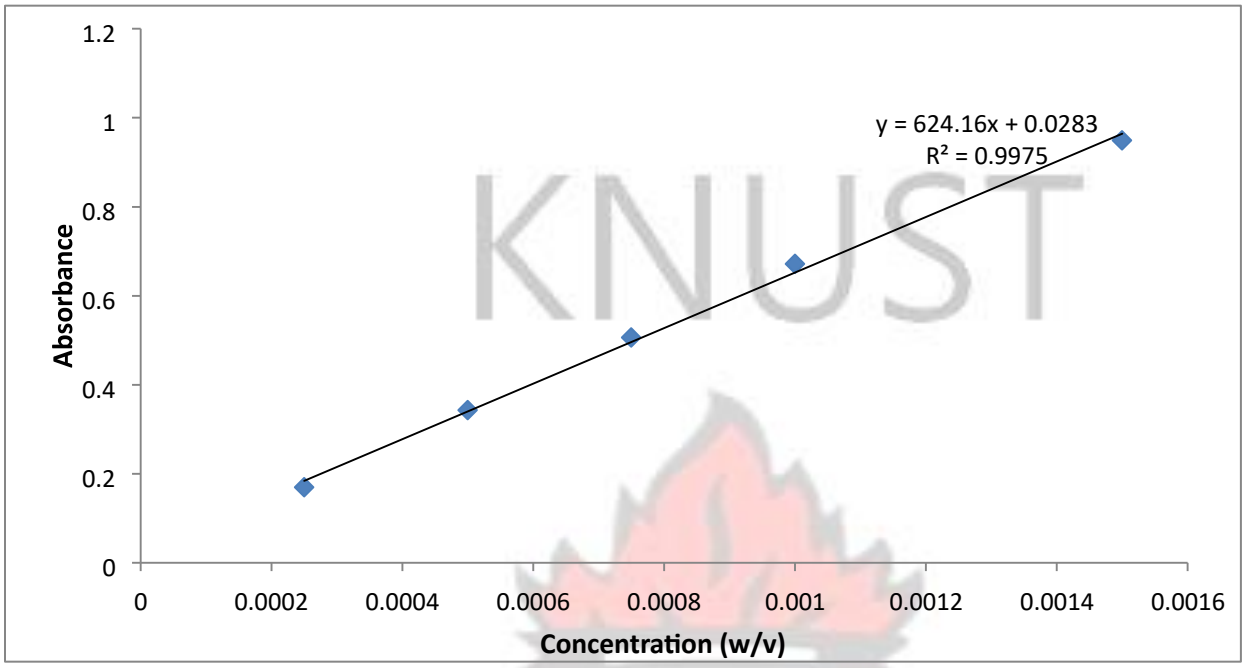

Figure 4. 11: Calibration curve of paracetamol in phosphate buffer (pH 5.8)

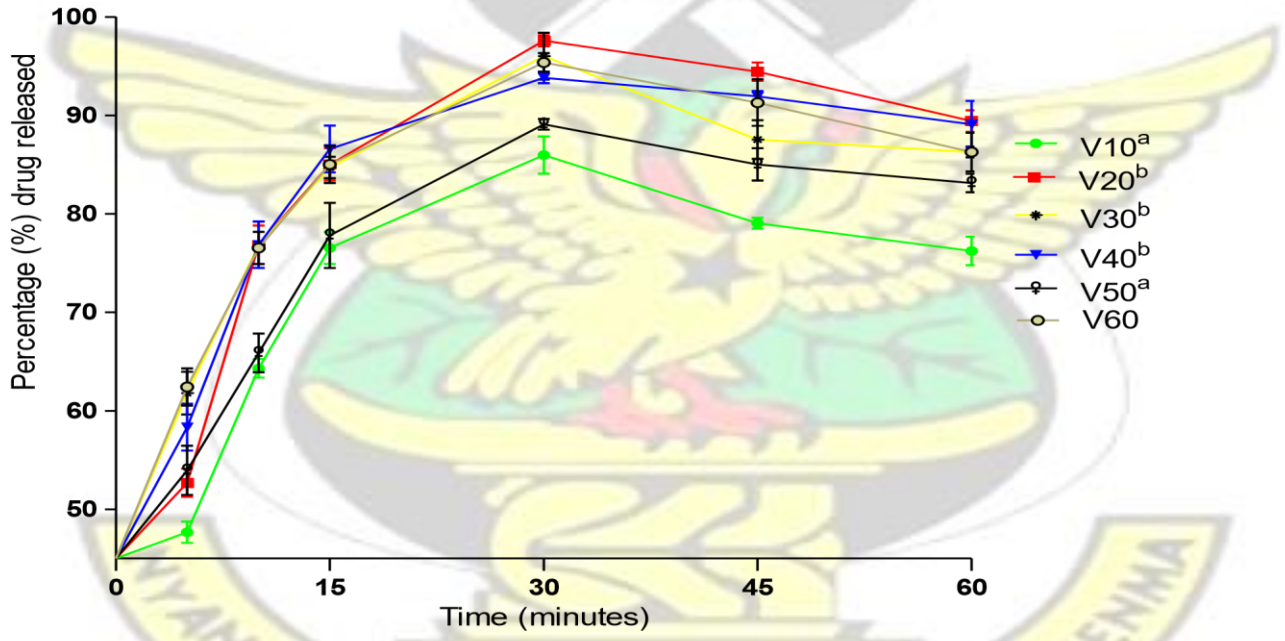

Figure 4. 12: *In vitro* drug release in tablet formulations containing 5 % starch as disintegrant in phosphate buffer pH 5.8. Drug released pattern followed by the same superscript are not significantly different ($p > 0.05$) while those followed by a different superscript are significantly different ($p < 0.05$).

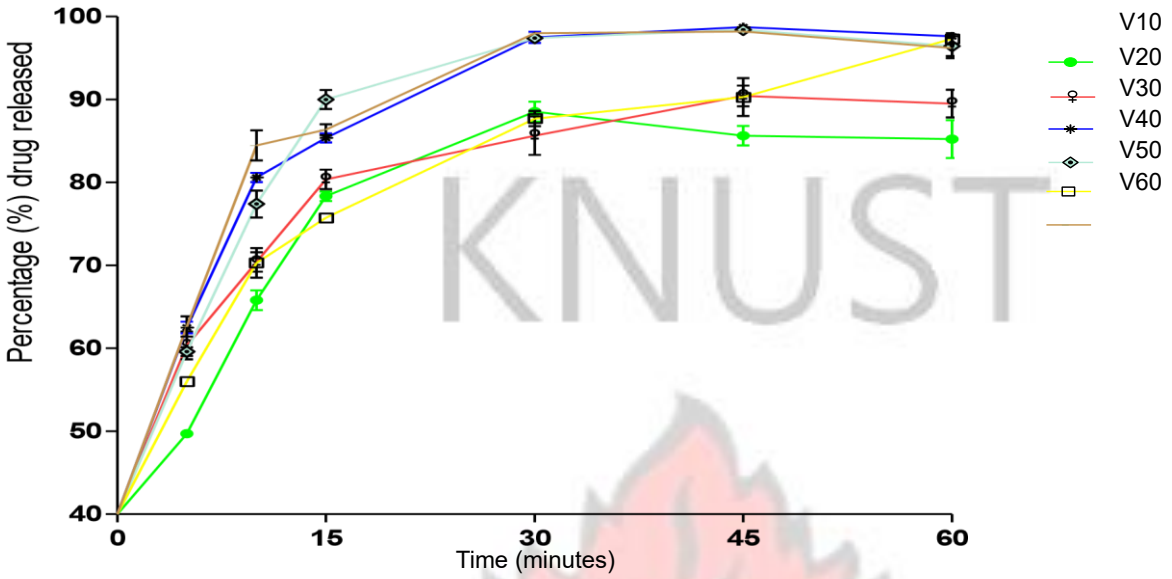

Figure 4. 13: *In vitro* drug release in tablet formulations containing 7.5 % starch as disintegrant in phosphate buffer pH 5.8. Drug released pattern followed by the same superscript are not significantly different ($p > 0.05$) while those followed by a different superscript are significantly different ($p < 0.05$).

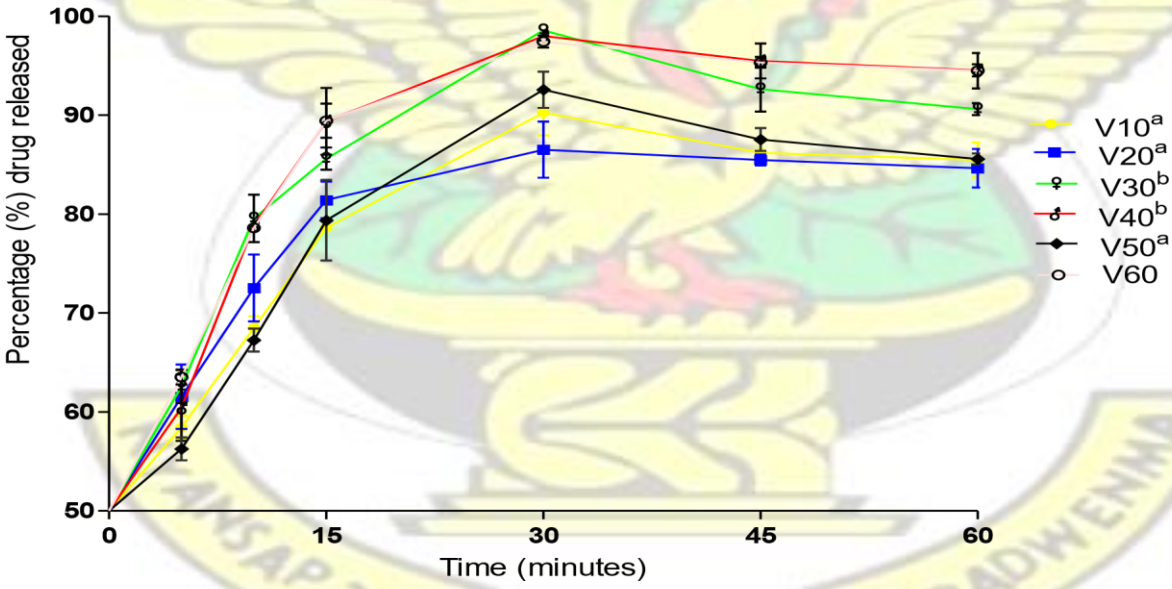

Figure 4. 14: *In vitro* drug release in tablet formulations containing 10 % starch as disintegrant in phosphate buffer pH 5.8. Drug released pattern followed by the same superscript are not significantly different ($p > 0.05$) while those followed by a different superscript are significantly different ($p < 0.05$).

Chapter 5

DISCUSSION

5.1 Cassava starch yield from fresh root tubers

The starch content of the cassava root at maturity is about 20 % to 32 % (International Starch Institute, 2014). Industries usually require cassava root tubers with starch content higher than 30 % for economic viability. All the five varieties of cassava (*Manihot esculenta*) had starch percentage yield ranging from 7.97 – 26.82 % as shown in Figure 4.1. From the results, it can be inferred that the percentage yield of the varieties, especially for V50 was less satisfactory. Cassava starch yield is known to be affected by the crop variety, the method of extraction, the season of harvest and the degree of association of granules with fibre (Rahman et al., 2003). Therefore, only variety V20 genotype confirmed higher starch yielding content (26.82 %) compared to the other cassava varieties (Figure 4.1).

5.2 Moisture content of the cassava starches

The moisture content is one of the important factors considered in pharmaceutical formulations. Information about the moisture content of a natural product is useful for determining the value of the raw materials storability, concentration or purity, nutritional value of the product, agglomeration (in the case of powders), viscosity, dry substance content, commercial grade (compliance with quality agreements), flow properties, legal conformity (statutory regulations governing food), microbiological stability and for output quality control (Crouter and Briens 2014). Starch moisture content greater than 15 % may have adverse effects on its quality which may reduce its shelf life by promoting the growth of moulds. This may also affect market value and starch quantity due to high losses on drying. In producing compacts with high tensile strength

and low friability, moisture in starch from 5% to 10 % is considered essential (Aulton and Taylor, 2013).

The moisture content of the starch powders ranks in the order V30 > V50 > V40 > V10 > V20 as shown in Table 4.1. The moisture content of V20 was significantly different from the other starches ($P < 0.05$). However, starches from V10, V30, V40 and V50 showed no significant difference ($P > 0.05$). This ranking could be as a result of the drying temperature and duration involved in the extraction procedure of the cassava starch before size reduction into fine powder. The starch moisture content may also be influenced by its crystallinity, humidity, particle size, hygroscopicity and the velocity of moist air (Nokhodchi, 2005). All the starches complied with the specifications of the British Pharmacopoeia (2013) which sets the standard for moisture content at not exceeding 15 %w/w.

5.3 Identification and organoleptic tests for the cassava starches

Results of identification test were shown in Table 4.2. The British Pharmacopeia (2013) identification test for starch carried out showed that V10, V20, V30, V40 and V50 were positive to iodine. The amylose component present in the starch is reported to form a characteristic dark blue colour complex with iodine (Konstantinos, 2008).

The starch powders had characteristic fine texture, odourless, bland taste and white colour (Table 4.3) which complied with BP (2013) organoleptic test for starch.

5.4 Physicochemical properties of the cassava starches

5.4.1 Bulk properties of the cassava starch

The bulk properties describe the density, consolidation and flow of a powder mass. It also gives an idea of how well the starch powders will be compressed since smaller particle sizes resist free because of the adhesion between the powders (Carr, 1999).

The particle density (1.863, 1.851. 1.848, 1.836 and 1.833g/cm^3), bulk density (0.693, 0.625, 0.612, 0.608 and 0.585833g/cm^3) and tapped density (0.818, 0.703, 0.682 and 0.643833g/cm^3) of the starches follow the same pattern of V20 > V30 > V50 > V40 > V10 as illustrated in Table 4.4. The particle densities of the cassava starch powders ranged from 1.863-1.833 g/cm^3. However, difference in bulk properties from V20 and V30 was not significant ($p > 0.05$) but were significantly different from V10, V40 and V50 ($p < 0.05$).

High density starches have been reported to possess good diluent power as they reduce volume of the powder mass substantially and also improve the consolidation and powder flow while low densities result when smaller particles are not filled in the void spaces created by larger powder particles which lead to consolidation of the powder particles (Aulton and Taylor, 2013). Muazu *et al*. 2011 also reported bulk densities (0.44, 0.71 and 0.52g/cm^3), tapped densities (0.59, 0.86 and 0.86g/cm^3) and particle densities (2.08, 1.50 and 1.48g/cm^3) for *Digitaria iburua* (native starch), pregelatinized starch (modified starch) and maize (Zea mays) starch B.P respectively. From current study it could be deduced that the investigative cassava starches had good bulking properties for pharmaceutical use.

5.4.2 Average diameter and Particle Size Distribution of the cassava starch

The results for the all cassava starches evaluated had mean particle size ranging from 162.2µm – 177.5µm. However, there was no significant difference between the mean particle sizes of the cassava starch powders as shown in Table 4.5. The starch particles were distributed between 75µm to 250 µm as illustrated in Figure 4.2.

Generally, fine powders (10–75 µm) are cohesive, poor flowing and easily adhere to surfaces which negatively affect uniformity of the dosage form, causing capping and lamination of tablets thus limiting their application in direct compressions (Aulton and Taylor, 2013). Therefore, all the starch powders had good average diameters and particle size distribution for optimum pharmaceutical formulation and production of quality tablets and capsules.

5.4.3 Solubility of cassava starch powders in various solvents

Generally, the amylopectin involved in the polysaccharide chain of starches makes them insoluble in organic and inorganic solvents. Starch granules are not soluble in cold water but swell and burst only when heated which forms a very viscous solution (Lachman *et al*., 1986).

The results for the solubility of the cassava starch powders in various solvents are shown in Table 4.6. There was a slight increase in the solubility of all the cassava starch powders in warm water compared to cold water. The starches from V20 and V30 were significantly different from the other starches ($p < 0.05$) and also V10, V40 and V50 showed no significant difference ($p > 0.05$) for solubility studies using cold water. An increase in temperature facilitates solubility because the semi-crystalline structure of the starch granules is lost and the smaller amylose molecules leach out of the granules which form a network that holds water and also increases the viscosity of the mixture (Lachman *et al*., 1986).

Practically, starches are insoluble in 96 % ethanol (BP, 2013). However, the cassava starch powders showed a slight solubility in both chloroform and 96% ethanol and also there was no significant difference between the starches ($p > 0.05$). The polarity of chloroform (polarity index, 4.1) is responsible for the slight solubility of the cassava starch powders in chloroform.

5.4.4 Swelling capacity of the cassava starch powders

The swelling power of starches is analyzed in theory to predict the swelling of tablets during disintegration test. Tester et al., (2004) reported swelling power of starch being attributed to amylopectin and also have a negative correlation with amylose. More water penetrates into starch granules because of the hydrophilicity of the carboxymethyl groups which results in swelling of the starch granule and dissolution in water (Wurzburg, 1986).

The swelling power of the cassava starches is presented in Table 4.7. The order of the swelling power was V30 > V20 > V40 > V10 > V50. Moreover, there was no significant difference between the starches ($p > 0.05$). The high swelling power of V30 will give good disintegrating properties. Hence, V30 is more hydrophilic and retains more water than the other starches under similar conditions. It can also be said that, all the cassava starch powders have good swelling and water retention capacities because they can swell up by 20 % of their initial volume (Corriher, 2006).

5.4.5 pH studies of the cassava starch powders pH is a numeric scale which is used to identify the alkalinity or acidity of an aqueous solution. It is the negative logarithm of the concentration of the hydrogen ion or hydroxonium ion. Acidic solutions have pH less than 7 and alkaline or basic solutions have pH greater than 7. pH studies on natural products is important due to changes in viscosity of some mucilages beyond a certain pH. Starches are mostly acidic with a few being neutral to basic. The pH of cassava slurry in water is neutral. The British Pharmacopoeia (2013) recommends a pH range of 4.0 - 7.0 for starch.

All the pH of the cassava starches ranged from 8.07 – 9.94 and are basic (Table 4.8). The starches showed no significant difference between the starches ($p > 0.05$). The starches can therefore be used more preferable in formulations of alkaline drugs since there will be no drug - excipient interaction (Johnson and Steer, 2006). Moreover, the effectiveness of excipients such as the parabens which act as antimicrobial preservatives would not be enhanced as they are more active in acidic conditions. Acidic natural products dissolve in an alkaline or acidic medium when dispersed in a liquid medium because of the effects on the gastro-intestinal tract absorption of the active drug since they encourage product instability.

5.5 Powder flow properties of the cassava starches

Both the compressibility index (Carr‟s index) and Hausner‟s ratio describe the compressibility of a starch powder. Angle of repose is used to characterize the flow properties of powders which is dependent on the interparticulate resistance or friction to movement between particles. Carr‟s index and Hausner‟s ratio are dependent on the technique employed. The angle of repose and other properties of the powder such as tapped density and bulk density depend on the particle shape, particle size distribution and the tendency of the particles to adhere together (Copley, 2008).

From Table 4.9, both the compressibility index and Hausner‟s ratio have a similar pattern of V20 > V50 > V30 > V40 > V10. In addition, the cassava starches had high angle of repose (35.87º – 46.57º), Hausner‟s ratio (1.09-1.18) and compressibility index (9.05 - 15.33). However, there was a significant difference between the flow properties of the starches ($p > 0.05$).

Granules exhibiting an angle of repose less than 30°, Carr‟s compressibility below 25% and Hausner‟s ratio below 1.25 is expected to have a good flow. Hausner‟s ratios which are greater than 1.2, starch powders can be said to have low interparticulate friction, thus are free flowing

powders (Aulton and Taylor, 2013). Hence, all the starches possessed better flow properties as indicated by the Carr‟s index and Hausner‟s ratio.

5.6 Toxic metal content and ash values of the cassava starch powders

Both qualitative and quantitative analyses were undertaken to determine the presence and amount of toxic metals in the cassava starch powders under study. An increase in heavy metal content of the soil may lead to an increase in plant uptake of toxic metals that may be hazardous for pharmaceutical applications.

Figure 4.3 and Figure 4.4 illustrate the toxic metals composition of the cassava starch powders. The toxic metals analyzed include lead, mercury, cadmium and arsenic and their respective percentage contents are shown. The toxicity analysis showed the presence of an insignificant amount of toxic heavy metals like arsenic, lead, cadmium but the mercury content was absent. This suggests the suitability of the cassava starches for use as excipient in the pharmaceutical industry. Igbozuruike *et al*., (2011) reported the presence of lead and cadmium in cassava with their critical concentrations of 35-180 $mgkg^{-1}$and 12-70 $mgkg^{-1}$ respectively.

Ashing is the process of mineralization for preconcentration of trace substances before chemical analysis. Ash values designate inorganic remnants present in natural products which represent the presence of inorganic salts such as calcium oxalate, carbonates, silicates, phosphates and other inorganic materials from external sources (Ashutosh, 2005). Ashing aids in checking and detecting any adulteration with extraneous materials in the soil, sand etc that may be included during treatment and harvesting. Table 4.10 shows the results for the total ash present in all the cassava starches which ranged from 0.56 - 0.98 %. However, there was no significant difference between the starches ($P > 0.05$). Adulteration may influence the total ash of starches because majority of these natural products contain calcium oxalate which varies often times. Shannon *et al*., (2009)

reported on ash contents of fresh natural products which rarely exceed 5%. The total ash values of all the cassava starches were low (< 5 %) and this is not conclusive as to whether there is no adulteration or otherwise.

When ash is treated with HCl, the ignition of the oxalate is soluble in the HCl which yields calcium oxide and carbonates. Hence, the acid-insoluble ash is a more accurate and specific way of determining any adulteration and the presence of earthly matter. Results for the acid-insoluble ash present in all the cassava starches ranged from 0.003 - 0.013 % (Table 4.10) and there was no significant difference between the starches ($p > 0.05$) with the exception of V10 ($p < 0.05$). The low values suggest that, the amounts of earthly materials or any adulteration present in the cassava starches are insignificant. This low amounts may be due to proper extraction methods, harvesting and handling of the material. Water-insoluble ash values for the starches ranged from 0.005 - 0.048 % and showed no significant difference between the starches ($p > 0.05$) except V30 ($p < 0.05$). Water-soluble (Table 4.10) ash gives an idea of components which have been extracted with water and no other reagent is required.

5.7 Investigation of possible drug-excipient interaction using FTIR spectroscopy

FTIR spectroscopy was performed to assess the compatibility of pure paracetamol with the cassava starches. Figures 4.5, 4.6, 4.7, 4.8 and 4.9 show the FTIR spectra of pure paracetamol, starch (V10, V20, V30, V40 and V50) and physical mixtures of the starch and pure paracetamol powder respectively. Analysis of pure paracetamol structure revealed functional groups in the spectrum (3322.03, 3159.39, 1561.11 and 1504.98 cm^{-1}) which are characteristic of the drug. Similar peaks were observed for all the cassava starches (V10, V20, V30, V40 and V50) and revealed intense functional groups at (3274.71, 1336.55 and 997.37 cm^{-1}) which characterized them as starches.

The results (Figures 4.5, 4.6, 4.7, 4.8 and 4.9) clearly indicate there were no shifting of peaks which indicates stability and compatibility of the starch and drug in physical mixtures of the starch and pure paracetamol powders. Therefore, the FTIR study indicates stable nature of paracetamol in the tablet formulations which confirmed that the drug and starches do not interact.

5.8 Pharmaceutical evaluations of the formulated paracetamol tablets

5.8.1 Uniformity of weight

The uniformity of weight indicates probable uniformity of content as a fundamental quality for all pharmaceutical dosage preparations to give consistency in dose of different dosage units of the same batch. Uniformity of weight test is performed to prevent the occurrence of overdosing or under dosing because if the active drug forms high a percentage of the dosage unit, any alteration in the weight undoubtedly influences a variation in the active drug (Ibezim *et al*., 2008). The amount of fill (granulation) or powder placed in the die of a tablet press, good flow properties of granules, regular movement of the lower punch and the uniform compression force determine the weight of the resulting tablet (Aulton and Taylor, 2013). In practice, slight variations in weight within a single batch are acceptable but the limits for these variations should be within specified limits defined as standards in British Pharmacopoeia (BP, 2013).

All the formulated tablets at different concentrations (5 %, 7.5 % and 10%) of V10, V20, V30, V40, V50 and V60 weighed more than 350 mg. The weights of the tablets ranged from 534 - 641 mg as shown in Table 4.11.

For tablets to pass the weight uniformity test not more than two of the individual tablet weights should deviate from the average weight by more than percentage deviation of ±5% and no tablet

should differ from the average tablet weight by more than twice that percentage (BP, 2013). All the formulated tablets at the different concentrations passed the BP (2013) uniformity of weight test except V50 at a concentration 10 % as shown in Table 4.11. Tablets that passed the test could be attributed to even feeding of the powder into the die cavity, good flow properties of granules, regular movement of the lower punch and the uniform compression force used in tablet compression (Aulton and Taylor, 2013). However, these qualities may not be associated with formulated tablets of V50 (at 10 % concentration) since the percentage deviation from the average tablet was more than 5%.

5.8.2 Tablet thickness and diameter

Tablet thickness may differ with no change in weight due to the density of granulation and compressional force.

The tablet thickness of all the formulations was similar as with average thickness ranging from 3.555 – 4.237 mm as shown in Table 4.12. From the results, formulated tablets with V10 (at 7.5 % concentration) showed the highest standard deviation value of ±0.217 while those with V20 (at 5 % concentration) also showed the least value of ±0.008 which indicates V20 (at 5 % concentration) was the most uniform in terms of thickness whereas V10 (at 7.5 % concentration) was the least. The results (Table 4.12) obtained from the study showed that, V30 at a concentration of 7.5 % had the least mean diameter of 3.03mm and V20 at a concentration 10 % also had the highest mean diameter.

These results could be attributed to the same compressional force used in tablet compression and the similarities of the bulk and tapped densities of the granules which resulted in good flow properties of the granules.

5.8.3 Tablet crushing strength and Tensile strength

Tablet crushing strength (Tablet hardness) gives an idea of how hard tablets should resist chipping, abrasion or breakage during storage, transportation and handling. Furthermore, hardness is important since it can affect disintegration and dissolution of tablets hence its determination are made during tablet production to determine the need for pressure adjustment. Too hard tablets do not disintegrate at the specified time to meet the dissolution specifications and too soft tablets are not able to withstand storage, transportation and handling during subsequent processing such as coating. Tablet hardness is dependent on the nature, the compression force and the amount of binder used. Tablet hardness with crushing force ranging
from 4-7 KgF is required or considered for a satisfactory tablet (Alfonso, 1990).

All the formulated tablets passed the hardness test as shown in Table 4.12. These results could be attributed to the incorporation of the right amount of binder as well as the right compression force used in the compression of the tablets. Tablet hardness mostly increases with the concentration of starch in all formulations with starch contributing to the bonding strength of the tablets (Uwaezuoke *et al*., 2014). However, the concentrations of both the cassava starches and the commercial maize (as disintegrants) appeared to have no direct correlation with tablet hardness as shown in Table 4.11. Hence, the starch concentration apparently had no direct influence on the bonding strength in the tablet.

The tensile strength of a tablet is an important parameter as the tablet needs to be mechanically strong enough to withstand pressure such as handling, film–coating and packaging but must be weak enough to release its contents after administration. The tensile strength of a tablet is dependent on the crushing strength, diameter and the thickness of the tablet (Sugimoto *et al*., 2001).

From Table 4.16, the tensile strength of the formulated tablets ranged from 6.902 - 12.849 Kg/cm^2 with V40 at a concentration of 10 % having the lowest and the highest attained by V60 at a concentration of 5 %. Formulated tablets of V20 (at a concentration of 7.5 %), V30, V50 and V60 at a concentration of 5 % was significantly different from the other starch concentrations of the formulated tablets. The formulated tablets had high tensile strength values which may be attributed to the incorporation of right amount of binder as well as the right compression force used in the compression of the tablets. Moreover, an increase in disintegrant (cassava starches and commercial maize starch) concentration in the formulations had no apparent effect on tensile strength (Table 4.16). This suggests that the disintegrant concentrations had no apparent effect on the mechanical strength of the tablets since they had no influence on the bonding strength in the tablets.

5.8.4 Friability and Crushing strength-friability ratio (CSFR)

Friability test is a mechanical property used to evaluate the ability of the tablet to withstand abrasion associated with handling, packaging, chipping and shipping. This property of the tablet is influenced by the amount of binder and the force of compression used. A maximum weight loss of 1% of the initial tablets weight after the friability test is considered acceptable for tablets (BP, 2013).

From Table 4.12, all the formulated tablets with the different concentrations of the starches passed the friability test with the exception of V10 (at 10 % concentration) which failed the friability test. The failure of tablets containing V10 (at 10 % concentration) could be due to the use of insufficient binder and inappropriate compaction force making these tablets friable. Tablets which passed the test could also be attributed to the amount of binder and force of compression used.

Odeku *et al*., (2005) reported about crushing strength-friability ratio (CSFR) as a better index than tablet hardness since it eliminates weakness related to friability in the quality assessment of the

mechanical strength of a tablet. Hence, mechanical strength of tablets can also be assessed by the crushing strength-friability ratio. Generally, stronger tablets have higher CSFR (Uwaezuoke, 2014). From Table 4.16, the order of CSFR for the formulated tablets was V50 > V40 > V60 > V20 > V10 > V30 at 5 % concentration of starch as disintegrant. At 7.5 % starch concentration, the order of CSFR was V20 > V60 > V40 > V50 > V30 > V10 and at 10 % starch concentration, the order of CSFR was V40 > V50 > V20 > V60 > V30 > V10. The formulated tablets at all starch concentrations had high CSFR which form strong tablets (Table 4.16) with the exception of V10 (at 10 % concentration) which was not determined due to failure of the friability test.

5.8.5 Assay

The active pharmaceutical ingredient in a dosage form is quantitatively determined as a routine part of pharmaceutical drug analysis. Assay determination helps to identify drugs which are substandard or fake. The assay of all the formulated tablets was carried out by ultraviolet visible spectroscopy to determine the content of paracetamol present in the tablets. A calibration curve was first drawn for paracetamol in 0.1 M NaOH as shown in Figure 4.10. The correlation coefficient obtained from the equation of the line depicts the linearity of the analytical procedure. According to the standards of the British Pharmacopoeia (2013), an immediate release paracetamol dosage unit must contain not less than 95 % and not more than 105 % of pure paracetamol.

From Table 4.14, the average content of paracetamol in the formulations ranged from 95.35 % - 103.42 % and also showed no significant difference between the tablets of the same starch concentration (P > 0.05). Hence, all the batches passed the BP (2013) assay test. The content of the paracetamol in all the formulated tablets were fairly uniform due to their low standard deviations estimated.

5.8.6 Evaluation of the cassava starches as tablet disintegrant

Pharmaceutical drug release process from tablets often includes a crucial step at which the tablet breaks into its smaller primary particles to release the drug(s**).** Complete disintegration occurs as no residue of the dosage form remains on the screen of the test apparatus, except fragments of insoluble coating or capsule shell. Tablet disintegration is dependent mostly on parameters such as the temperature of the water in the disintegration apparatus, nature and amount of binder used, the force of compression, the nature and concentration of disintegrant. The British Pharmacopoeia (2013) recommends a disintegration time of 15 minutes or less for immediate release tablets.

From the results (Table 4.15), all the formulated tablets at different starch concentrations passed the test since they all had disintegration time less than 15 minutes. The disintegration times were comparable for starches of the same concentration. The used starch concentrations showed influence on the disintegration time as the starches concentrations increase with decreasing disintegration times. There was no significant difference in the disintegration time between the tablets of the same starch concentration. However, at 10 % concentration of starch, V30 and V60 were significantly different from V10, V20 and V50 ($P < 0.05$).

This could be attributed to the use of appropriate amount of binder, adequate amount of the starch disintegrant and compression force used. Aulton (1988) also reported that starch added to dry granules before compression enhances the disintegration time because the surface surrounding the starch pushes the granules apart due to expansion and also acts as a pathway for water penetration (in the case of water repellant drugs). Hence, the tablet disintegration times could also be attributed to these observations.

5.8.7 Crushing strength-friability/disintegration time (CSFR/DT)

To evaluate all negative effects on disintegration time and weakness related to friability in measuring tablet mechanical strength, the CSFR/DT has been reported as a better parameter of measuring tablet quality compared to the crushing strength-friability ratio (CSFR) (Alebiowu and Adeagbo, 2009). Generally, a better balance between disintegration and binding properties give higher values of the CSFR/DT (Upadrashta, *et al*., 1992).

As illustrated in Table 4.16, the order of CSFR/DT for the formulated tablets was V50 > V40 > V60 > V20 > V10 > V30 at 5 % concentration of starch as disintegrant. At 7.5 % starch concentration, the order of CSFR/DT was V20 > V60 > V40 > V50 > V30 > V10 and at 10 % starch concentration, the order of CSFR was V40 > V20 > V50 > V30 > V60 > V10. From the results shown in Table 4.16, increasing the disintegrant concentration had no apparent influence on the CSFR/DT of the formulated paracetamol tablets with the exception of V20 (5 and 7.5 %) which showed increasing CSFR/DT with increasing starch concentration. Moreover, for V10 (at 10 % concentration) the CSFR/DT was not determined due to failure of the friability test.

The increased in CSFR/DT with starch concentration of V20 (5 and 7.5 %) could be due to formation of stronger bonds and reduced porosity leading to higher crushing strength and longer disintegration times. The reverse could account for why increasing the starch concentration for the other starches had no direct effect on increasing CSFR/DT.

5.8.8 Influence of the cassava starches as disintegrant on in-vitro drug release

One of the most effective ways in the treatment of diseases is the oral route of administration. Dissolution testing distinguishes the influence of pharmaceutical manufacturing parameters such as mixing effect, granulation procedure, binder effect and predicting product behaviour in vivo (Papadopoulou *et al*., 2008). Industries face difficulty in optimizing the amount of active drug

available to the body which makes studying the release rate of the active drug very vital and worth studying. The efficacy of a dosage form in the gastrointestinal fluid and the subsequent absorption for systemic circulation is dependent on the disintegration and dissolution of the dosage form.

At 45mins, the results obtained from the study (Figures 4.12, 4.13 and 4.14) revealed that the percentage of the active drug released for all the different starch concentrations of the formulated tablets were above 70%. This complies with the British Pharmacopoeia (2013) requirements for dissolution of immediate release forms where it is stated the amount of active drug in solution should not be less than 70% within 45 minutes. Therefore, it could be said that all the starches (cassava starches and commercial starch) passed this acceptance BP (2013) criterion and also showed comparative effectiveness as disintegrants (cassava starches and commercial starch) to paracetamol tablets (Figures 4.12, 4.13 and 4.14). However, the differences in drug release pattern from the formulated paracetamol tablets containing different starch (cassava starches and commercial maize) were not significant ($P > 0.05$).

The results obtained could be attributed to the wetting followed by disintegration of the tablet, binder used, compression force, granules behaviour and granulation procedure.

CONCLUSIONS

The following conclusions could be made from the experiments conducted and the deductions made in the discussion:

- The starch yield of all the five Ghanaian cassava varieties was low (<30 %). The percentage yield obtained from the extraction of V10, V20, V30, V40 and V50 was 10.4 %, 26.82 %, 9.15 %, 11.17 % and 7.97 % respectively. The residual moisture content of all the cassava starches was within limits specified by the official monographs (< 15 % w/w).
- All the cassava starches possessed better flow properties, high swelling and water retention capacities with superior bulk properties.
- The toxic metal analysis showed the absence of mercury and an insignificant amount of toxic heavy metals like arsenic, lead and cadmium. This suggests the suitability of all the cassava starches for use as pharmaceutical excipients.
- The FTIR study on the cassava starches indicates stable nature of paracetamol in the tablet formulations which confirmed that the drug and the starches do not interact.
- All the formulated paracetamol tablets containing different concentrations of starch as disintegrant complied with compendial (BP, 2013) or non-compendial tests for uniformity of

weight, crushing strength, tensile strength, diameter and thickness tests. However, for uniformity of weight test, V50 at a concentration of 10 % failed to meet the required specification. Moreover, V10 (at 10 % concentration) also failed to meet the required specification for the friability test.

- This study has revealed that, all the starches are valuable tablet disintegrants as the formulated tablets met the required specification for the disintegration of immediate release tablets. Furthermore, all the formulated tablets containing the same starch concentration showed comparable disintegration times as an increase in starch concentration decreased the disintegration time.
- The use of CSFR and CSFR/DT ratio for the assessment of the mechanical strength of the paracetamol tablets indicated that all the tablets had high values (formed strong tablets) of CSFR and CSFR/DT ratio like that of the commercial maize starch. However, CSFR and CSFR/DT for V10 (at 10 % concentration) were not determined due to failure of the friability test.
- All the formulated tablets passed the assay and dissolution tests for immediate release dosage forms with fairly uniform content of paracetamol.

RECOMMENDATIONS

- Further work on granule modification of starch from the all cassava varieties should be undertaken to further enhance its swelling and disintegrant capacity.
- The determination of binder quality and optimum binder concentration of the cassava starches should be undertaken.

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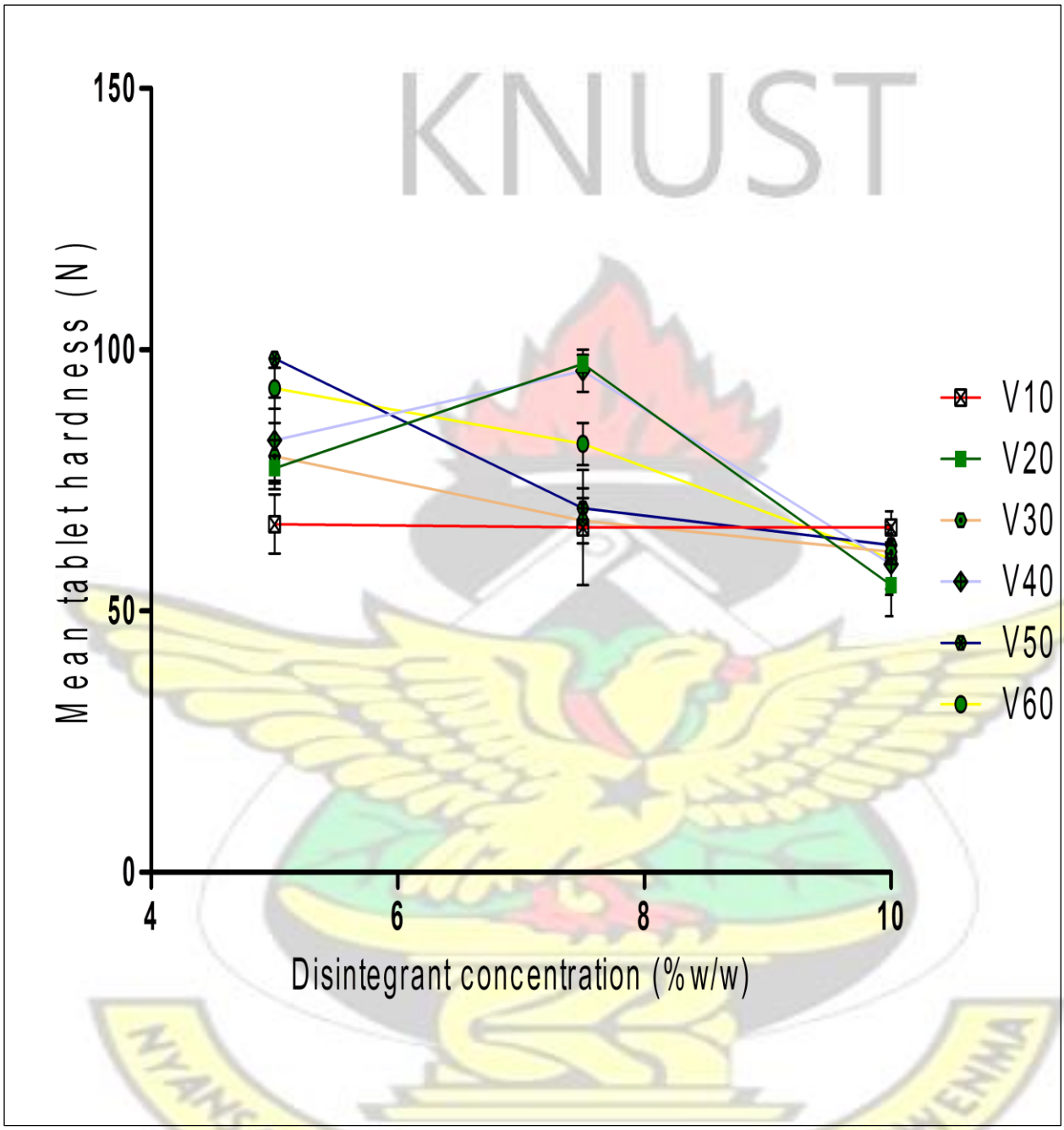
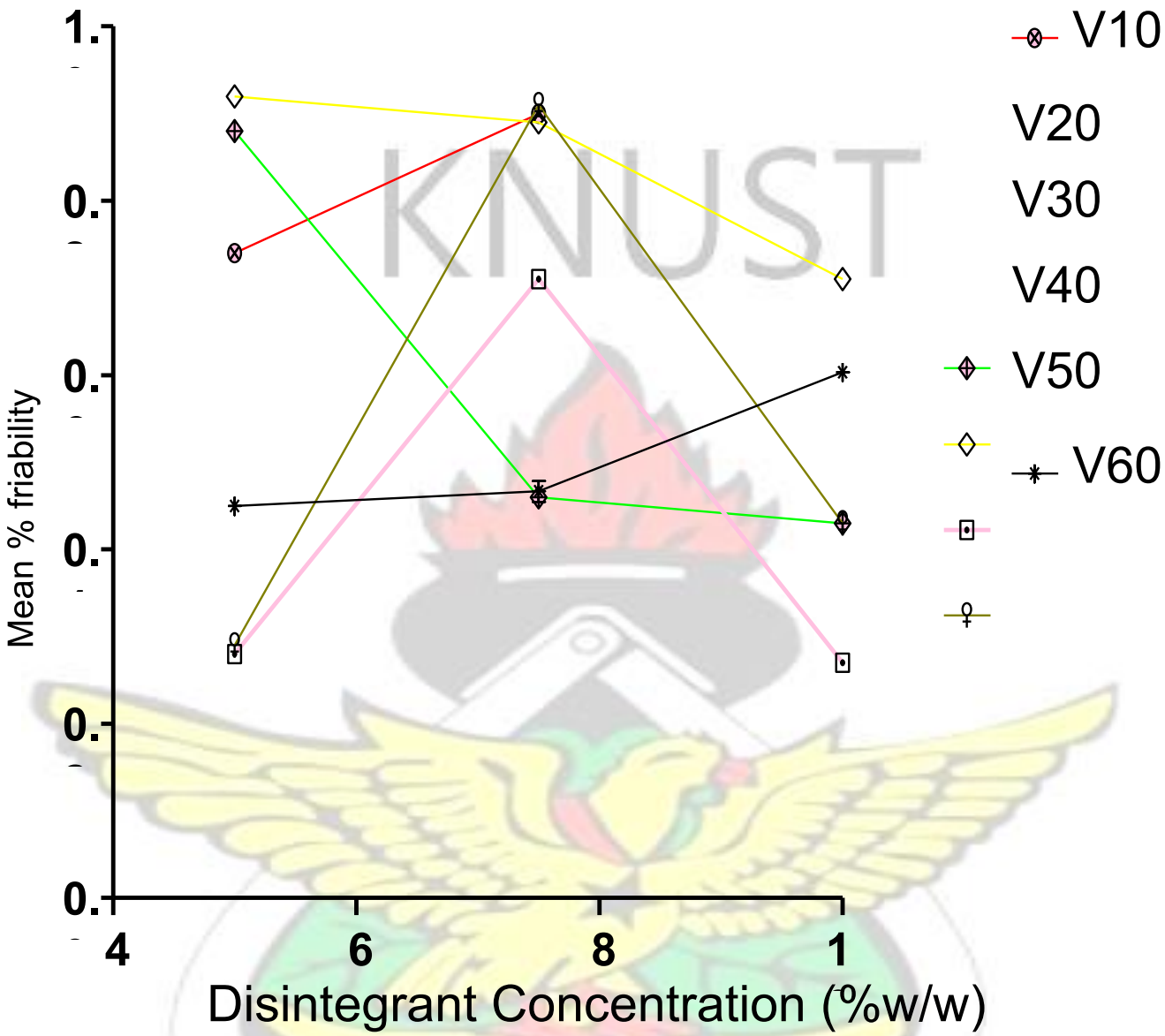
APPENDICES

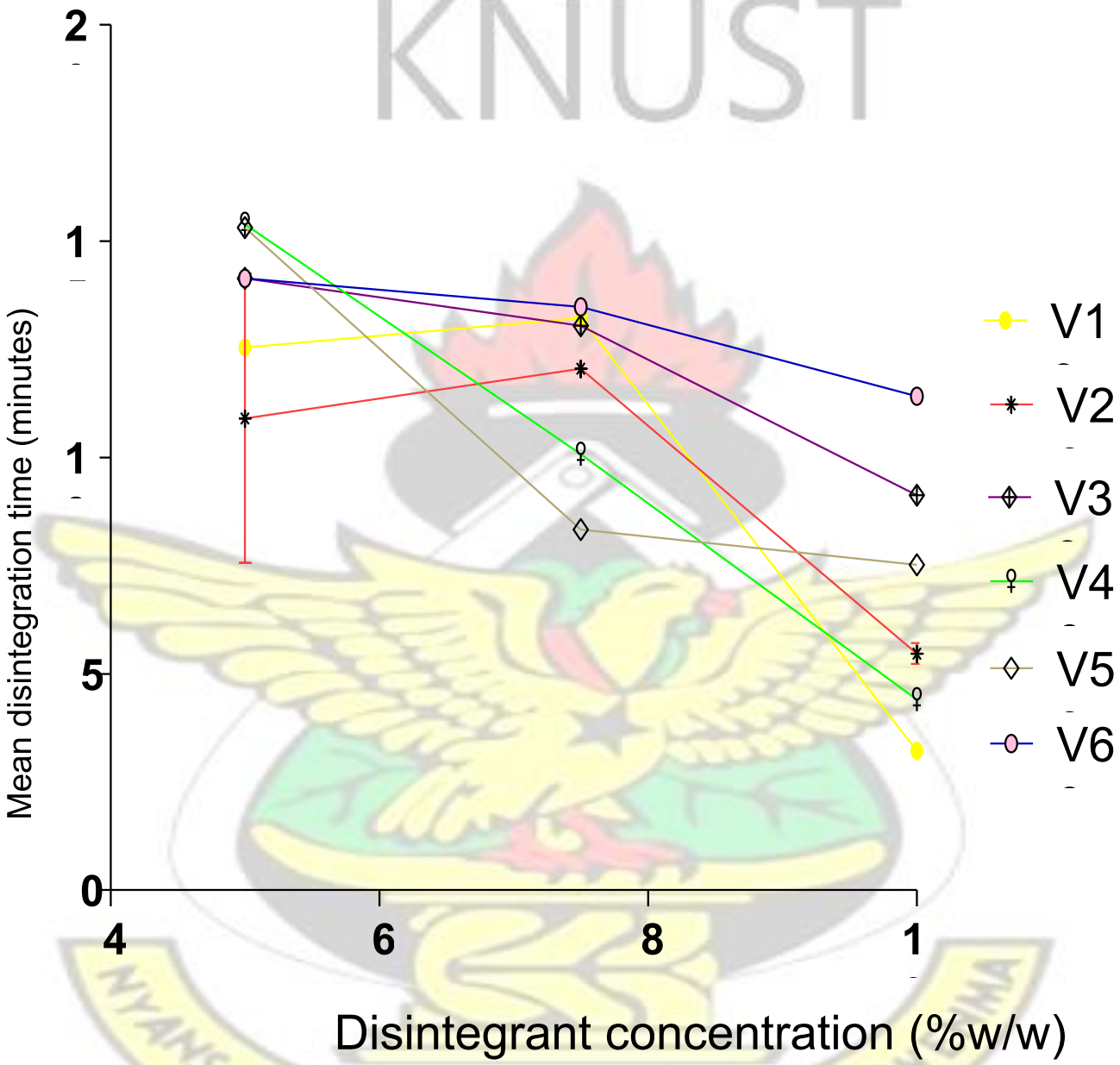
APPENDIX A: Comparison of the hardness of paracetamol tablets at different disintegrant concentrations



APPENDIX B: Comparison of the friability of paracetamol tablets at different disintegrant concentrations



APPENDIX C: Comparison of the disintegration time of the paracetamol tablets at different starch concentrations



APPENDIX D: In-vitro drug release of the paracetamol tablet formulations at different concentrations of cassava starches

	Percentage (%) drug released at various time intervals

Starch	Starch concentration (% w/w)	5 minutes	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
V10	5.0	47.5 ± 1.09	64.3 ± 0.94	76.6 ± 1.63	86.0 ± 1.89	79.1 ± 0.54	76.2 ± 1.44
	7.5	49.7 ± 2.07	65.9 ± 2.11	78.2 ± 1.71	88.9 ± 0.92	85.9 ± 0.98	85.2 ± 2.33
	10.0	58.4 ± 1.77	68.9 ± 1.01	78.7 ± 0.65	90.0 ± 1.21	86.1 ± 2.02	85.9 ± 1.97
V20	5.0	52.7 ± 1.44	76.9 ± 1.96	85.0 ± 1.63	97.6 ± 0.94	94.4 ± 0.54	89.4 ± 1.08
	7.5	60.2 ± 2.75	70.8 ± 0.42	80.4 ± 1.19	85.7 ± 0.98	90.2 ± 2.64	89.7 ± 2.10
	10.0	61.5 ± 2.32	72.5 ± 1.22	81.5 ± 0.43			
V30	5.0	61.8 ± 2.17	76.9 ± 2.37	84.7 ± 1.09	86.9 ± 0.07	85.7 ± 1.09	84.8 ± 2.32
					96.0 ± 2.37	87.5 ± 1.96	86.3 ± 0.54
	7.5	62.5 ± 0.74	80.7 ± 0.32	85.1 ± 2.11	97.2 ± 1.21	98.7 ± 0.43	97.6 ± 0.12
	10.0	62.7 ±1.73	79.8 ± 1.04	85.7 ± 1.09	98.8 ± 1.43	92.8 ± 0.96	90.7 ± 1.22
V40	5.0	58.3 ±2.37	76.9 ± 1.07	86.6 ± 2.21	93.8 ± 0.34	91.9 ± 0.54	89.1 ±2.37
	7.5	59.8 ± 1.55	77.2 ± 1.04	90.0 ± 0.09	97.4 ± 1.21	98.4 ± 1.52	96.4 ± 0.31
	10.0	60.3 ± 2.03	78.9 ± 0.87	89.5 ± 1.32	98.0 ± 0.91	95.3 ± 2.01	94.7 ± 1.12
V50	5.0	53.9 ± 2.49	65.9 ± 1.96	77.8 ± 3.31	89.1 ± 0.54	85.0 ± 1.63	83.1 ± 0.94
	7.5	56.0 ± 2.01	70.1 ± 1.32	75.7 ± 1.22	87.2 ± 0.97	93.2 ± 1.01	97.3 ± 0.09
	10.0	56.2 ± 0.85	67.2 ± 1.42	79.4 ± 1.88	92.4 ± 0.91	87.6 ± 1.23	85.6 ± 0.91
V60	5.0	62.4 ± 1.88	76.5 ± 1.64	85.0 ± 1.89	95.4 ±0.94	91.3 ± 2.37	86.3 ± 1.96
	7.5	62.9 ± 2.41	84.5 ± 1.91	86.7 ± 1.17	98.0 ± 0.09	98.2 ± 2.02	96.2 ± 0.21
	10.0	63.4 ± 1.21	78.6 ± 0.62	89.7 ± 0.23	97.4 ± 0.41	95.3 ± 1.41	94.7 ± 1.32