EVALUATION OF MODIFIED STARCHES AND MUCILAGE DISPERSIONS OBTAINED FROM *IPOMOEA BATATAS* L. LAM (CONVOLVULACEAE) AS BULK EXCIPIENTS IN CHEWABLE TABLET FORMULATIONS

BY

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A DISSERTATION SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA IN PARTIAL FULFILMENT FOR THE AWARD OF DOCTOR OF PHILOSOPHY IN PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY, FACULTY OF PHARMACEUTICAL SCIENCES,

AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA

MAY, 2014

DECLARATION

I declare that the work in the dissertation entitled '**Evaluation of Modified Starches and Mucilage Dispersions obtained from *Ipomoea batatas* L. Lam (Convolvulaceae) as Bulk Excipients in Chewable Tablet Formulations**' has been performed by me in the Department of Pharmaceutics and Pharmaceutical Microbiology, under the supervision of Dr. T.S. Allagh, Prof. H. Musa and Dr. A.B. Isah. The information derived from literature has been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at any university.

Mohammed ACHOR		May, 2014
.....	.....	.....
Name of student	Signature	Date

CERTIFICATION

This dissertation entitled "**Evaluation of Modified Starches and Mucilage Dispersions obtained from *Ipomoea batatas* L. Lam (Convolvulaceae) as Bulk Excipients in Chewable Tablet Formulations**'' by Mohammed ACHOR meets the regulations governing the award of the degree of Doctor of Philosophy of Ahmadu Bello University, Zaria, and is approved for its contribution to knowledge and literary presentation.

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This dissertation is dedicated to Almighty Allah.

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ABSTRACT

Increasing attention has been paid to incorporating hydrocolloids into starch-based products due to their unique functional properties and bio-safety. The aim of this work was to determine the suitability of modified starch and mucilage dispersions obtained from *Ipomoea batatas* as direct compression excipients in chewable tablet. Native starch (SPS) and mucilage were extracted from *Ipomoea batatas*. Subsequently, SPS was pregelatinized (PPS) and acid modified (APS) and dispersions of mucilage with SPS, PPS and APS in a ratio 1:20, 1:10, 2:10, 3:10 and 4:10 respectively were produced. The dispersions were characterized using standard methods for their particle size, flow properties, moisture sorption capacity, true density, porosity, hydration and swelling capacity. Pasting and thermal properties, syneresis, dilution capacity, lubricant sensitivity, compaction studies using the Heckel and Kawakita parameters, panel assessment of formulated chewable tablets and accelerated stability studies was also carried out. Generally, an increase in particle size, flow properties, moisture sorption capacity, true densities and a decrease in porosity, hydration and swelling capacity were observed as the mucilage concentration increased. Dispersions of SPS, PPS and APS in mucilage showed an increase in peak time, pasting temperature and enthalpy change as the mucilage concentration increased and a decrease in peak viscosity, syneresis (except SPS), peak temperature (except APS) as the mucilage concentration increases. Dispersions in mucilage generally led to an increase in disintegration time, crushing and tensile strength with a decrease in friability of formulated compacts (placebo). Optimized dispersions of mucilage in SPS, PPS and APS in a ratio 3:10 (i.e. 30-MSPS, 30-MPPS and 30-MAPS respectively) were used for further studies. The order of mean yield pressure (P_y) for native and modified starches were APS > PPS > SPS and for their dispersions, 30-MSPS > 30-MPPS > 30-MAPS while P_k was in the order SPS > PPS > APS. In other words, modification of starch increases the plastic deformation of the native starch but reduces the

plastic deformation of their dispersions in the order: 30-MAPS > 30-MPPS > 30-MSPS. The elastic recovery and brittle fracture index were in the order SPS > APS > PPS, while for their dispersions, which showed a decrease in elastic recovery and brittle fracture index as compared to their parent forms, were in the order; 30-MAPS > 30-MPPS > 30-MSPS. The order of dilution capacity index was MCC > 30-MPPS > 30-MAPS > 30-MSPS > mannitol. The overall order of lubricant sensitivity ratios at lower pressure was MCC < mannitol < 30-MPPS < 30-MAPS < 30-MSPS and at higher pressures, 30-MAPS < 30-MPPS < 30-MSPS < MCC < mannitol. All ascorbic acid chewable tablets made from starch dispersions were round and brown in colour without any tablet defects and had a characteristic sweet potato flavour. Generally, formulations F1 – F6 which contained starch dispersion alone had acceptable friability (< 1 %), crushing strength (> 3 Kgf) and disintegration time (< 15 min). Increase in concentrations of binary mixtures of mannitol and maltitol gave tablets with unacceptable properties. Tablets with acceptable friability, crushing strength and disintegration time were used to determine the degree of acceptance of the formulated ascorbic acid chewable tablets. Formulation F6 had the highest degree of acceptance while formulation F20 had the lowest. Formulations F4 – F6, which had higher degree of acceptance, were subjected to acceleration stability studies at 40 ^{0}C/75 % relative humidity for 3 months. There was a gradual decrease in disintegration time and crushing strength within the duration of study for all formulations. There was no significant difference ($p < 0.05$) within the cummulative drug release of optimized formulations. Modified starch and mucilage dispersion possessed excellent properties as excipient for ascorbic acid chewable tablet formulations using the direct compression method in view of its physicochemical and material properties as well as its positive panel assessment and stability over time.

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ACRONYMS

Acronyms	Meaning
AOAC	Association of Analytical Chemist
AUC	Area under the Curve
APS	Acid Modified Sweet Potato Starch
BC	Before Christ
BFI	Brittle Fracture Index
BP	British Pharmacopoeia
DCI	Dilution Capacity Index
ER	Elastic Recovery
FAO	Food and Agricultural Organization
FDA	Food and Drug Administration
FD&C	Food Drug and Cosmetic
FTIR	Fourier Transform Infra Red
LSR	Lubricant Sensitivity Ratio
MCC	Microcrystalline Cellulose
OSA	Octenyl Succinic Anhydride
PPS	Pregelatinized Sweet Potato Starch
RVU	Rapid Visco Unite
USA	United States of America
SEM	Scanning Electron Micrographs
SPS	Sweet Potato Starch
UHT	Ultra High Temperature
WSI	Water Solubility Index

CHAPTER ONE

1.0 INTRODUCTION

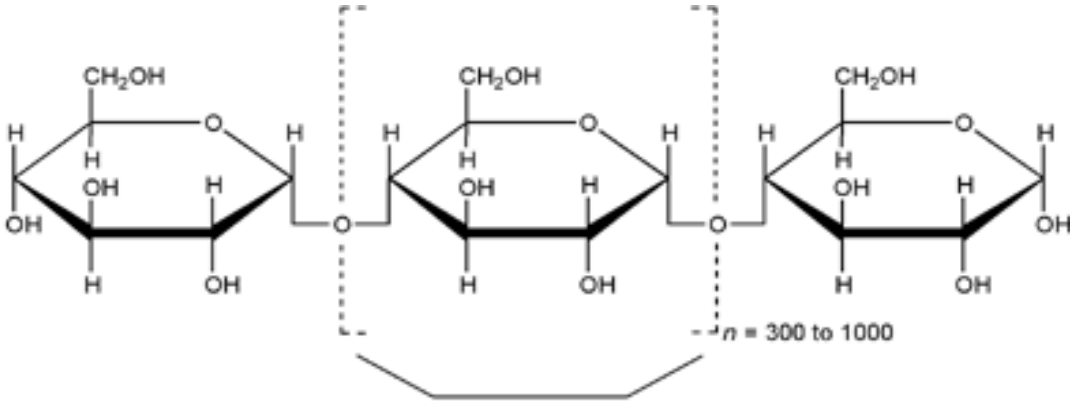
Starch is present in the form of granule, which may differ in size, shape, or the position of hilum (Pomeranz, 1985; Blanshard, 1987; Hoover, 2001). Generally, root and tuber starches have voluminous and oval-shaped granule with eccentric hilum (Pomeranz, 1985; Hoover, 2001). Granules of cereal starches may have polygonal or round shape, while legume seed starch granules have a central elongated or starred hilum (Blanshard, 1987). Usually, the size of starch granules is expressed as a range or as an average length of the longest axis. The range of granule size is 2-100 μm (Cui, 2005). In general, granules of root starches are bigger than that of cereal starches (Swinkles, 1985).

Amylose and amylopectin are the major starch fractions (Fig. 1.1). Amylose comprises of 23-31 % of starch dry weight, while amylopectin comprises of 69-73 %. In amylose, long chains of glucose units are joined together by α-1, 4 linkages. Amylose can be depicted as either a straight chain or a helix. The interior of the helix contains hydrogen atoms that allow amylose to form complex with free fatty acids, alcohols, lipids, or iodine. Amylopectin is a highly branched polysaccharide, which consists of α-D-glucopyranose residues linked mainly by several (1-4) linkages and many non-random (1-6) linkages to give a highly branched structure (Thomas and Atwell, 1977; Galliard and Bowler, 1987). Another feature of amylopectin is the presence of phosphate monoester that is covalently linked to the C3 or C6 position of the glucose monomers. The presence of phosphate monoester in high amount is usually observed from starches derived from tubers such as potato and cannas (Hizukuri *et al.,* 1970). Proteins, phosphate, lipids,

moisture, and ash are present in small amounts within the starch granules. Based on their location, these components can be classified into three groups, namely particulate material, surface components, and internal components. Particulate materials are fragments of non-starch materials. These components may interfere during starch separation process and cause impurity in the final starch or in products prepared thereafter. Surface components are materials that are associated with the surface of granules and may be removed by extraction procedure without disrupting the granule internal structure (Galliard and Bowler, 1987).

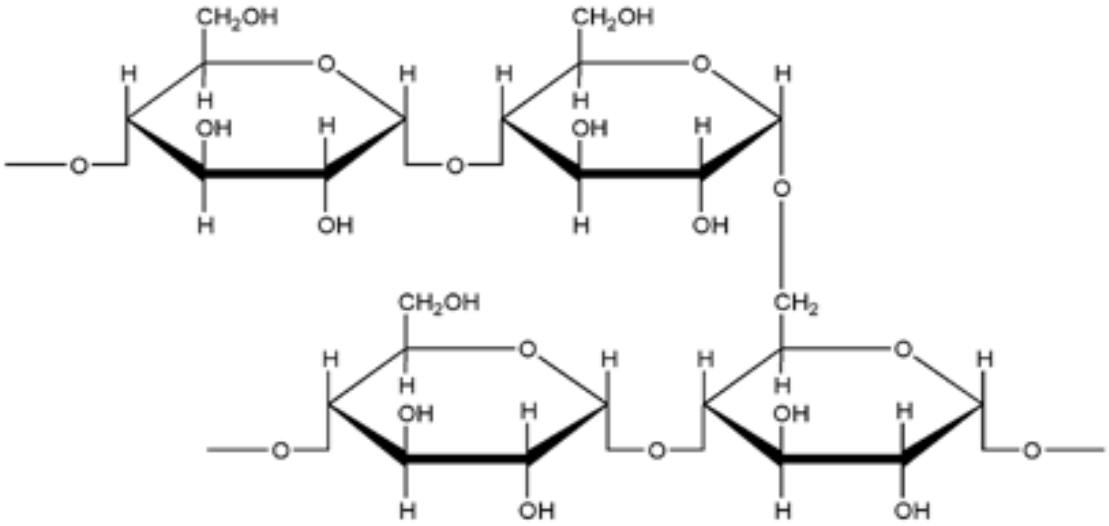
Surface starch granule proteins are loosely associated with the surface of granules and can be extracted using salt solution. The main components of surface lipids are triglycerides, free fatty acids, glycol-lipids and phospholipids. Internal components are materials that are buried within the starch granules and required more rigorous extraction. The amount of these components varies among different sources of starch. In addition, even though they are present in small amount, these components play important roles in physicochemical properties of starch. In various starches, phosphorus is present as phosphate monoesters (esterifies phosphorus), phospholipids, or inorganic phosphate (Taggart, 2004). Compared to cereal starch, root and tuber starches contain higher amount of phosphorus. In root and tuber starches phosphorus is present as phosphate monoester in which a major part is linked to C- 6 and C- 3 hydroxyl groups of the glucose units of amylopectin (Hizukuri *et al.,* 1970). Phosphate monoesters could contribute to the high viscosity, high transparency, water binding capacity, and freeze thaw stability of starches. Repulsion between phosphate groups on adjacent amylopectin chains may increase the hydration by weakening the extent of bonding between the crystalline domains (Galliard and Bowler, 1987). In addition, phosphate monoester on long β-chains of amylopectin

may decrease the gelatinization temperature by decreasing the interaction between double helices (Jane *et al.,* 1997).



Amylose

Glucose unit



Segment of amylopectin molecule

Fig. 1.1; Structures of Amylose and Amylopectin (Adapted from Cui, 2005)

In contrary, cereal starches contain only small amount of phosphorus, which is present as phospholipids. These phospholipids tend to form complex with amylose and long branched chain of amylopectin which result in limited swelling (Taggart, 2004). Compared to tuber and legume starches, cereal starches contain higher levels of lipids associated with amylose. The effects of surface lipids on starch properties have been explained by Swinkels (1985). According to this author, surface lipids affect the diffusion of water into starch granules. As a consequence, it may alter starch properties by reducing water binding capacity, swelling and solubilization of starches. In addition, surface lipids may also create undesirable flavours by oxidation of unsaturated lipids. This layer may also prevent amylose from contributing to the thickening power of gelatinized starch by forming complex with amylose in starch paste.

Protein content within starches varies depending on the botanical sources. In general, cereal starches have higher protein content than tuber and root starches. The presence of protein can cause unwanted color in starch and starch hydrolysis products via reaction between amino acid groups and reducing sugars (Mialard reaction). Moreover, proteins may also affect surface charge and the rate of hydration (Cui, 2005). Besides main components that have been discussed above, tubers and roots also contain viscous polysaccharide polymers called mucilage. This substance is mainly composed of water-soluble glycoproteins containing a number of different sugars such as L-arabinose, D-galactose, L-rhamnose, and D-xylose. Due to the presence of high

amount of hydroxyl groups, mucilage have a great water binding capacity. Consequently, the mucilage could affect gelatinization which is due to the interaction between mucilage and its respective starch. This interaction could also lower viscosity and reduce pasting. This effect is dependent upon the type of starch and mucilage concentration (Jiang and Ramsden, 1999).

1.1 Functional Properties of Starches

Gelatinization, pasting, retrogradation, and syneresis are the most important functional properties of starch. The study of these properties might help our understanding of the relationship between the structural and functional properties of starch. In addition, it might also help to determine further application of starch and its relative flours.

1.1.1 Gelatinization

Gelatinization is the process of disruption of semi-crystalline structure of starch, when a starch suspension is subjected to heating in the presence of large amount of water. During this process, heat disrupts hydrogen bonds between polymer chains weakening the granules. Then, the amorphous region, which contains less hydrogen bond and is more susceptible to dissolution, starts to imbibe water and increase in size (swelling). Amylose begins to solubilise and leaches out from the granule into the aqueous solution causing the increase of viscosity (Thomas and Atwell, 1977). The range of temperature when a starch begins to undergo this change is called gelatinization temperature range. The mechanism of gelatinization has been studied using several analytical techniques. Microscopic examination of granules that undergo gelatinization could

reveal the integrity and size of swollen granule as well as the degree and duration of swelling (Cooke and Gidley, 1992). The X-ray diffraction technique could be used to study the changes in crystallinity and to characterize the change in crystal structure during gelatinization (Nara *et al.,* 1978). The FTIR technique could detect the absorption of different bond vibrations in starch molecules during gelatinization (Goodfellow and Wilson, 1990). The loss of structural order within granules during gelatinization could be studied using NMR technique (Cooke and Gidley, 1992). In addition, calorimetric technique, for example differential scanning calorimetry (DSC) can be used to detect the changes in heat flow associated with both first-order and second-order transitions of starch polymers. As a result, enthalpy for the phase transition and melting temperature of starch crystallites can be determined. This technique has been widely used to investigate gelatinization properties of root, legume, and cereal starches (Donovan, 1979). Gelatinization characteristics are influenced by some factors, such as temperature, moisture content of starch-water mixture, starch crystallinity, the botanical source of starch, and the environmental conditions such as pressure, mechanical damage, physical modification (e.g. annealing and heat-moisture treatment), and chemical modification (e.g. substitution). In addition, gelatinization temperature may increase with the presence of solutes such as sugar or salt, which may hamper the ingress of solvents into the granule (Tester *et al*., 1999).

1.1.2 Pasting

Pasting is the state that follows gelatinization of starch. During this process, if heating continues, more granules become swollen accompanied by the increase in leaching of amylose and amylopectin from granule as well as the increase in viscosity. When most of granules have

undergone this process, the starch is considered to be pasting and peak viscosity is reached (Thomas and Atwell, 1977). Thus, a starch paste is defined as a two phase system composed of a disperse phase swollen granules and a continuous phase of leached amylose. During cooling, aggregation of amylose phase with linear segments of amylopectin will result in a strong gel (Ring, 1985). The ability of starch to form paste is useful for starch as ingredient to improve food texture. Rheological properties of starch play important roles in food and industrial processing application. Heating and shearing treatment usually applied during processing might cause rheological changes of the paste and subsequently might affect the final product (Katayama, 2002). There are several techniques that have been applied to study the rheological behavior of starch paste during heating process. Dynamic rheology assesses the dynamic module during temperature and frequency sweep testing of the starch suspension. The storage modulus (G') represents the energy stored in the material while the loss modulus (G") indicates the energy dissipated or lost per cycle of sinusoidal deformation. Tan delta (δ), which indicates the degree of elasticity is the ratio of G" to G' for each cycle. These parameters (G", G', and tan δ) are used to evaluate rheological properties of starch samples and its products (Eerlingen *et al*., 1995). Pasting viscosity can be recorded using Brabender Viscoamylograph, Rapid Visco Analyzer (RVA) or other viscometers which record continuously the viscosity of pastes as a function of heating, holding and cooling temperatures (Fig. 1.2). When starch granule is heated up to gelatinization temperature in excess of water, the granule swells and viscosity increases rapidly with the rise in temperature. Temperature at the onset of this rise in viscosity is called pasting temperature (PT). As temperature increases, more starch granules gelatinize. With the increasing temperature, the starch granules begin to breakdown and at peak viscosity this breakdown gets to

the maximum. With the continuous stirring and increase in temperature, the granules rupture causing an increase in the release of amylose and amylopectin. This process caused a decrease in viscosity of the paste (Zaidul *et al*., 2007; Leon *et al*., 2006).

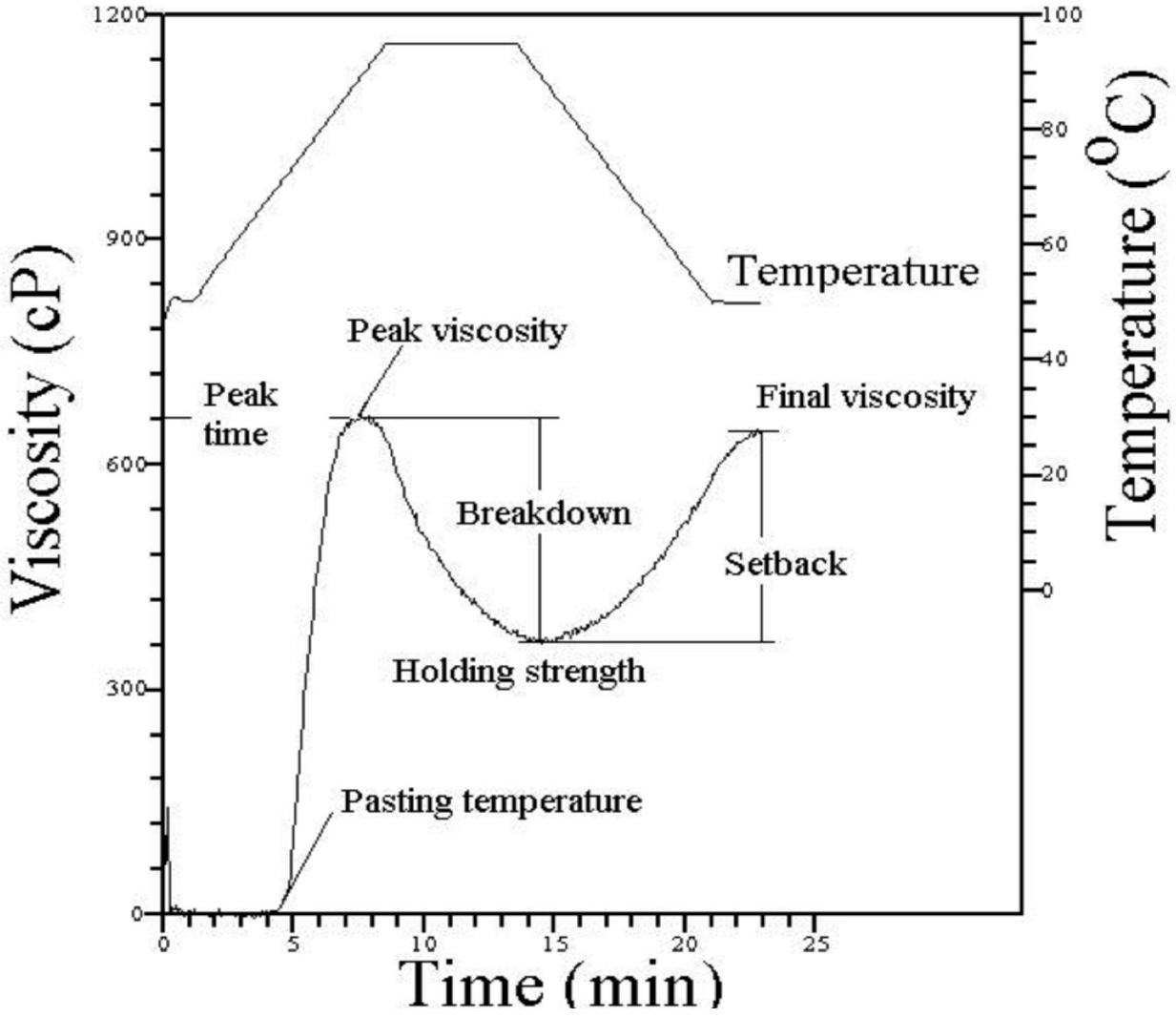


Fig. 1.2 Pasting Properties Profile (Adapted from Leon *et al*., 2006)

1.1.3 Retrogradation

When the gelatinized starch is cooled, starch molecules especially amylose with its linear structure will re-associate tightly at various degrees leading to formation of a firm gel. This phenomenon is termed retrogradation (Zaidul *et al*., 2007; Leon *et al*., 2006). Retrogradation occurs in two stages. The first stage is the formation of crystalline regions from retrograded amylose. The second stage involves the formation of an ordered structure within amylopectin. At first, the formed gel is elastic and cuttable. However, with time, this gel tends to transit into rubbery structure and release water (syneresis) (Leon *et al*., 2006; Zaidul *et al*., 2007). The ability of starch to aggregate and crystallize is important since it determines the texture of starch-based food products. Retrogradation and syneresis are undesirable traits especially in refrigerated or frozen foods (Thomas and Atwell, 1997). Moreover, retrogradation also increases stiffness of food products during storage (Taggart, 2004).

1.2. Sweet Potato *(Ipomoea batatas*)

Sweet potato *(Ipomoea batatas*) is a crop plant with large, starchy, and sweet tasting roots which belongs to the family Convolvulaceae (which is also known as morning glory). Its roots also contain a high quantity of dietary fiber and mucilage that have antioxidative properties (Jiang

and Ramsden, 1999). The plant is a herbaceous perennial vine, bearing alternate heart-shaped or palmately lobed leaves and medium-sized sympetalous flowers. The young leaves and shoots are sometimes eaten as greens. Of the approximately 50 genera and more than 1,000 species of convolvulaceae, *Ipomoea batatas* is the only crop plant of major importance. Some others are used locally, but many are actually poisonous. The sweet potato is only distantly related to potato (*Solanum tuberosum*) (Austin, 1988). Among the world's root crop, it is second only to white potato (*Solanum tuberosum*) in importance (Horton, 1998). While in Africa, it is the third most important root crop after cassava (*Manihot esculenta*) and yam (*Dioscorea spp*), (Scott *et al*, 1992). The edible tuberous root is long and tapered with a smooth skin whose colour ranges between white, purple red, brown and beige. Its flesh ranges from beige through yellow, orange, cream and purple.

Sweet potatoes are cultivated throughout tropical and warm temperate regions wherever there is sufficient water to support their growth. They grow well in many farming conditions. In 2010, the world average annual yield for sweet potato crop was 13.2 tons per hectare. The most productive farms of sweet potato breeds were in Senegal, where the nationwide average annual yield was 33.3 tons per hectare. Yields as high as 80 metric tons per hectare have been reported from farms in Israel (James, 1983). Presently, Nigeria is the number two producer of sweet potato in Africa with annual output of 2.80 million metric tons (FAO, 2011) and globally the third largest producer after China and Uganda.

The plant does not tolerate frost. It grows best at an average temperature of 24 ^{o}C (75 ^{o}F), abundant sunshine and warm nights. Annual rainfall range of 750 - 1,000 mm (30-39 inch.) is considered most suitable, with a minimum of 500 mm (20 inch.) in the growing season. They

grow well in many farming conditions and have few natural enemies; pesticides are rarely needed. Sweet potatoes are grown on a variety of soils, but well-drained, light-medium- texture soil with a pH range of 4.5 to 7.0 are more favorable for the plant (Woolfe, 1992).

1.3 Early History of Starch Utilization

Although the early history of starch use is mainly unrecorded, some interesting examples of industrial uses are known. Strips of Egyptian papyrus stuck together with a starchy adhesive that date back to 4000 BC are some of the earliest examples. In 170 BC, Cato described a process used by Romans for separating starch from grain and 300 years later, Celsus, a Greek physician, described starch as a wholesome dietary product. Starch was also used to produce an "artificial honey" with saliva for treating wounds. Around 312 AD, starch was shown to provide resistance to ink penetration in Chinese paper. Starch was introduced into Northern Europe to whiten and stiffen linen and for cosmetic use as a hair powder. Blue starch was employed by the Puritans until Queen Elizabeth banned its use in 1596.

1.4 Early Modification of Starch

In 1804 production of dextrin was first reported by roasting of starch in search for an industrial substitute for gum arabic and tragacanth. However, dextrins only came into widespread industrial use after the accidental discovery of the torrefaction method for producing dextrins, now termed British gums. In 1821, a fire occurred in a Dublin textile mill that used starch as a sizing additive. After the blaze was extinguished, one of the workmen noticed that some of the starch had been turned brown by the heat and dissolved easily in water to produce a thick, adhesive paste. When access to cane sugars in the West Indies was restricted by the Napoleonic wars, this

technology was applied to the development of alternative sweeteners (Schenk and Hebeda, 1994). Starting around 1830 and concurrent with the opening of large potato starch mills, sugar from starch came into use in wines in Germany.

Commercial use of starch in foods grew with the packaged food industry. At the end of the 1930s fluidities, or acid hydrolyzed starch, were used to allow more starch and higher gel strengths in jelly gum candies. The use of starch as a thickener was limited due to the poor textures possible in foods with prolonged distribution after processing. Blends of native starches were used to overcome the weakness of one starch used alone. The quality attainable with food starch thickeners improved dramatically in the 1940s with the introduction of cross-linked starches and waxy maize. Cross-linking is the addition of chemical bonds between starch polymers which allow the starch granule to swell but not disintegrate during processing. Cross-linking with bifunctional reagents was first patented in 1943 and commercialized in the late 1940s. Phosphorous oxychloride, which forms starch phosphate diesters, was among the first reagents and continues to be widely used (Felton and Schopmeyer, 1943). Soon after, distarch glycerol's came into use (Kerr and Cleveland, 1957).

With regard to food starch thickeners, the second major event during the 1940s was the commercialization of waxy maize starch. Waxy maize starch, which contains nearly 100 % amylopectin, has built-in textural stability due to the near absence of the more linear amylose molecule. Unlike those of dent corn starch, solution of waxy maize can be recovered by reheating; the gel melts and separated water is re-absorbed. Waxy maize was first discovered in China in 1908 by an American missionary. Crosslinked waxy maize starches, available since

1948, revolutionized the industry by providing unprecedented quality and gained popularity in canned goods.

1.5 Developments of the 1950s to Date: Development of Mono-substitution

The outstanding achievements of the 1950s were the commercialization of mono substituted or stabilized starches and high amylose starches. The observed reduced retrogradation in waxy maize relative to dent corn, suggested that mono-substitution, like increased branching, might increase starch stability. It was thought that the introduction of blocking groups might prevent the long linear segments of amylopectin branches from aligning during storage, thus reducing the deterioration at low temperatures. Acetylation, achieved with acetic anhydride, was the first form of mono-substitution applied to food starches (Wurzburg, 1960). Acetyl groups added at the level of 1-2.5 % were found to minimize loss of clarity and syneresis in cereal and tuber starches. Waxy-maize based acetylated distarch adipates came into use in the mid-1950s driven by demand for pie fillings with improved stability to winter distribution.

Ever since the strength and flexibility of high amylose films were demonstrated by Meyer in 1940, starch scientists wondered whether high amylose grain could be produced. In 1952, Vineyard and Bear (1952) reported a mutant gene which allowed increased amylose levels without marked reductions in starch content, as was characteristic of previous high amylose genes. Commercial high amylose (55 %) starch was produced from specially adapted hybrids around 1958. As expected, high amylose starches have unique properties for gelling and film forming. Subsequent breeding efforts have led to commercial hybrids with more than 70 %

amylose and experimental lines with 90 % amylose, both with corresponding enhancement of functionality.

The 1960s heralded the era of instant convenience. Convenience is not just a buzzword for consumers; manufacturers also demand convenience. For consumers, convenience means preparation of a food item with minimal time and effort. To the food processor, it means energy savings during processing, faster operation and no need for special equipment – ingredients mainly requiring blending and packaging. Instant starches play a role in both cases, especially in the area of dry mixes. Drum dried, cross-linked and stabilized starches first became commercially available around 1960. An instant or pre-gelatinized starch is produced when aqueous slurry of starch is dried on a heated drum to produce a starch that has already been cooked and that readily thickens upon addition to water. Pregelling allows manufacturers to dispense with the starch preparation altogether. The benefits of instant starches include greater processing efficiency, convenience (ease of preparation) and superior stability in the end product. One the earliest reported work on the use of locally available starches as pharmaceutical raw materials was by Mital and Ocran (1968). They evaluated the disintegrant properties of starch from yam and cassava tubers.

The 1970s witnessed three major developments: the advent of hydroxypropylated starches, still higher levels of amylose in corn and starches for encapsulation and stability of emulsions. The use of hydroxypropylation in distarch phosphates and distarch glycerol's was commercialized in the early 1970s and provided higher stability and richer texture than previously possible (Kessler and Hjermstad, 1950). Hydroxy propylation and cross-linking have been combined to provide starches that withstand very high temperatures, shear forces and

extremes of pH. They are sufficiently robust to cope with disruptions in production, enabling a consistent viscosity to be attained throughout the process. Their exceptional flexibility ensures consistent end-product quality in a wide range of different applications and under varying storage conditions, from vacuum-packed to chilled or frozen. These newer modified starches demonstrate their performance in Ultra High Temperature (UHT) processing of dairy foods, for instance where, during processing; the starches resist gelatinization to give a low viscosity to assist flow through the plant. While waxy maize-based hydroxypropylated starches perform well in most flavored systems, the tapioca-based hydroxypropylated starches are so neutral in flavor that they are the product of choice for delicately flavored foods.

Emulsion stabilizing dextrins came into use in the mid-1960s for encapsulation and corresponding modified food starch came into use in the mid-1970s for use in beverage emulsions (Caldwell and Wurzburg, 1953). In the early 50s, we saw that granular starch was reacted with substituted hydrophobic alkenyl succinic anhydrides to produce starch monoesters of substituted succinates. These modified starches offered a new functionality—interfacial properties for use in stabilizing oil-in-water emulsions. Encapsulating starches may involve the addition of lipophilic groups. Modification with octenyl succinic anhydride (OSA) enables starch to be used in flavor encapsulation stabilization. These came into use in the 1970s as octenyl succinate substituted starch, hydrolysate which is used in beverage emulsions and encapsulation. PURITY GUM® BE starch (early 1970s) and CAPSUL® starch (1970) were introduced. This modification is also used to make starch more free-flowing for dusting applications, as in DRYFLO® starch, which was patented in 1952.

Although traditional pre-gelatinized starches were easy to use, they exhibited a grainy texture, less sheen and less flexibility to processing conditions than cook-up starches. Thus, a sacrifice in quality was made for convenience. A new physical modification improved instant starch quality, allowing for the production of starches with smooth short texture, excellent sheen and clarity and increased processing and storage stability. The new cold water swelling (CWS) starch granules combine the high quality of cook-up starches with the ease of preparation of an instant system. Later versions permitted ready dispersion, making pre-blending of dry ingredients a thing of the past. In the mid-1980s, a growing trend for gratifying but less fattening foods led to the development of starch-based fat replacers. Tapioca dextrin's and maltodextrin provide creaminess to reduced fat foods with little or no gelling. Other starch improvements in the 1980s centered on emulsion stabilization and flavor encapsulation.

1.6 Acid Modified Starch

Acid modified starch is a starch material in the form of superficially unchanged granule obtained by the action of acid on starch in water suspension at sub-gelatinization temperature and characterized by the following differences from its parent starch; less hot paste viscosity, higher alkaline number and higher ratio of cold to hot paste viscosity (Schildneck and Smith, 1965). Acid modified starch differs characteristically from its parent starch as to behavior in hot water. The modified granules fragment more and appear to swell less during gelatinization. The gelatinized granules yield a lower volume proportion of discontinuous gel phase in the paste, a structural feature primarily responsible for reduced viscosity. The smaller sediment volume and the reduced swelling of the granules in hot water are due to depolymerization of starch chain by the acid. The alkaline number of the acid modified starch, which rises progressively with

increasing degree of acid treatment, is a measure of chain length rather than a quantitative determination of aldehyde content (Gallay, 1936).

Hydrolysis of starch by mineral acid ultimately produces D-glucose in nearly quantitative yields. The course of hydrolysis may be conveniently followed by iodine reaction which changes successively from blue-black to purple to red to no reaction. The relative extent of hydrolysis depends on such things as starch consistency, acidity of the medium, hydrolysis temperature and duration of hydrolysis. From measurement of osmotic pressure of the triacetates of amylose and amylopectin fractions prepared from a viscosity graded series of acid modified corn starch, Kerr (1952) concluded that acid preferentially cleaves amylopectin chains in the early stages of acid modification, up to about twenty fluidity.

In industry, acid modified starches are generally designated or classified according to fluidity number, an inverse measure of viscosity. Mayer and Bernfield (1940) advanced the theory that the point of early attack lies in the amorphous inter micellar regions of the granules through which the gigantic branched amylopectin passes as it extends from one crystalline micellar region. Reduction in paste viscosity of the acid modified starch was attributed to disintegration of these amorphous regions and consequent weakening of the granule structure, permitting granule fragmentation with little swelling.

1.7 Pregelatinized Starch

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules. Partially pregelatinized starch is used in oral capsules

and tablet formulations as a binder, diluent (Mattson and Nystrom, 2001) and disintegrant (Rudnic *et al*., 1982). In comparison to starch, partially pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry compression or direct compression processes (Shiromani and Clair, 2000). In such processes, pregelatinized starch is self lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to the formulation. Full pregelatinization produces a cold-water soluble starch that can be used to make soft capsules, shells, and coatings as well as binders in wet granulation.

Typically, pregelatinized starch contains 5 % of free amylose, 15 % of free amylopectin and 80 % of unmodified starch. Normally the fully pregelatinized starch contains 20 – 30 % amylose and the rest amylopectin, which is about the same ratio (1: 3) as for the partially pregelatinized form. Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e. no 'maltese crosses' characteristics of the starch birefringence pattern. Partially pregelatinized forms shows retention of birefringence patterns typical of unmodified starch granules. Pregelatinized starch can be deformed plastically under high compression pressures to produce tablets with adequate hardness. However, at lower compression pressures, pregelatinized starch appears less compressible and compactable, which lead to tablets with low hardness (Bolhuis and Chowhan, 1996).

1.8 Background of Study

Starch and mucilage are most commonly used as adjuvant in pharmaceutical preparations, with wide range of applications. In recent years, plant derived polymers have evoked tremendous interest due to their diverse pharmaceutical applications such as diluent, binder, disintegrant in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository (Zatz and Kushla, 1989); they are also used in cosmetics, textiles, paints and paper-making (Jania *et al*., 2009). These polymers such as natural gums and mucilage are biocompatible, cheap and easily available and are preferred to semi-synthetic and synthetic excipients because of their lack of toxicity, low cost, availability, soothing action and non-irritant nature (Kulkarni *et al.,* 2005). Demand for these substances is increasing and new sources are being developed. The excipient industry to date has been an extension of the food industry (Steinberg *et al*., 2001). However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipient to achieve the desired set of functionalities.

Root and tuber crops, such as yam, taro and sweet potato, are important food staples for millions people and are grown almost exclusively in the tropical and semi-tropical regions of the world. Approximately 80 g/100 g of root and tuber crops' dry matter is made up of carbohydrates, which consist mainly of starch, mucilage, and sugars (Huang *et al*., 2007). Due to their high starch content, root and tuber crops play a significant role in the manufacturing, and are also used as ingredients of fabricated foods and pharmaceuticals around the world. Increasing attention has been paid to incorporating hydrocolloids into starch-based products due to their unique functional properties, such as increasing the stabilization of low caloric salad dressing, increasing the viscosity of starch systems (Sajjan & Rao, 1987), or improving syneresis and freeze-thaw

stability (Yoshimura *et al*., 1999). Tropical roots and tubers generally contain different levels of mucilage. These mucilage exhibit unique rheological properties with considerable potential as a food thickener and stabilizer (Fedeniuk & Biliaderis, 1994) and as well as in pharmaceuticals. These mucilage were shown to be composed of both neutral sugars and uronic acids, as well as proteins (Lin & Huang, 1993). The beneficial effects of mucilage in pasting properties of tuber crops products has been recognized and applied commercially for starchy foods, such as mash taro, mash yam, taro paste or poi (Hawaiian staple food), and sweet potato paste. However, the presence of mucilage in tuber crops itself, has received little attention, particularly the effects of mucilage on the material, compaction and consolidative properties of extracted starches in relation to tablet production.

1.9 Mixtures of Hydrocolloids and Starches

The term 'hydrocolloids' refers to a range of polysaccharides and proteins that are widely used in a variety of industrial sectors to perform a number of functions including thickening and gelling aqueous solutions, stabilizing the process of freeze thawing. Polysaccharide hydrocolloids including mucilage's, gums and glucans are abundant in nature and commonly found in many higher plants. These polysaccharides constitute a structurally diverse class of biological macromolecules with a broad range of various applications in pharmacy and medicine. Although found in plant organs, their physiological function in most cases is unclear. Mucilages found in rhizomes, roots and seed endosperms may act primarily as energy reserves whereas foliar mucilages appear not to serve as storage carbohydrates. Due to the high concentration of hydroxyl groups in the polysaccharide, mucilages generally have a high water-binding capacity. blending of starches with other biopolymers is a well-known technique to modify texture or

maintain desirable texture during a long storage period (Lee *et al.,* 2002; Tester and Sommerville, 2003). When a starch/hydrocolloid mixture is used as a texture modifier, understanding of its rheological and thermal properties is important. Thus, various studies on rheological and thermal properties of mixtures between starches and hydrocolloids have been reported (Shi and BeMiller, 2002; Sudhakar *et al.,* 1995). In general, the viscosity of a mixed system is greatly higher than starch alone since most biopolymers are strongly hydrophilic and compete with starch for water (Christianson *et al.,* 1981; Sudhakar *et al.,* 1995). The extent of starch granule swelling or melting of crystalline parts during gelatinization is influenced by the presence of hydrocolloids and synergistic interactions between hydrocolloids and starch may be anticipated (Closs *et al*., 1999). Retrogradation of the starch can be altered depending on the type and concentration of individual components in the mixed systems during storage. For example, the freeze-thaw stability of sago starch containing galactomannan was improved by preventing the aggregation of amylose and amylopectin (Ahmad and Williams, 2001), while xyloglucan molecules prevent the gelatinized corn starch structure reordering after 7 days of storage by decreasing the retrogradation and syneresis of the corn starch pastes (Yoshimura *et al.,* 1999). Non-ionic solutes, such as saccharides have been found to increase the gelatinization temperature of starch depending on the sugar concentration (D'Appolonia, 1972; Lelievre, 1976; Maaurf, 2001). The addition of saccharides into starch generally increase the gelatinization temperature due to the retardation of the swelling of starch granules (Baek *et al.*, 2004; Chinachoti *et al.*, 1990; Eliasson, 1992; Gonera and Cornillon, 2002; Lee *et al.*, 1998; Ikeda *et al.*, 2001; Kohyama and Nishinari, 1991; Kruger *et al.*, 2003; Maaurf *et al.*, 2001; Spies and Hoseney, 1982) and changes in the structure of water phase. However, the effect of sugars on starch showing

different behaviors depends on types of starch and saccharide, concentration and preparation methods. There are many studies on mixed starches and hydrocolloids such as corn starch and xyloglucan (Freitas *et al.*, 2003), guar, tara and locust bean gum with wheat starch (Funami, 2005), xanthan and guar gums with yam starch (Mali, 2003), starch and acacia (Olowosulu *et al*., 2011), pregelatinized starch and carrageenan (Chaudemanche and Budtova, 2005), corn starch and konjac-glucomannan (Yoshimura *et al.,* 1996).

1.10 Chewable Tablets

Recent developments in dosage form technology are concentrating on presenting the patient with viable dosage alternatives which provide good palatability and ease of administration at the same time. This is especially valid when the preparation is to be administered to an infant or to an elderly patient. In such cases, powders for reconstitution, suspensions, syrups, elixir solutions and chewable tablets are considered to be suitable alternatives which solve the above- mentioned problems in some cases and satisfy the needs of such patients. It is worth mentioning, though, that some patients still find inconvenience in taking the liquid dosage forms, in measuring the exact dose accurately or in carrying the package along while travelling. All the mentioned reasons make chewable tablets one of the excellent alternative choices as an easy method of drug administration for these patients. In fact, the FDA has invited pharmaceutical manufacturers to develop and produce proper dosage forms especially for pediatric patients. Up until 1999, more than 60 chewable tablet medications were approved for patient use in the U.S.A. The list includes a wide range of medications such as analgesics, cold preparations vitamins, anti-

infectives, anti-convulsants and antacids. In this context, chewable tablets are known to be advantageous over liquid dosage forms in many aspects, such as higher palatability, better availability, stability, dose precisions, portability and ease of administration especially during travelling.

1.11 Applications of Starch in Pharmaceutical Formulation or Technology

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially non-toxic and non-irritant material (Weiner and Bernstein, 1989). Starch is therefore widely used as an excipient in pharmaceutical formulations. Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant. As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix, (York, 1980) and to improve powder flow, especially when using dried starches. Starch quantities of 3–10 % w/w can act as an anti adherent and lubricant in tablet and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20 % w/w (usually 5–10 %, depending on the starch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25 % w/w; (Lowenthal, 1973 and Shangraw *et al.,* 1981). A typical concentration is 15 %. When using starch, a prior granulation

step is required in most cases to avoid problems with insufficient flow and segregation. However, starch that is not pregelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations. (Bos *et al.,* 1987). Balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting (Shlieout *et al.,* 2002 and Berthomieu *et al.,* 2010)

Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin. Starch has been investigated as an excipient in novel drug delivery systems for nasal (Callens *et al.,* 2003), and other site-specific delivery systems. (Palviainen *et al.,* 2001). The retrogradation of starch can be used to modify the surface properties of drug particles (Rein and Steffens, 1997). Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion (Henrist *et al.,* 2001), and they can improve the bioavailability of poorly soluble drugs. Some specific starch varieties, especially waxy corn starch and high amylose corn starch, are valuable candidates to replace MCC in extrusion/spheronization processes, (Otero-Espinar, 2010) and may also be used for colon-targeting applications (Karrout *et al.,* 2011).

Commercial starch is generally cohesive and has poor flow characteristics. The flow properties depend strictly on the moisture content (Shimada *et al.,* 2003), and drying can result in a free-flowing material. All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity (Faroongsarng and Peck, 1994). The approximate equilibrium moisture is characteristic for each starch, at 50 % relative humidity. The use of granular starch in direct compression applications could also be improved by compounding. Lactose–starch and

mannitol–starch compounds have been introduced on the market, using starch for improving the tableting process and the faster disintegration of the tablets produced (Wagner and Dressler, 2002).

1.12 Research Problem

Native starch exhibit limited application due to low shear stress resistance and thermal decomposition, high retrogradation and syneresis. In addition to poor processing and solubility in common organic solvents, starch forms soft and highly friable tablets and deforms elastically when compressed. Physically modified starch provide fair to good binding properties and dilution potentials, poor flowability compared to other directly compressible adjutants and shows higher lubricant sensitivity. Starch and mucilage are most commonly used as adjuvant in pharmaceutical preparations, with wide range of applications. Generally, gum and mucilage when used as tablet binder forms a very strong compact (Row *et al*., 2006). Therefore to meet the demanding technological needs of today, the properties of starch are modified by a variety of modification methods. This modification is aimed at correcting one or some of the above mentioned shortcomings, which will enhance its versatility and satisfy consumers' demand.

1.13 Justification of Research Study

Research into natural gums and starches has received tremendous attention in recent years due to thier characteristics of being biodegradable, low cost, non-toxic, environmentally friendly

processing, local availability and better patient tolerance as well as public acceptance (Girish *et al*, 2009). In view of the large income generated by developing countries from exportation of pharmaceutical excipients, it is expedient that local plants that are sources of starch and mucilage should be properly evaluated for better efficacy which in turn leads to reduced cost of importing other excipients and ultimately leads to reduced cost of production and eventually generation of income. This is in line with Robbins (1988) who stated that, "in spite of the problems which have beset the gums market in recent years, the fact remains that in many cases the gums provide a valuable source of income for many poor smallholders or itinerant laborers, either in very poor countries or in the poorest regions of rather more developed countries. As such they are important commodities". Roots and tubers are good source of starch and mucilage; most times the starches are only isolated and other constituent discarded. Since there is a renewed interest in co-processed excipient especially between starch and mucilage/gums, it would be beneficial to evaluate the constituents from the same sources since it would be cost effective and relatively available. Traditional attitude that viewed excipient as "inert" material is long outmoded. It is now well accepted that they are not merely place fillers but can be true "partners" of the active ingredient in many medicinal products and have the potentials to enhance or possible adversely affect performance (Patrick and Luigi, 2007). Generally, gum or mucilage when used as tablet binder forms a very strong compact (Rowe *et al*., 2006). Therefore, dispersions of modified starch and mucilage obtained from *Ipomoea batatas* to form a new product should combine good flowability (due to particle aggregation impacted by the mucilage) and stronger compact (impacted by the mucilage and modified starches) and rapid disintegration due to the modified starch. Improved fluidity and compatibility of the new dispersion consisting modified starch and

mucilage should make it suitable for direct compression tableting process especially in chewable tablets in view of the fact that sweet potato can be used to enhance food product through colour, flavor, natural sweetness and supplemented nutrients (Maruf *et al*., 2010).

1.14 Research Aim and Objectives

The aim of this work was to determine the suitability of modified starch and mucilage dispersions obtained from *Ipomoea batatas* as a direct compression excipient in chewable tablet. The more specific objectives were to:

1. Extract and characterize starch and mucilage obtained from *Ipomoea batatas*
2. Modify and characterize starch obtained from *Ipomoea batatas*.
3. Characterize the modified starch and mucilage dispersions.
4. Determine compression and consolidation characteristics of native starch, modified starches and modified starch and mucilage dispersions obtained from *Ipomoea batatas*.
5. Prepare and evaluate ascorbic acid chewable tablets by direct compression method using optimized modified starch and mucilage dispersions.
6. Carry out accelerated stability studies for the optimized formulations

CHAPTER 2

2.0 TABLETS AND TABLETING TECHNOLOGY

The tablet is still the most frequently administered dosage form for medical applications (Jivraj *et al*., 2000). A tablet has numerous advantages over other dosage forms, among which are the convenient way of administration to patients and the stability of a drug substance in a dry dosage form (Jivraj *et al*., 2000). Furthermore, tablets are easy to handle, store, distribute and manufacture in large quantities. A tablet is not only a carrier of the active component, the drug substance, but must also comply with a whole scale of demands. One of these demands is that the strength of a tablet should be sufficiently high to withstand the different handlings in the logistic chain from producer to patient. Basically, tablets are produced by the compaction of powders. The compaction of powders preceded only by mixing of the individual materials is called "direct compaction". To make tablet production by direct compaction possible, it is

necessary that the powders to be compacted fulfill a number of criteria (Jivraj *et al*., 2000). Therefore, various excipients specifically designed for direct compaction have been introduced during the last forty years (Armstrong, 1997). For an excipient to be useful as a "filler-binder" (direct compression excipient), it should meet the following requirements;

1. The material should enhance the tablet strength.
2. It should have a good compaction pressure-tablet strength profile.
3. It should have a low lubricant sensitivity.
4. It should have a good flowability.
5. It should be compatible with all types of drug substances.
6. It should not interfere with the bioavailability of drug substances.
7. Mixtures with various drug substances should have a low tendency for segregation.
8. It should not show any physical or chemical change on ageing and should be stable to air, moisture and heat.
9. It should have a high dilution capacity, which is defined as the amount of active ingredients that the filler-binder can successfully carry in the direct compaction technique. The dilution capacity is generally expressed in terms of percentage of non-compressible material or as optimum drug to filler-binder ratio.
10. It should be relatively cost effective.

However, not a single excipient fulfils all these requirements. It is a general practice to use a combination of two (sometimes more) filler-binders in a tablet formulation in order to

obtain a compact with acceptable properties. Among the various requirements, one of the most important functions of a filler-binder is the enhancement of the tablet strength. For this reason, most of the research on direct compaction focuses on the compaction behavior and binding properties of existing and new filler-binders. Tablets produced by the pharmaceutical industry contain several ingredients. In addition to one or multiple filler-binders and drug substances, generally a disintegrant, a lubricant and other substances such as glidants are present in the tablet formulation. It should be realized that every component in a formulation may affect the compaction properties of the powder blend and may influence the tablet strength or other mechanical properties. Even low-concentrated additives in a tablet formulation can have enormous effects on the tablet strength. For example, the interactions between lubricants and filler-binders in relation to tablet strength are well described (De Boer *et al*., 1978, Zuurman *et al*., 1999).

2.1 Chewable Tablets

These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste (Lachmann *et al*., 1989).

2.1.1 Potential Advantages of Chewable Tablets

Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not expected to be swallowed intact. The purpose of chewable tablet is to provide a unit dosage form

of medication which can easily be administered to children or to the elderly who may have difficulty in swallowing a tablet intact. Chewable tablets have some specific advantages:

1. Effectiveness of the therapeutic agent is improved by the reduction in size that occurs during mastication of the tablet before swallowing.
2. Better bioavailability through bypassing disintegration (and perhaps increase dissolution)
3. Improved patient acceptance (especially paediatric) through pleasant taste.
4. Patient convenience; need no water for swallowing.
5. Possible to use as a substitute for liquid dosage forms where rapid onset of action is needed.
6. Absorption of drug is faster.
7. Product distinctiveness through marketing prospective.
8. The large size of the dosage form is difficult to swallow. In such case chewable tablet offers advantage over it.

There are, of course, limitations to the use of chewable tablets. Bad tasting drugs and those having extremely high dosage levels present the formulator with significant obstacles to be overcome.

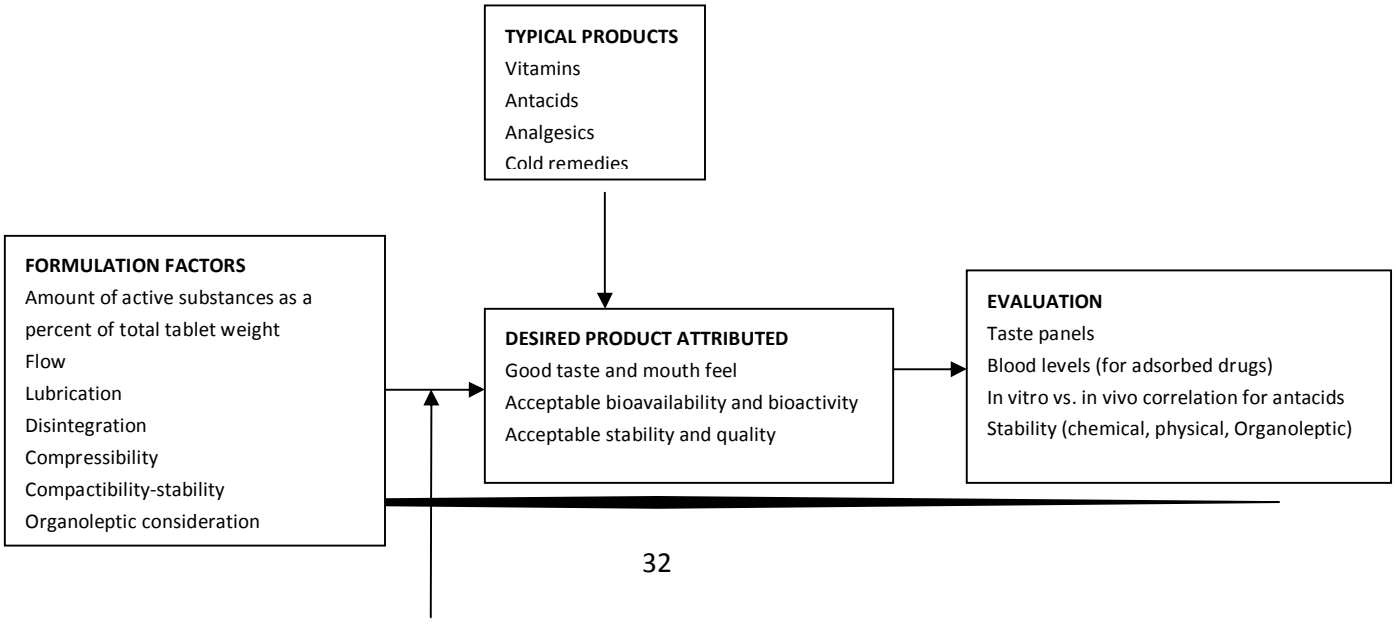
2.2 Formulation Factors

Various factors involved in the formulation of a chewable tablet can be schematically represented in Figure 2.1. The first four formulation factors shown in the schematic diagram are common to regular (swallowed) and chewable tablets; however, the organoleptic properties of the active drug substance (or substances) are of primary concern here. A formulator may use one

or more approaches to arrive at a combination of formula and process that result in a product with good organoleptic properties. Such a substance must have acceptable flow, compressibility, and stability characteristics.

2.2.1 Taste and Flavor

Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There are four basic types of tastes; salty, sour, sweet, and bitter. Salty or sour tastes are derived from substances capable of ionizing in solution. Many organic medicinal compounds stimulate a bitter response even though they may not be capable of ionizing in an aqueous medium. Most saccharides, disaccharides, some aldehydes, and a few alcohols give a sweet taste. Substances incapable of producing a sensory stimulation of the buds are referred to as bland or tasteless. The term flavor generally refers to a specific combined sensation of taste and smell (olfaction). For example, sugar has a sweet taste but no flavor, whereas honey has a sweet taste and a characteristic smell-the combination of the two being known as honey flavor.



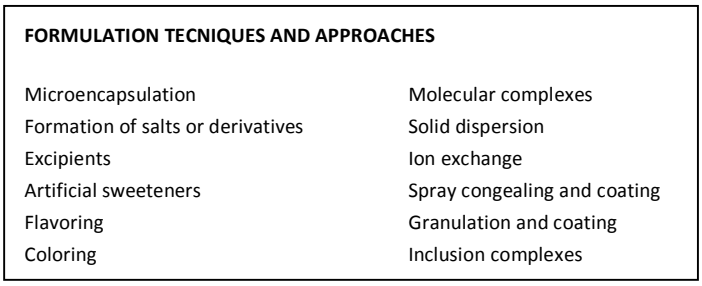


Fig. 2.1 Flow Chart of Various Aspects to be Considered in Connection with Chewable Tablet (Adapted from Leon *et al*., 1989)

2.2.2 Aroma

Pleasant smells are generally referred to as aromas. For example, a well formulated, orange-flavored, chewable tablet should have a characteristic sweet and sour taste and an aroma of fresh orange.

2.2.3 Mouth-feel

The term mouth-feel is related to the type of sensation or touch that a tablet produces in the mouth upon chewing. As such, it has nothing to do with chemical stimulation of olfactory nerves or taste buds. However, for a formulation to be successful, the overall effect in the mouth is important. In general, gritty (e.g., calcium carbonate) or gummy textures are undesirable, whereas a soothing and cooling sensation (e.g., mannitol) with smooth texture is preferred.

2.2.4 After Effects

The most common after effect of many compounds is aftertaste. For example, some iron salts leave a "rusty" aftertaste; saccharin in high amounts tends to leave a bitter aftertaste. Another common after effect is a numbing sensation of a portion of the whole surface of the tongue and mouth. Bitter antihistamines such as pyribenzamine hydrochloride and promethazine hydrochloride are typical of this class of drugs.

2.3 Assessment of the Formulation Problems

Wherever feasible and practical, the first step in the formulation of a chewable tablet is to obtain a complete profile of the active drug. This usually leads to the most efficient formulation of a stable and quality product as the drug usually dictates the choice of fillers, carriers, sweeteners, flavor compounds, and other product modifiers. The drug profile ideally should contain information on the following:

1. Physical properties like
    a. Color, Odor, Taste, aftertaste, mouth-feel
    b. Physical forms like crystal, powder, amorphous solid, oily liquid, etc
    c. Melting or congealing temperature

d. Existence of polymorphs

e. Moisture content

f. Aqueous solubility

g. Active drug's stability on its own

h. Compressibility if applicable

2. Chemical properties like

a. Chemical structure and chemical class

b. Major reactions of this chemical class

c. Major incompatible compounds or class of compounds

d. Drug dose and any limit on final dosage size

This active drug profile would eliminate potentially incompatible excipients, flavors and the likes at the outset, leading to the use of excipients that would best compliment the drug chemically, physically, and organoleptically. The choice of excipients and other product modifiers would involve judgment balancing their cost with their functionality. The use of low-calorie and non-sugar-based excipients may represent a marketing advantage, especially with consumers concerned about calorie intake and dental caries.

2.4 Formulation Techniques

Almost invariably, the formulation problem involves at least one of the following: undesirable taste, bad mouth-feel, or aftertaste. The desired product should prevent or minimize stimulation of the taste buds, contain a suitable flavor and sweetener, and achieve good mouth-feel and compressibility. The following techniques are used to solve one or more of the above.

- Coating by wet granulation
- Microencapsulation
- Solid dispersions
- Adsorbate formation techniques (Solvent method and melting method)
- Ion exchange
- Spray congealing and spray coating
- Formation of different salts or derivatives
- Use of amino acids and protein hydrolysates
- Inclusion complexes
- Molecular complexes

2.5 Manufacturing of Chewable Tablet

2.5.1 General Considerations

Four important aspects of chewable tablet manufacture are the proper incorporation of the coloring agent, assurance of necessary particle size distribution, maintenance of correct moisture content, and achievement of proper tablet hardness. All of these are the routine responsibility of the manufacturing department once the parameters have been established during development. It is therefore critical that process development and scale-up considerations be thoroughly explored in order to ensure the establishment of proper specifications. If colour is added as a lake following granulation (or to a direct-compression blend) then the blending operation consists of the addition of coloured powder to uncolored (white) granules. Again, it is assumed that the coloured powder will uniformly coat the white granules. However, during compression, the

granules fracture and release fresh white material to the surface, resulting in white spots on a coloured background, or vice versa ("speckling"). In either case, the result is a less than elegant finished product. Since the visible problem in both cases may be reduced through lessening the colour contrast between the materials, two common approaches are the use of low concentrations of light colors and the use of high-intensity mixing of reduced particle size materials in order to assure thorough blending.

2.6 Chewable Tablet Excipients

Special consideration, however, needs to be given to those materials that form the basis for chewable tablet formulation. The acceptability in the marketplace of chewable tablets will be primarily determined by taste and, to a lesser degree, appearance. Therefore, appropriate selection and use of components that impact on these properties are of extreme importance. Of course, the formulator must not become as concerned with these properties as to lose sight of other pharmaceutical and biomedical considerations; the resultant product must be as pure, safe, efficacious, and stable as any other. The wet granulation, dry granulation, direct compaction processes are as applicable to chewable as to any other type of tablet. The concerns such as moisture content and uptake, particle size distribution, blending and loading potentials, flow and compressibility are no less important, and must be addressed by the formulation/process development pharmacist as for any product. However in the case of chewable, the new concerns of sweetness, chewability, mouth-feel, and taste must also be considered. Major excipients, such as fillers or direct-compaction vehicles have the major role in the outcome of these concerns; process, a lesser (but certainly not minor) role. Many of the excipients commonly used in tablet formulation are especially applicable for use in chewable tablets due to their ability to provide

the necessary properties of sweetness and chewability. In general these fall into the sugar category (Table 2.1), although a combination of bland excipients with artificial sweeteners may provide a satisfactory alternative.

2.6.1 Dextrose

Dextrose is the sugar obtained through the complete hydrolysis of starch. Its sweetness level is approximately 70 % that of sucrose, and it is available in both anhydrous (but more hygroscopic) and a monohydrated form.

2.6.2 Lactose

Lactose is a monosaccharide produced from whey, a byproduct of the processing of cheese. Although generally acknowledged as the most widely used pharmaceutical excipients in the world. Its applicability to chewable tablets is minor at best, due to its extremely low sweetness level (15 % of sucrose). This deficiency requires the addition of an artificial sweetener of sufficient potency to overcome lactose's blandness. For wet granulation applications, regular pharmaceutical grades (hydrous fine powders) are available. For direct compression, an anhydrous grade having good flow and compressional characteristics is available as Lactose DT® (Sheffield Products Co.).

2.6.3 Mannitol

Mannitol is a white, crystalline polyol approximately 50 % as sweet as sucrose. It is freely soluble in water and, when chewed or dissolved in the mouth, imparts a mild cooling sensation due to its negative heat of solution. This combined with an exceptionally smooth consistency has

made mannitol the excipient of choice for chewable tablet formulation. Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all

Table 2.1: Common Chewable Tablet Excipients (Adapted from Leon *et al*., 1989)

S/no	Common name	Trade name	Source
1	Brown sugar	Brownulated	Amstar
2	Molasses granules	CrystaFlo	Amstar
3	Compressible molasses	Mola-tab	Ingredient Technology
4	Compressible honey	Honey-Tab	Ingredient Technology
5	Compressible sugars	Di-Pac	Amstar
		Nu tab	Ingredient Technology
6	Dextrose/fructose/ maltose	Sweetrex	Mendel
7	Dextrates	Emdex	Mendel
8	lactose	DT	Sheffield
		Fast-Flo	Foremost
9	Mannitol		ICI Americas
10	Sorbitol	Sorb-tab	ICI Americas
		Tablet type	Pfizer

vegetables. An acceptable daily intake of mannitol has not been specified by the World Health Organization since the amount consumed as a sweetening agent is not considered to represent a hazard to health. Mannitol is widely used in pharmaceutical formulations, and as such, it is primarily used as a diluent (10–90 %, *w*/*w*) in tablet formulations where it is water-soluble, non-hygroscopic, and produces a semi-sweet, smooth, and cool taste (Armstrong, 2006). Because of its low hygroscopicity, mannitol is potentially an excellent excipient since it is compatible with the majority of active pharmaceutical ingredients. However, crystalline mannitol is excessively friable, leading to the formation of fine particles that are particularly detrimental to its flow properties. In addition, because of its compact crystal structure, mannitol obtained by crystallization from water exhibits poor solubility. This slow dissolution rate is a major disadvantage and thus restricts its use in pharmaceutical formulations (Erik *et al*., Patent No. 6,743,447).

2.6.4 Sorbitol

Sorbitol occurs as an odorless, white or almost colorless, crystalline, hygroscopic powder. It is particularly useful in chewable tablets owing to its pleasant, cooling, sweet taste and has approximately 50 – 60 % of the sweetness of sucrose. Sorbitol is a slightly sweeter and considerably more hygroscopic isomer of mannitol. For direct compression, it is available commercially as SorbTab® (ICI Americas) and Crystalline sorbitol (Pfizer Chemical).

2.6.5 Maltitol

Maltitol occurs as a white, odorless, sweet, anhydrous crystalline powder. It's a disaccharide consisting of one glucose unit linked with one sorbitol unit via α- (1-4) bond. It is widely used in the pharmaceutical industry in the formulation of oral dosage forms. It is a non-cariogenic bulk sweetener, approximately as sweet as sucrose, well adapted as diluents for different oral dosage forms, wet granulation, and sugar-free hard coating. It has a good thermal and chemical stability, does not undergo browning reactions with amino acids and absorbs atmospheric moisture only at relative humidity's of 89 % and above, at 20 ^{O}C.

2.6.6 Maltodextrin

Maltodextrin occurs as a nonsweet, odorless, white powder or granules. The solubility, hygroscopicity, sweetness and compressibility of maltodextrin increase as the dextrose equivalenght increases. It is used in tablet formulation as a binder and diluents in both direct compression and wet granulation or agglomeration processes (Symecko *et al*., 1993). Maltodextrin appears to have no adverse effect on the rate of dissolution of tablet and capsule formulation. It has been used as a carrier in sprayed dried redispersible oil in water emulsion (Dollo *et al*., 2003), tablet film former in aqueous film coating processes, increases the viscosity of solution and prevent the crystallization of syrup.

2.6.7 Sucrose

Sucrose is a sugar obtained from sugar cane, sugar beet and other sources. It occurs as colorless crystals, crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste. It is used in tableting as a binder in wet granulation, tablet coating agent, bulking agent and sweetener in chewable tablets and lozenges (Sugimoto *et al*., 2006). Tablets that

contain large amount of sucrose may harden to give poor disintegration. It has good stability at room temperature and at moderate relative humidity. It absorb up to 1 % moisture, which is released upon heating at 90 ^{o}C.

2.6.8 Xylitol

Xylitol occurs as white, granular solid comprising crystalline, equidimensional particles having a mean diameter of about 0.4 – 0.6 mm. It is odorless, with a sweet taste that imparts a cooling sensation. It is available as powder, granular and direct compressible forms. Xylitol is used as a non-cariogenic sweetening agent in a variety of pharmaceutical dosage forms, including tablets, syrups and coatings. It is also widely used as an alternative to sucrose in foods and as a base for medicated confectionary. Xylitol is finding increasing application in chewing gum (Soderling *et al*., 1997), mouth rinses (Cobanera *et al*., 1987) and toothpaste (Sintes *et al*., 1995) as an agent that decreases dental plague and tooth decay. As xylitol has an equal sweetness intensity to sucrose, combined with a distinct cooling effect upon dissolution of the crystals, it is highly effective in enhancing the flavors of tablets and syrups and unmasking the bitter or unpleasant flavor associated with some pharmaceutical actives and excipients. Granulates of xylitol are used as diluents in tablet formulations, where they can provide chewable tablets with a desirable sweet taste and cooling sensation, without the chalky texture experienced with some other tablet diluents.

2.6.9 Avicel HFE®

Avicel HFE-102® is a new, proprietary co-spray dried MCC/mannitol excipient. The co-processing of MCC and mannitol creates a synergistic functionality, providing superior benefits versus the use of individual or dry-blended components. Avicel HFE-102® offers improvements in flow, compaction, and disintegration properties compared to traditional MCC grades. The product also exhibits less sensitivity to lubrication.

2.7 Sweeteners

Most of the excipients described in Table. 2.1 as appropriate bases for chewable tablets have as their major property, a level of sweetness that contributes positively to the overall taste of the product. Often, the sweetness imparted by these excipients is insufficient to overcome the bad taste of the drug. In these cases, the formulator must often use artificial enhancers (Table 2.2) to increase the overall sweetness impact.

2.8 Flavours

Flavouring agents, both natural and artificial, are available in a variety of physical forms from a large number of suppliers specializing in these materials. Virtually all offer technical support services. Forms available include water-miscible solutions, oil bases, emulsions, dry powders, spray-dried beadlets, and dry adsorbates. A typical flavor house might catalog 50 or more basic flavours, while having the capability of producing several hundred combinations for a given application.

2.8.1 Flavouring

From the perspective of consumer acceptance, taste is almost certainly the most important parameter of the evaluation of chewable tablets. Taste is a combination of the perceptions of mouth-feel, sweetness, and flavour. Mouth-feel is affected by the heat of solution of the soluble components (negative being preferable), smoothness of the combination during chewing, and hardness of the tablet. These factors are directly and almost entirely related to the active ingredient and major excipients. Sweetness, at an appropriate level, is a necessary background to any flavour. The primary contributors to sweetness in a chewable tablet are the drug, natural sweeteners, and artificial sweetness enhancers that may be incorporated in the formulation.

Table 2.2 Approximate Relative Sweetness of Different Vehicles and Auxiliary Sweeteners (Adapted from Leon *et al*., 1989)

Material	Relative sweetness
Aspartame	200
Cyclamates	30-50
Glycyrrhizin	50
Saccharin's	450
Dextrose (glucose)	0.7
Fructose (levulose)	1.7
Lactose	0.2
Maltose	0.3

Mannitol	0.5-0.7
Sorbitol	0.5-0.6
Sucrose	1.0

2.8.2 Flavour Selection and Formulation

Initially, the inherent taste of the active drug must be evaluated to determine its probable contribution to the formulation. Next, a decision must be made relative to formulation components that would impact on both the pharmaceutical properties and organoleptic characteristics of the tablet. Throughout the steps in formulation development, these considerations must be maintained and eventually optimized. The goal must be a baseline formulation having acceptable properties such as hardness, friability, and dissolution, while providing a suitable mouth-feel and sweetness background for flavouring. Having succeeded in the preparation of one or more unflavored bases, the development pharmacist should next prepare several basic flavoured preference samples. These should be designed to narrow the flavour focus to one or more groups or categories of flavour preferred by decision makers within

the company. Tables 2.3 and 2.4 provide general guidelines for such preliminary choices based on baseline taste and drug product type.

Table 2.3 Suggested Flavour Groups for General Baseline Taste Types (Adapted from Leon *et al*., 1989)

Baseline taste	Flavour
Sweet	Vanilla, stone fruits, grape, berries, maple, honey
Sour (Acidic)	Citrus, cherry, raspberry, straw berry, root beer, anise, liquorice
Salty	Nutty, buttery, butterscotch, spice, maple, melon, raspberry, mixed citrus, mixed fruit

Bitter	Liquorice, anise, coffee, chocolate, wine, mint, grapefruit, cherry, peach, raspberry, nut, fennel, spice
Alkaline	Mint, chocolate, cream, vanilla
Metallic	Grape, burgundy, lemon-lime

Table 2.4 Several Commonly Recommended Flavour Applications (Adapted from Leon *et al*., 1989)

Antacid	Cough/cold	vitamins
Chocolate	Anise birch	Fresh pineapple
Mint (peppermint, spearmint)	Black current	Grape

Mint anise	Rum peach	Passion fruit
Orange	Spice vanilla	Raspberry
Vanilla	Wild cherry	Strawberry
Bavarian cream	Clove	Almond
butterscotch	Honey-lemon	Blueberry
Cherry cream punch	Menthol-eucalyptus	Toasted nut

2.8.3 Flavour/ Colour Integration

The final aspect of taste psychology requires that the flavour and colour match or correspond. A mismatch may detract from consumer acceptance. Table 2.5 provides a general guideline for such matching.

Table 2.5 Flavours' and Corresponding Colour Guidelines (Adapted from Leon *et al*., 1989)

Flavour	Colour
Cherry, wild cherry, tutti- frutti, raspberry, Strawberry, apple	Pink to red
Chocolate, maple, honey, molasses, butterscotch, Walnut, burgundy, nut Caramel	Brown
Lemon, lime, orange, mixed citrus, custard, banana, Cherry, butterscotch	Yellow to orange
Lime, mint, menthol, peppermint, spearmint, pistachio	Green
Vanilla, mint, spearmint, peppermint, Nut, banana, Caramel	Off white to white
Grape, plum, liquorice	Violet to purple
Mint, blueberry, plum, liquorice, mixed fruit	Blue

2.9 Colourants

Colorants are used in the manufacture of chewable tablets for the following reasons:

i. To increase aesthetic appeal to the consumer
ii. To aid in product identification and differentiation

iii. To mask unappealing or non-uniform colour of raw materials

iv. To complement and match the flavor used in the formulation

The Food Drug and Cosmetic Act of 1938 created three categories of coal tar dyes, of which only the first two are applicable to the manufacture of chewable tablets.

1. FD&C colors: These are colorants that are certifiable for use in foods, drugs, and cosmetics.
2. D&C colors: These are dyes and pigments considered safe for use in drugs and cosmetics when in contact with mucous membranes or when ingested.
3. External D&C: These colorants, due to their oral toxicity, are not certifiable for use in products intended for ingestion but are considered safe for use in products applied externally.

Dyes and lakes are two main forms of colorants used in the manufacture of chewable tablets depending on whether the process of manufacture is by wet granulation or direct compression.

2.9.1 Dyes

Dyes are chemical compounds that exhibit their coloring power or tinctorial strength when dissolved in a solvent (Roche *et al*., 1993). They are usually 80 to 93 % (rarely 94 to 99 %) pure colorant material. Dyes are also soluble in propylene glycol and glycerin.

2.9.2 Lakes

Lakes have been defined by the FDA as the "aluminum salts of FD&C water soluble dyes extended on a substratum of alumina." Lakes prepared by extending the calcium salts of the FD&C dyes are also permitted but to date none has been made. Lakes also must be certified by the FDA.

2.10 Densification of a Powder Bed

The compaction of a tablet starts with applying pressure to a powder bed. The bulk volume of the powder bed decreases as an effect of a series of processes that happen sequentially or in parallel (Duberg and Nyström, 1986). The first stage of the consolidation process is characterized by particle rearrangement at low pressures. At a certain relative density, the particles are more or less in a fixed arrangement. Due to the resistance of a material against deformation (strain), the stress inside the particles increases. If the applied stress is released before the deformation reaches a specific critical value, the particles deform elastically, i.e. the deformation is reversible, and the particles inside the powder bed regain their original shapes. Until this critical value, the stress is linearly proportional to the deformation and is characterized by the elastic or Young's modulus (E, Fig. 2.2a). The following stage can be divided into two main deformation mechanisms:

a) Particles fragment into smaller units at a certain stress value (σf, Fig. 2.2b). This stress is the fracture strength. These materials are referred to as brittle materials.
b) After a critical stress (σy, Fig. 2.2c), the particles yield and start to deform plastically. This critical stress is the yield strength of a material. Whereas elastic deformation is a reversible process, plastic deformation results in a permanent change of the particle

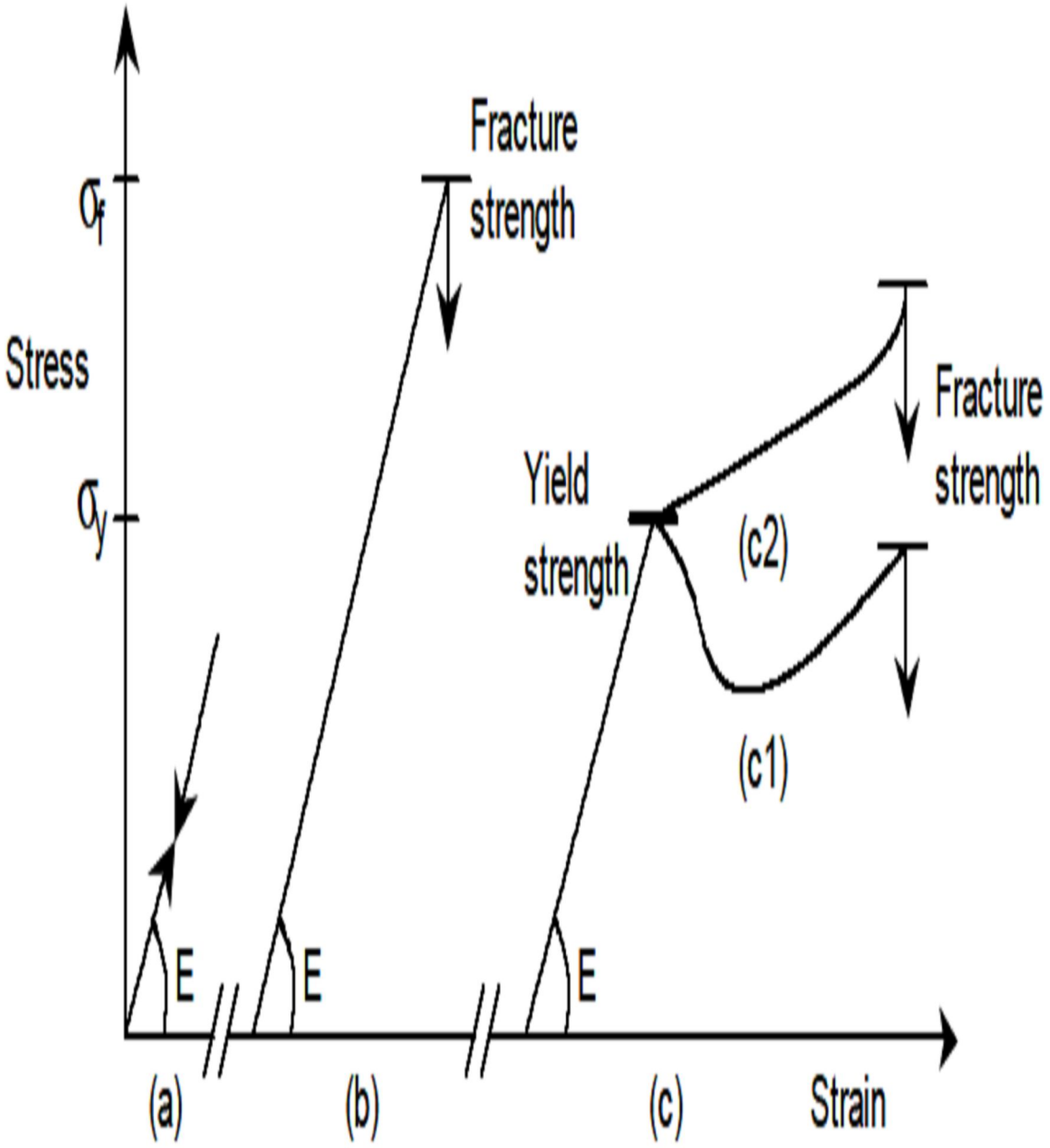


Fig. 2.2 Macroscopic Stress-Strain Relations: a. Reversible Elastic Deformation; b. Brittle Behavior; c. Ductile Behavior (c1. Normal Plastic Flow; c2. Strain-Hardening), (Adapted from Bert, 2003)

shape. These materials are referred to as ductile or plastic materials. Material fracture will eventually occur at higher deformations.

Whether particles become ductile or brittle under compression depends on the material and its physical condition. Roberts and Rowe (1987) demonstrated that materials possess a critical particle diameter at which the densification mechanism turns from brittle to ductile when the particle size decreases (Fig. 2.3). The stress necessary to cause particle fracture increases when the particle size decreases, whereas the stress causing plastic deformation of a material is independent of the particle size. When the fracture stress reaches the level of the yield strength, particles with diameters lower than the critical diameter will yield instead of fracturing. Many materials used as a filler-binder in the pharmaceutical industry can be classified into groups of materials that only have a brittle or ductile deformation behavior due to their extremely low (e.g. inorganic compounds) or high (e.g. celluloses and starches) critical particle diameters (Roberts and Rowe, 1996). The critical particle diameters of other materials are close to the particle sizes of powders used in practice, such as α-lactose monohydrate.

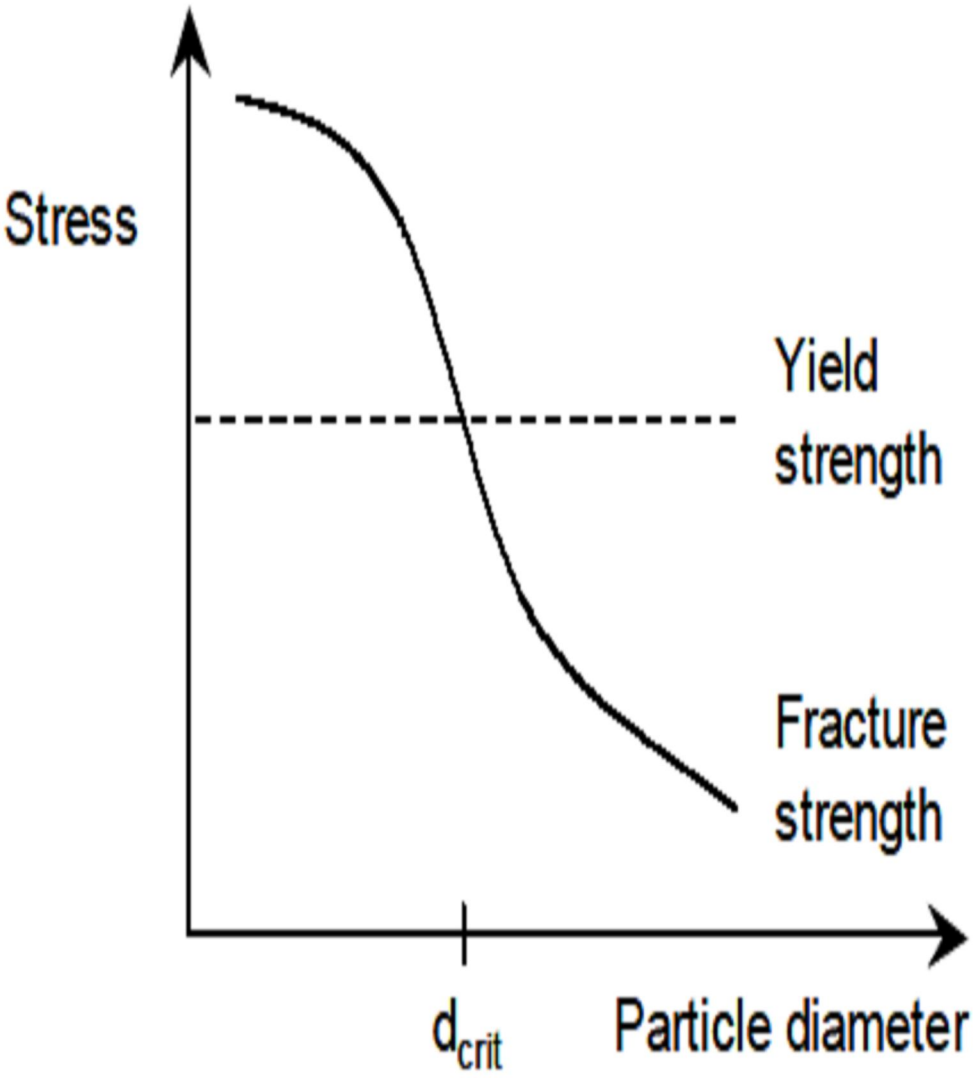


Fig. 2.3 Schematic Representation Depicting the Effect of Particle Size on Yield Strength or Fracture Strength (Adapted from Bert, 2003)

2.10.1 Characterization of Powder Densification

The determination of the densification behavior of a powder is usually based on the measurement of the relative density of the powder bed as a function of the pressure necessary to obtain that relative density. Table 2.6 shows an overview of relations used to describe the effect of the pressure on the degree of densification.

2.10.1.1 *The Heckel Equation*

The Heckel equation (1961) is the most well-known and most commonly used compaction parameter. The equation is based on the assumption that compression of powders is analogous to a first-order chemical reaction, the pores being the reactant and densification of the bulk being the product. The equation was first developed and applied on compression of metals, materials known to deform predominately plastically.

This equation assumes a linear section of the relationship between the logarithm of the relative density under pressure and the applied pressures (Table 2.6).

A Heckel profile is normally distinguished by three different regions, an initial non-linear part (Region I), followed by a linear part where the data obey the expression (Region II), and finally a non-linear region (Region III) (Fig. 2.4). The expression of these three different regions is normally explained with the underlying rate controlling compression mechanisms that dominate the respective regions.

Table 2.6 Powder Densification-Compaction Pressure (P) Relations used to Characterize the Densification Mechanism of a Powder Bed (Adapted from Bert, 2003)

Name	Equation	Parameters
Heckel equation	$\ln\frac{1}{1-Pr} = Kp + A$	Pr is the relative density of the powder bed. K and A are constants
Kawakita equation	$\frac{Vi-Vp}{Vp} = \frac{abP}{1+bP}$	V_i and V_p are the initial volume and volume under pressure of the powder respectively. a and b are constants
Cooper and Eaton equation	$\frac{Vi-Vp}{Vi-Vt} = C1\ exp^{\left[\frac{-K1}{P}\right]} + C2\ exp^{\left[\frac{-K2}{P}\right]}$	V_t is the true powder volume, C1,C2,K1 and K2 are constants
Walker and Bal 'shin equation	$Vr = C3 - k3 \log P$	Vr is the relative density of the powder, C3 and K3 are constants

For region I, two main explanations could be seen in the literature; firstly that the curvature is regarded to be dependent on particle rearrangement during compression and secondly that the curvature is due to particle fragmentation (Duberg and Nystrom, 1982). Regarding the second region, it is generally widely accepted that particle deformation, either plastic or elastic, is the controlling mechanism. And for region III it is argued that elastic deformation of the compact controls the process (Sun and Grant, 2001).

The parameter *A* in the Heckel equation is said to reflect low pressure densification by interparticulate motion. From the linear region, the inverse of the slope (parameter *k*) is calculated. This is referred to as the Heckel parameter or the yield pressure, *Py*, and is commonly used as an indication of the plasticity or hardness of a particle. This assumption originated from an empirical relationship between the parameter *k* and the yield strength ($\sigma 0$) (Eq. 1) (Heckel, 1961). The relationship has been further established through studies done on single particles (Yap, 2008), or derived from bulk compression (Hassanpour and Ghadiri, 2004). The latter provided that a critical ratio between Young's modulus of elasticity and yield stress is exceeded; a criterion that is met for many pharmaceutical materials, but nevertheless indicating that a Heckel analysis does not have general validity.

$$1/k = py = 3\sigma_o \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 1$$

Negative porosities in the upper pressure part of the profile have also been reported, which could lead to substantially lower retrieved yield pressures, and might contradict the assumption that the particle density is constant during compression (Sonnergaard, 2000).

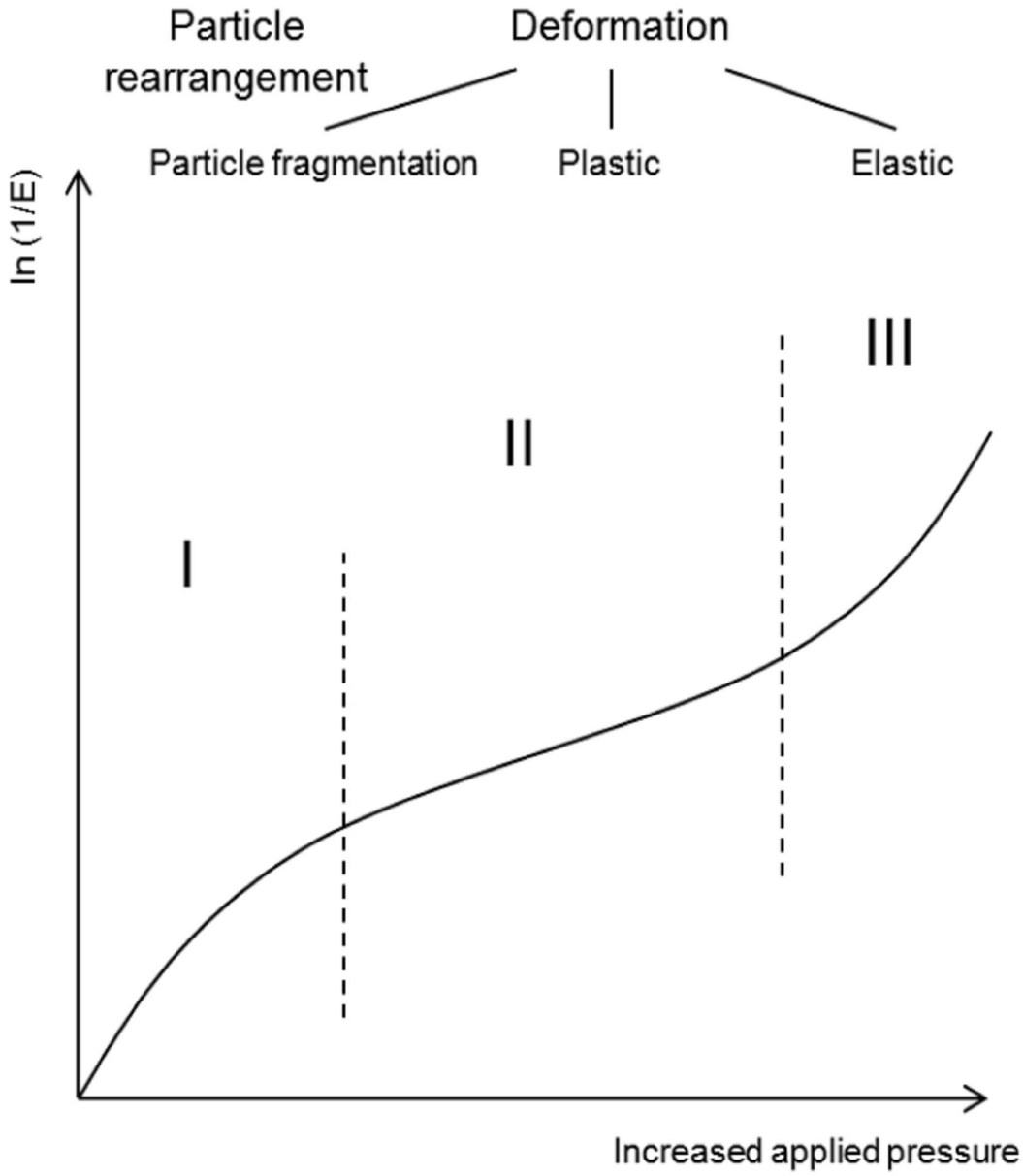


Fig. 2.4 Schematic Illustration of the Three Different Regions Dominating the Heckel Profile (Adapted from Klevan, 2011)

Finally, and most importantly, experimental conditions affect the result of the Heckel parameter, e.g. maximum applied pressure, punch velocity or the punch diameter (Patel *et al*., 2010). As Heckel attributed the linear section to plastic deformation, Heckel equation is in principle only appropriate to examine the densification behavior of plastic materials. Nevertheless, Roberts *et al*. (1989) modified the yield pressure *Py* to the deformation stress σ_d, which is a plastic deformation stress, a fracture deformation stress or a combination of both, in order to calculate the fracture stress of particles with diameters larger than the critical diameter. Furthermore, particle size (Katikaneni *et al*., 1995, Nokhodchi and Rubinstein, 2001), compaction speed (Nokhodchi and Rubinstein, 2001, Roberts and Rowe, 1985) and moisture content (Rees and Tsardaka, 1994, Van der Voort *et al*., 1997) influence the slope of the linear section of Heckel equation and consequently the value of the yield pressure.

2.10.1.2 *The Kawakita Equation*

Another way of representing compression data is to relate the volume reduction (engineering strain) of a powder bed to the applied pressure, and the most familiar expression in this class is the Kawakita equation, Eqn. 2 (Kawakita and Lüdde, 1971).

$P/C = 1/ab + P/a$ …….. 2

Where C is the degree of volume reduction, ($C = (Vo - V)/Vo$, where Vo is the initial volume of the powder bed and V is the volume under applied pressure), P is the applied pressure, a and b are constants.

The linear relationship between P/C and P makes it possible to derive values of the parameters a and b. The parameter a represents the maximal engineering strain, $Cmax$ of the powder bed, and mathematically the parameter b is equal to the reciprocal of the pressure when the value, C, reaches one-half of the limiting value ($C=Cmax/2$), as illustrated in Fig. 2.5.

The Kawakita equation is often considered to be best suited for analysis of soft, fluffy powders compressed under low pressures (Denny, 2002). However, setting the start volume for the calculations is a critical point that should be carefully considered; as this influence the outcome of the parameters retrieved to a large extent (Sonnergaard, 2000). The physical interpretation of the Kawakita parameters has been discussed in the literature, and the inverted b-parameter is claimed to reflect the agglomerate strength (Adams *et al.*, 1994), fracture strength of single particles (Yap, 2008) or the plasticity of a granule (Nordström, 2008). The physical interpretation of the b-parameter in terms of bulk powders has been more complicated to address and represent a resistance towards compression.

The Kawakita equation may also be applied to tapping of bulk powders, as a measure of fluidity and cohesion, replacing the pressure term (P) in Eq. 2 by N – the tapping number (Yu and Hall, 1994). Regarding the physical significance of the Kawakita parameters, the parameter a still represents the maximum degree of volume reduction now at infinite tapping and is considered to

correspond to fluidity. The *b* parameter represents the tapping ability and hence, the inverted *b* parameter is considered to be related to interparticulate cohesion.

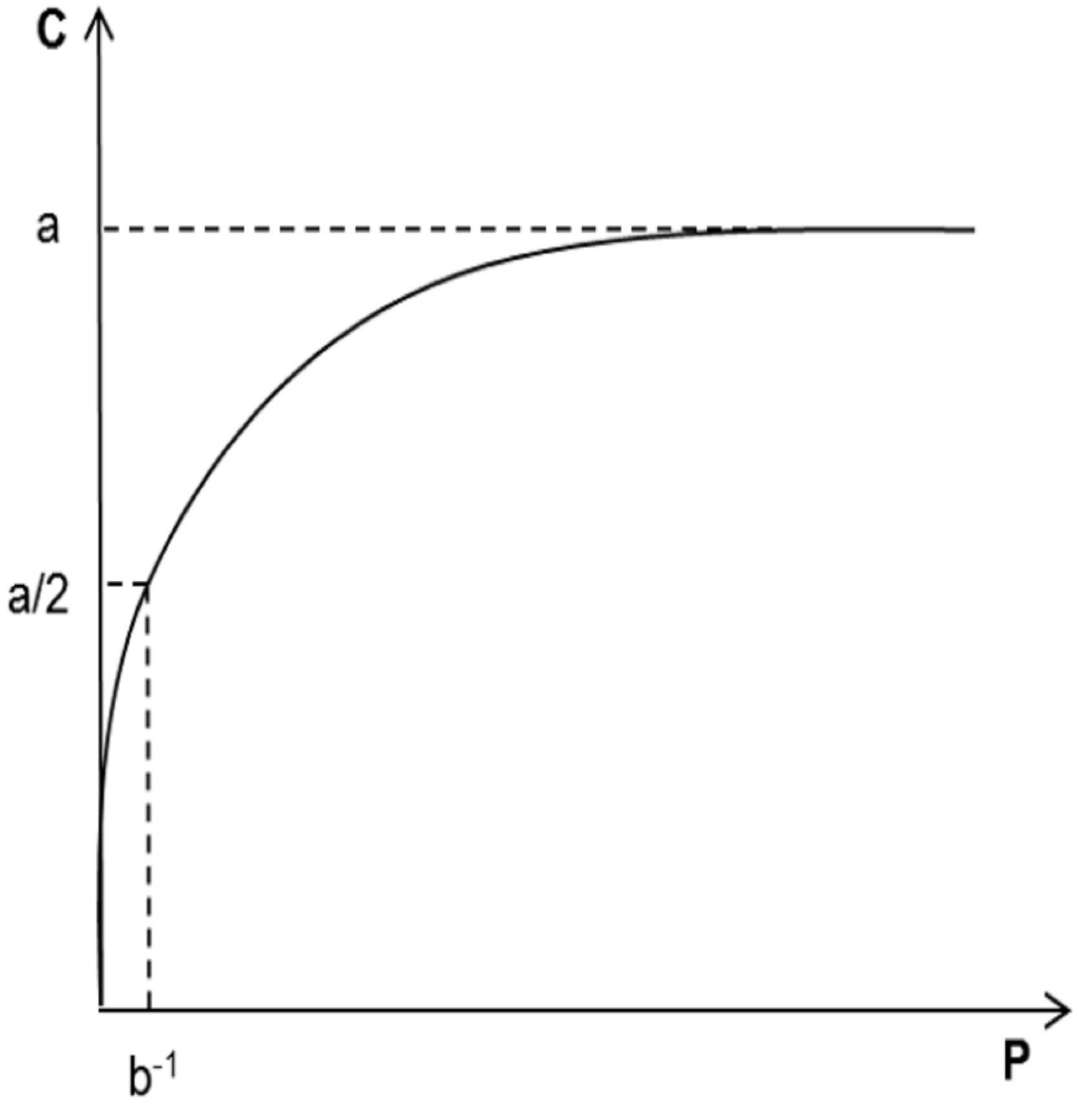


Fig. 2.5 Schematic Illustration of a Typical Engineering Strain – Pressure –Curve and Mathematical Interpretation of the Kawakita Parameters (Adapted from Kawakita and Lüdde, 1971)

2.11 Powder Compaction

During the powder compression process the particle surfaces are brought closer together and interparticulate attraction occurs. This enables bonding between particles. Bond formation during compression is critical for the formation of a tablet of sufficient mechanical strength, and the total tablet strength is reflected in the sum of number of bonds and the strength of each bond. For compaction of dry powders, the bonding mechanisms may roughly be divided into three main types: solid bridges, attraction forces and mechanical interlocking (Nyström and Karehill, 1996). Particle fragmentation increases the number of surfaces available for bonding, while particle plastic deformation contributes mainly to the bonding force. Thus, these two particle deformation mechanisms are bond producing and have a positive effect on tablet strength. Particle elastic deformation can lead to breakage of bonds after removal of the applied pressure as the tablet recovers in height. Thus, particle elastic deformation has a negative effect on tablet strength (Duberg and Nystrom, 1986). Regarding particle size and shape, it is generally recognized that small particles form harder compacts (due to large surface areas available for bonding), while the effect of particle shape is most prominent for ductile materials, i.e. large increase in compactibility going from regular to irregular particles (Wong and Pilpel, 1990). In addition, processing conditions affect the resulting tablet strength. As previously remarked, the tableting speed is of importance for strain-rate-sensitive materials (Tye *et al*., 2005). Tablet formulations mostly comprise several components and prediction of tablet strength is difficult due to the complex nature of the process itself, and is further complicated through interactions between the different components in the formulation (Vromans and Lerk, 1988).

2.11.1 Compaction Studies

One essential functionality related characteristic of a powder material intended for tableting is its mechanical properties, or how the solid particles respond to mechanical stresses during handling and compression. Three main approaches for mechanical properties testing are found in the literature: confined compression of the powder, testing of the finished compact and testing of single particles (Kuentz and Leuenberger, 2000).

Compression analysis is the method of applying pressure to a powder bed in a confined die, while data for the punch movement and applied forces is sampled (Ragnarsson, 1996). The method is attractive for many reasons: small amounts of material are needed, fine and poorly compactable materials can be tested, the data acquisition is often very accurate and large data sets are assembled. The data material is transformed into volume-pressure or porosity-pressure – relationships (Paronen and Ilkka, 1996), more commonly known as compression models, from which compression parameters can be retrieved. Preferably, the models should be based on good understanding of the process described and the parameters should reflect a physical property of the material. A powder could be seen as a special case of a disperse system, where particles (the solid phase) are dispersed in air (the gas phase). The term powder compression describes the volume reduction of a powder bed in a confined space caused by the application of a force. Hence, the compressibility describes the ability of a powder to decrease in volume. When a powder is compressed, the gas-phase is reduced and the particles are brought closer together. The

interparticulate bonds become increasingly stronger and finally the bulk powder transforms into a coherent mass or a compact (Führer, 1996). This phenomenon is denominated compaction, and the ability of a powder to form a compact of specified strength is referred to as the compactibility (Leuenberger, 1982).

There are several different views regarding the mechanistic conception of the powder compression process, but the description of it as a process occurring in a sequence of consecutive, albeit overlapping stages is considered the most common (Holman, 1991). Each stage represents a certain part of the pressure range used, and is associated with one or more dominating compression mechanisms. Also, a wide spread of interpretation regarding this sequential perception exist in the literature, both in terms of number of stages or regions represented and regarding which physical processes that are dominating each region. However, there are four-stages comprising initial particle rearrangement, particle fragmentation, particle plastic deformation and finally elastic deformation of the compact (Denny, 2002).

Initially, at low compression pressures the particles are brought closer together and the powder bed porosity and volume is reduced. At a certain applied pressure, the particles reach a maximum attainable packing structure and any further particle movement becomes impossible. The following volume reduction is therefore associated with changes in the dimensions of the particles. These changes might occur both temporarily by elastic deformation and permanently by plastic deformation (Fig. 2.6). The particles dimension could also change by brittle fracture into smaller particles, which subsequently undergo a secondary particle rearrangement followed by plastic and/or elastic deformation. Thus, one particle may undergo this cycle of events several times. As a particle successively is reduced in size, a transition from brittle to ductile behavior

may occur (Rowe and Roberts, 1996). In the decompression phase, i.e. when the applied pressure is removed, the particles (or the compact) may expand due to elastic recovery. All the above mentioned physical processes occur to a different extent in different pressure regions depending on the properties of the material(s).

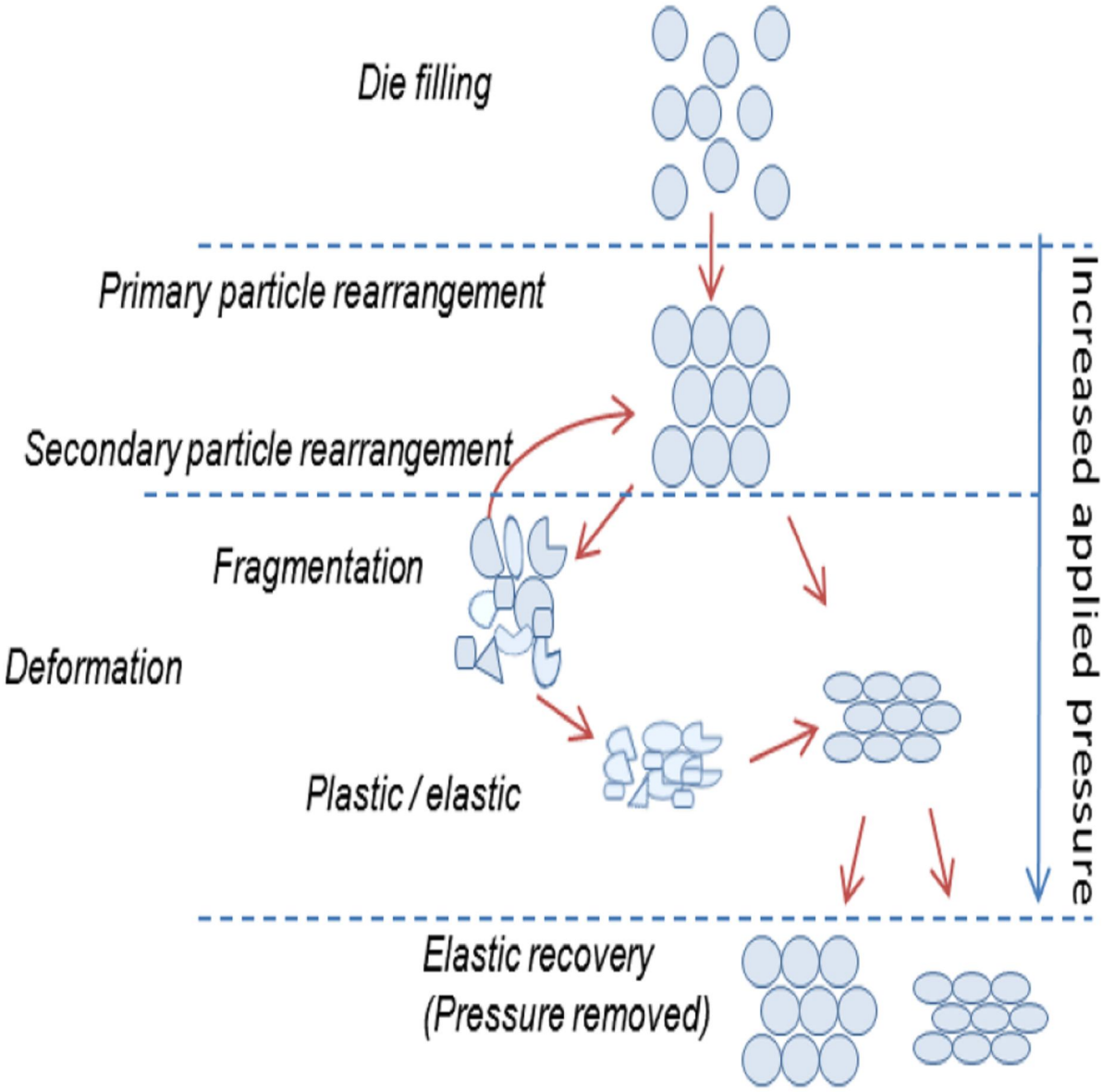


Fig. 2.6 Schematic Illustration of the Powder Compression Cycle (Adapted from Klevan, 2011)

Furthermore, not all materials possess these dominating compression mechanics expressed in all regions, while other materials possess several mechanical properties. In addition, the loading conditions (e.g. temperature, applied pressure, punch velocity and total duration time for the compression cycle) affect the degree of fragmentation, plastic and elastic deformation (Antikainen and Yliruusi, 2003). When punch speed and loading time affect the deformation, the behavior of the materials is referred to as viscoelastic and/or viscous (strain-rate-sensitive) deformation, a behavior often observed for pharmaceutical materials (Armstrong, 1989).

2.12 Tablet Relaxation

During and after the removal of the applied load, a compressed powder bed generally shows an elastic recovery of its volume as an effect of stress relaxation. In case of a permanent deformation, the volume expansion will be small, whereas large tablet relaxations are caused by an important elastic component (Duberg and Nyström, 1986). The driving force for tablet relaxation has been suggested to be the elastic energy stored in the particles during densification (Van der Voort *et al*., 1997). On the other hand, the bonding between particles is regarded as the counteracting force against tablet relaxation. Tablet relaxation is commonly expressed by a change in tablet height, volume or porosity (Van der Voort *et al*., 1996, Doelker, 1993). During densification, some compacts may even show an increase in density above their own material density at high compaction pressures. The total tablet relaxation can be a combination of a fully reversible decrease of the true density to the material density and an increase in tablet porosity. The tablet expansion expressed as porosity expansion was found to be independent of the applied load (Van der Voort *et al*., 1996). Similarly as has been described for the densification of a powder bed, the relaxation propensity of a tablet is influenced by the compaction speed

(Nokhodchi and Rubinstein, 2001, Van der Voort *et al*., 1996), moisture content (Steendam *et al.*, 2001, Van der Voort *et al*., 1997) and particle size (Katikaneni *et al*., 1995, Nokhodchi and Rubinstein, 2001). Malamataris *et al.* (1984) defined the plasto-elasticity of materials as the ratio between the stress relaxation (change in tablet height under maximum load for a certain period of time; *SR*) and the elastic recovery (change in tablet height after ejection from the die; *ER*). This *SR*/*ER* ratio describes the ability of a material to deform plastically under load and recover elastically after the application of the load.

2.13 Tablet Structure

The final tablet structure is the combined result of the consolidation of the powder bed and relaxation of the tablet. As both processes are influenced by the different factors, the final tablet structure also depends on these factors. In all situations, the internal tablet structure can be seen as a combination of particles and voids. But, the axial compaction of powders leads to anisotropy and heterogeneous tablet structures (Train, 1956).

The predominant bonding mechanisms between particles in compacts compressed from pharmaceutical materials are intermolecular forces, i.e. van der Waals forces, electrostatic forces and hydrogen bonding (Ferrari *et al*., 1996), and solid bridge formation in case of salts such as sodium chloride, potassium chloride and sodium bicarbonate (Adolfsson *et al*., 1999). Different approaches and techniques have been developed to describe and measure quantitatively the surface energy and bonding capacity of materials, e.g. the solubility parameter, which equals the root of the cohesive energy density (Rowe, 1998), atomic force measurements (Sindel and Zimmermann, 2001), inverse gas chromatography (Levoguer *et al*., 2000) or tablet strength

measurements in liquids with different dielectric constants (Karehill and Nyström, 1990, Adolfsson, *et al.,* 1998). With the help of the solubility parameter, theoretical estimations of an adhesive interaction parameter can be made between different materials in powder blends (Barra *et al.,* 1998, Rowe, 1988). The particles inside the tablet structure directly influence the size of voids. Mercury intrusion porosimetry, a commonly used technique to measure the pore size distribution, is based on the pressures necessary to force mercury into pore openings. According to Bockstiegel's observation for compacts of iron particles (Bockstiegel, 1966, 1967), tablets compacted from ductile materials show a decrease of the larger pores at increasing compaction pressures, while the smaller pores do not change in size and number (Westermarck *et al*., 1998, Juppo, 1996, Vromans, *et al.,* 1985). The fragmentation of particles of a brittle material results in an increase of smaller particles and consequently a different change in the pore size distribution as an effect of compression. The disappearance of larger pores is accompanied by an increase in the amount of small pores (Juppo, 1996, Vromans, *et al.,* 1985). In tablets compressed from ductile materials, the pore size will be dependent on the initial particle size. Brittle fracture will to a large extent eliminate the effects of the initial particle size.

2.14 Mechanical Properties of Compacts

Mechanical properties of compacts such as tensile strength, elastic modulus and indentation hardness are known to be largely dependent on the compact structure. Mechanical properties commonly decrease with an increase of the tablet's porosity. The change in mechanical property as a function of the porosity is normally fitted by an exponential relationship (Duckworth, 1953, Spriggs, 1961). The extrapolated value at zero porosity of this function is normally regarded as an indication of the material property. However, this interpretation has been questioned in

several studies; different authors showed that a smaller initial particle size leads to an increase of the mechanical property (Sun and Grant, 2001, Bin Baie *et al*., 1996). However, it is interesting to note that direct relationships have been demonstrated between the calculated cohesive energy densities of several materials and their elastic moduli (Roberts and Rowe, 1991), tensile strengths and the critical stress intensity factors (Roberts *et al*., 1995).

The tablet relaxation after compaction results in an increase of the tablet porosity and consequently into a decrease of the tensile strength. Remarkably, some crystalline materials, such as sodium chloride and potassium chloride, have been found to give an increase in tablet strength after compaction (El Gindy and Samaha, 1983, Eriksson and Alderborn, 1994). The authors postulated that the stress relaxation caused by recrystallization creates extra bonding forces between particles.

2.14.1 Friability

Friction and shock are the forces that most often causes tablet to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shock as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1 % of the weight of the tablets being tested during the friability test is considered generally acceptable and

any broken or smashed tablets are not picked up. Normally, when capping occurs, friability vales are not calculated.

2.14.2 Crushing Strength

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the mid 1930s. It is now designated as either the Monsanto or Stocks hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Strong-Cobb, Pfizer and Schleuniger apparatus which were later introduced measure the diametrically applied force required to break the tablet. Hardness which is now appropriately called crushing strength is determine during tablet production and is used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specification; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 – 10 kg. However, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder between 10 – 20 kg (Odeku and Itiola, 2003).

Another measure of the mechanical strength of pharmaceutical tablets that have been used is the crushing strength-friability ratio (CSFR). The crushing strength provides a measure of tablet strength while friability is a measure of tablet weakness. Studies have shown that the higher the CSFR values, the stronger the tablet (Odeku and Itiola, 2003).

2.14.3 Tensile Strength

A non-compendia method of measuring the mechanical strength of tablets that is now widely used is the tensile strength. This is the force required to break a tablet in a diametral compression test. The radial tensile strength, T, of the tablets can be calculated from the equation:

$T = 2F/\pi dH$ …… 3

Where F is the load needed to break the tablet, π is a constant, and d and H are the diameter and thickness respectively. Several precautions must be taken when using the equation. Various factors e.g. test condition, deformation properties of the material, adhesion conditions between compacts and its support and tablet shape may influence the measurement of the tensile strength.

Some authors have suggested the determination of axial tensile strength because of the sensitivity of the radial tensile strength measurements to crack propagation variations. The axial tensile strength (T_x) can be calculated from the following relationship:

$T_x = 4F/\pi d^2$ ……....4

Tensile strength has been used in combination with indentation hardness to evaluate tableting performance of materials. The indentation hardness is a time dependent property used to measure

the plastic yield of a material. It can be determined by either static methods (e.g. the Brinell, Vickers and Rockwell hardness tests) or the dynamic methods. The static indentation methods involve the formation of a permanent indentation on the surface of the material tested and the harness is determined by means of the load applied and the size of the indentation formed. In the dynamic indentation test, either a pendulum is allowed to strike from a known distance or an indenter is allowed to fall under gravity unto the surface of the test material. The hardness is then determined from the rebound height of the pendulum or the volume of the resulting indentation. Using an apparatus consisting of a steel sphere pendulum acting as an indenter, Hiestand and Smith (1984) estimated the hardness (i.e. the mean deformation pressure) of compacted materials by dividing the energy consumed during the impact by the volume of indentation.

2.14.4 Brittle Fracture Index (BFI)

Hiestand *et al* (1984) have studied the effects of decompression on the tableting performance of pharmaceutical materials. He stated that whether or not fracture occurs during the shear deformation which accompanies decompression depends on the ability of the material to relieve stress by plastic deformation without undergoing brittle fracture and this ability is a time dependent phenomenon. Those materials that relieve rapidly are less likely to cap or laminate. The brittleness test is based on the Griffith fracture theory which states that, for crack growth to occur, the energy stored at the tip of a crack must just exceeds the energy required to form two new surfaces resulting from the propagation of the crack. Also, the amount of energy stored at the tip of a crack is a function of the dimensions of the crack.

In the light of this theory, Hiestand *et al.,* (1984) showed that when compacts are made with a small axially oriented round hole at their center, the compact is nearly always weakened. Under the conditions of the tensile strength test, elasticity theory predicts that the stress concentration factor for the hole should be about 3.0. Hiestand *et al* (1984) showed that for isotropic materials, the ratio of compressive stress at the center of a compact to the tensile stress which causes fracture has a value of 3.7. However, recent studies have shown that for a ratio of the hole diameter to disc of about 0.1, the stress concentration factor, i.e. the ratio between tensile stress at the inner boundary of the hole and the tensile stress of a tablet having no hole should be around 10.

Thus, the BFI is obtained by comparing the tensile strength of the tablets with a hole at their center, which acts as a built in stress concentration defect, with the tensile strength of tablets without a hole, both at the same relative density. The brittle fracture index of the tablets was calculated using the following equation

$$BFI = 0.5[(T/T_o) - 1] \quad \ldots\ldots 5$$

Where T is the tensile strength of the tablet without a hole and To, the tensile strength of a tablet with a hole. The theoretical value of BFI range is 0 – 1 when the stress concentration factor is 3. Since the BFI is an inverse measure of localized stress relief, it should indicate the tendency of a tablet to laminate or cap. Robert and Row (1986) extended the determination of the BFI to compact of 'tablet-sized' dimensions. This allows the BFI to be measured at strain rates and conditions approaching those normally used in tableting. They found the BFI values for microcrystalline cellulose and heavy magnesium carbonate to be in good agreement with the

results of previous workers. Itiola and Pilpel (1986) using both granular and powdered metronidazole formulations studied the mechanical properties of the tablets and differentiated between the bond strength of the tablets as measured by their tensile strength and the tendency of the tablets to laminate or cap as measured by the BFI vales. They found that tablets made from granules had lower tensile strength than those made from powders but were also less brittle.

The BFI have also been used to characterize the mechanical properties of pharmaceutical formulations and some local starches, namely cassava, potato and yam starches. Tablets of these starches were shown to posses low tensile strength values, but also had low BFI values. Studies have also shown that the BFI is affected by the nature and concentration of binding agent, compressional pressure and compressional speed. Generally, the higher the BFI values, the more friable a tablet is likely to be depending on the material type.

2.15 *In-vitro* Evaluation of Tablets

2.15.1 Disintegration

In immediate release dosage forms, the first step toward the dissolution of drug substance is disintegration of a dosage form into its primary granules or particles. Disintegration increases surface of contact between formulated drug and liquid, which thereby facilitates drug dissolution. Disintegration represents a limiting factor of dissolution, especially for low soluble drugs in water or in biological fluids. Thus disintegration times are often directly correlated to dissolution rate constants (Carstensen *et al*., 1983). Disintegration involves the submersion of the dosage form into the dissolution medium or in water at approximately 37 °C. Disintegration time is the time required for a dosage form to disintegrate completely. The viscosity, surface tension and

contact angle of the penetrating solution also influence the disintegration of the tablet accompanied with the mean diameter of the capillaries in the tablet, and as the mean capillary diameter alters with different compaction forces (Nogami *et al*., 1963). It is clear that disintegration is a very important parameter to observe when changing tableting presses or scaling up.

2.15.2 Mechanism of Disintegration

Although disintegrants are important components in solid dosage forms, their mechanism of action has not been clearly elucidated. The mechanisms proposed in the past include water wicking, swelling, deformation recovery, repulsion, and heat of wetting. It seems likely that no single mechanism can explain the complex behavior of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

2.15.3 Dissolution

The dissolution of a dosage form is one of the most important parameters to keep an eye on throughout development, scale-up and equipment and process changes. Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. The process by which a solid substance dissolves is controlled by the affinity between the solid substance and the solvent. Drug absorption into systemic circulation from a solid dosage form after oral administration depends on the release of the drug substance, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. The dissolution characteristics of drugs can be influenced by different factors such as the

physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the disintegration, disaggregation and swelling process of the dosage form. A pharmaceutical tablet disintegrates into granules, and these granules disaggregate in turn into fine particles.

2.16 Bond Summation Mechanism

Two main theories have been developed to describe the important factors controlling the strength of a porous compact. One of these theories is the bond summation mechanism. The tablet strength is the sum of antiparticle bonding forces between surfaces with spherical curvatures in the diametrical failure plane of the compact (Hiestand, 1985; Rumpf *et al*., 1970). The surface area taking part in the antiparticle attraction is small and difficult to measure. Therefore, secondary definitions of bonding surface areas of powders and tablets are used to explain changes in tablet strength (Adolfsson *et al*., 1999; Eriksson and Alderborn, 1995). The specific surface area of tablets compressed from crystalline lactose has been found to be directly related to the tablet strength (Vromans *et al.,* 1985). A similar relationship has been reported for tablets compressed from binary mixtures of different types of crystalline lactose (Riepma *et al*., 1990). However, this relationship could not be established for other materials (Adolfsson *et al*., 1999; Eriksson and Alderborn, 1995). Recently, views are more focused on fracture mechanism theory.

2.17 Fracture Mechanism

The fracture mechanism theory is based on the assumption that pores in the tablet structure act as stress concentrators. Fracture of a porous material occurs when the stress of the pores at the bonding sites of the particles is higher than the cohesive energy of the material and high enough

to initiate fracture. To continue tablet fracture, the elastic energy released must be higher than the energy necessary to form new pore openings. Inglis (1913) was the first author to postulate that pores or cracks perpendicular to the applied load concentrate stress at their tips and consequently decrease the fracture strength of a material (Fig. 2.7). The ratio between the material strength with or without a crack for elastic-brittle fracture is given by:

$$\sigma\ material/\ \sigma\ measured\ = 1 + 2\sqrt{l/p} \quad \ldots\ldots\ldots\ldots\ 6$$

Where σ *material* is the cohesive strength of the material, σ *measured* is the measured compact strength, *l* is the length of the pore and ρ is the diameter of the curvature of the pore tip.

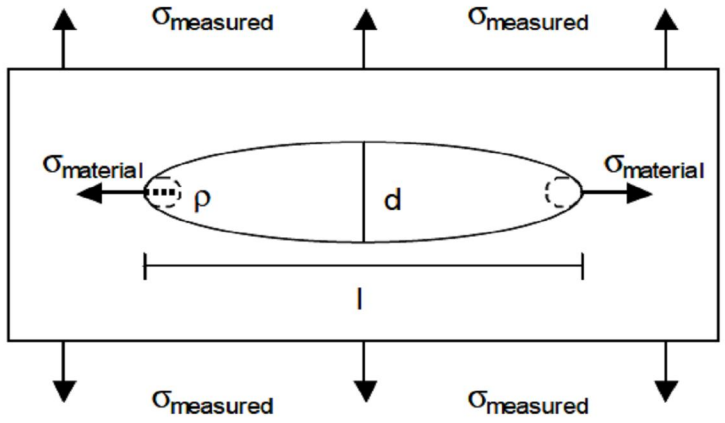


Fig. 2.7 Inglis-Griffith Crack Theory (Adapted from Bert, 2003)

Griffith (1920) further developed equation 6 into a universal theory based on thermodynamically considerations. He argued that two energies have to be taken into account when a crack

propagates: a release of elastic energy that is stored in the material and an increase of surface energy. The combination of these two energies resulted into:

$\sigma\ material = \sqrt{2E\gamma s/\pi a}$ 7

Where E is the elastic modulus of the body, γs is the surface energy and a is the half of pore length l. The stress around a crack in a material is reflected by the critical stress intensity factor Kic [= (2Eγs) ½] and is a measure of the stress necessary to start and develop a failure surface (Mashadi and Newton, 1987).

The theory of elastic-brittle fracture can also be applied to tablet fracture. Stanley (2001) states that the fracture of porous compacts behaves in a brittle fashion i.e. no plastic deformation occurs before fracture starts. As defined by Griffith's equation, larger cracks or pores give a higher decrease of the tablet strength. In literature, there are indications that the tablet strength is related to the median pore diameter, which is primarily affected by the larger pores (Liu, 1997, Johansson *et al*., 1995).

2.18 Dilution Capacity

By definition, direct compression diluents are intended to be mixed with other ingredients. Therefore, not only should the pressure – tablet strength profile of the diluents be determined, but also should those of mixtures of the diluent with an active ingredient. The capacity of a direct compression diluent is the proportion of another ingredient that can be mixed with it while still obtaining tablets of acceptable quality. The definition of "acceptable" will depend on the purpose for which the tablets are required. The magnitude of the effect that a given active ingredient will have on tablet properties will clearly depend on the tableting properties of that substance. If it is

also capable of direct compression, then the effect will not be great. If, however, it is a substance that is difficult to compress into tablets, then it will cause a marked deterioration in tablet quality when mixed with the diluent. Therefore, for a reliable test of capacity, the direct compression diluent should be mixed with a "standard" substance and tabletted under standardized conditions. The pressure – strength profiles of the mixtures can then be constructed. Paracetamol and ascorbic acid have been used as standard (Leuenberger, 2006).

The powder behavior upon compaction can be studied through the physical characterization of tablets after manufacturing. Accordingly, all radial tensile strength of binary mixtures are plotted versus compaction pressure and the Points fitted into a quadratic polynomial equation. The area under the plotted curves (AUC) is calculated using the trapezium method. Using the method proposed by Habib *et al* (1996), the AUC of each mixture is divided by the AUC of each pure excipient, to give a value known as work potential or area ratio. All ratios are plotted against the % (w/w) of active drug for each excipient. Linear regression and back extrapolation to zero area ratios gives the values of dilution capacity.

2.19 Ascorbic acid (Vitamin C)

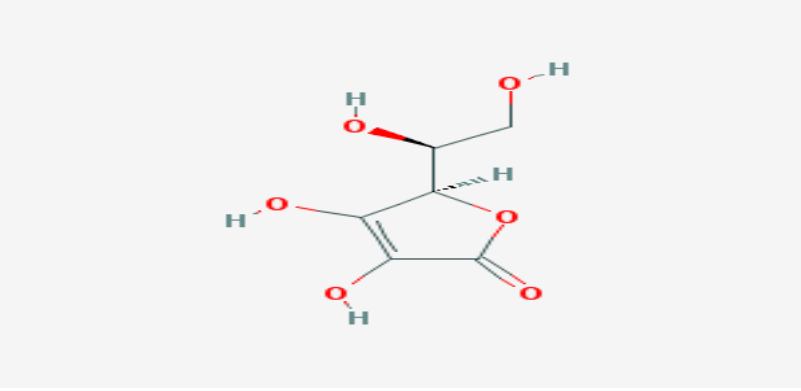


Fig. 2.8 Structure of Ascorbic Acid (Adapted from PubChem, 2014)

Ascorbic acid is a white or colorless or very pale yellow crystalline odourless powder with a sharp acidic taste and contains not less than 99 % of $C_6H_8O_6$. It has a melting point of 190-192 ^oC and a density of 1.65 g/cm^2. A 5 % solution of ascorbic acid has a pH of 2.2 to 2.5. Ascorbic acid has two symmetric carbon atoms (Fig. 2.8), with a specific rotation $[a]^{20}$ D = $+21^o$ in water and $+48^o$ in methanol. D-ascorbic acid, which differ from L-ascorbic acid only in its configuration about the fourth carbon atom, is physiologically inactive (BPC, 2010). The acidic properties of ascorbic acid are not due to the carboxyl group, which is tied up in lactones form, but to the ionization of the enol group on third carbon atom. Ascorbic acid is the enolic form of 3-oxo-1–gulofuranolactone. It is a strong acid with pk_1 of 4.17 and pk_2 of 11.57. At neutrality, the vitamin has an absorption maximum in the ultra violet region of the spectrum at 225 nm, which shifts towards the shorter wavelength with decreasing pH. Ascorbic acid crystals are stable in air for two years. But in solution it is easily oxidized; the instability being maximum at about pH 4 and increasing with increasing pH in the alkaline range. Mild oxidation such as that produced by air, hydrogen peroxide, ferric chlorides, quinine, iodine in acid or neutral solution or 2, 6-dichlorophenol indophenols converts the vitamin to dehydro-ascorbic acid. Dehydro-ascorbic acid is an inactive form of ascorbic acid.

Vitamin C can be obtained from many natural sources. The best known sources are the citrus fruits: oranges, lemons, tangerines, limes and grape fruits. The fruits with the highest natural concentrations are citrus fruits, rope hips, and acerola cherries. As a natural supplement it is available as time-released tablets, chewable tablets, and in liquid form. It is also available as various mineral ascorbate salts such as sodium or calcium ascorbate.

2.19.1 Functions of Ascorbic Acid

Vitamin C has many functions that benefit the human body; it forms and maintains collagen, it metabolizes tryptophan; it acts as an antioxidant, it acts as a detoxifier and colour stabilizer; it helps increase thyroid hormones and decrease cholesterol (BPC, 2010).

Daily consumption of ascorbic acid must balance the quantity that is excreted or destroyed by oxidation. Up to 3 % to 4 % of the daily body stored ascorbic acid is lost in healthy human beings daily. So, to maintain the stored body ascorbic acid of 1500 mg or greater in an adult, a daily consumption of minimum amount of 60 mg daily is required. Values for vitamin C requirement of other age groups are based on these same reasons.

Ascorbic acid is unstable, especially in alkaline solution, readily undergo oxidation even at atmospheric oxygen, the change being accelerated by light and heat, it exhibits maximum stability in solution at about pH 5.4. The first stage in the oxidation is reversible and results in the formation of dehydroascorbic acid (BPC, 2010). Ascorbic acid should be stored in an airtight container free from contact with metal and protected from light, humidity and in room temperature, in absence of heavy metals and excessive heat (BPC, 2010).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials

3.1.1 Reagents and Excipients

- Ethanol (96 %), butan-1-ol, sodium metabisulphite and sucrose (BDH Chemicals Ltd, Poole England)

- Xylene and potassium iodide (Fisher Scientific Ltd, Leicestershire, UK)
- Hydrochloric acid, iodine sublimed, sodium hydroxide, D-mannitol, talc and magnesium stearate (R & M Chemicals, Essex, UK)
- Glacial acetic acid (QRëc Chemicals, Thailand)
- L-Ascorbic acid, potassium chloride and sodium chloride [System (Chem AR®), UK]
- Xylisorb 700 (Xylitol), sweet pearl P2000 (maltitol), Avicel PH101, Avicel HFE-102 and maltodextrin (Roquette, France)
- Polyplasdone® INF-10 (Crosspovidone) (ISP Technologies INC, USA)
- Sodium saccharine (CK Chemicals, Sdn Bhd, Malaysia)

3.2 Methods

3.2.1 Collection and Identification of *Ipomoea batatas*

The *Ipomoea batatas* (white skin, cream flesh variety) was bought from Sokoto central market, Nigeria and identified by the Institute of Agricultural Research, Ahmadu Bello University, Zaria.

3.2.2 Flour Extraction

Flour extraction was conducted as established by Alves *et al.* (2002). The tubers were peeled, washed, cut into 1-2 cm cubes, and sliced into thick chips (~5mm). This chip was then soaked in sodium metabisulphite solution (0.075 %) for ~5 min and oven dried at 30 ^{0}C for 40 h until it reached 13 % moisture. Subsequently, the dried chips were milled (PZ, Barnerx Chem Ltd.

England) into flour and sifted through a 500 µm sieve (BS), and stored under dry conditions at room temperature.

3.2.3 **Mucilage Separation**

The mucilage concentrate was prepared following the method described by Jiang and Ramsden (1999) with little modification. Flour sample (100 g) was dispersed in 300 ml of sodium metabisulphite (0.075 %) solution and stored at 4 ^{0}C overnight. This dispersion was centrifuged (TDL-4, Zhejiang, China) at 14,000 x g for 20 min and the supernatant (mucilage) collected. This was followed by pellet dissolution in metabisulphite solution and centrifuged as described before. The resulting supernatant was filtered using a filter paper (110 mm diameter) and purified as follows: 150 ml of the supernatant was treated with 0.5 % saturated solution of calcium chloride and left overnight. Subsequently, the supernatant was carefully collected and further treated by heating (DKZ-2, Uniscope, Shangai, China) at 95 ^{o}C for 30 min and allowed to cool to room temperature. The resulting supernatant was precipitated using three times its volume of ethanol (96 %) and then dried in an oven (FN-055, Nuve, Turkey) 40 ^{0}C.

3.2.4 **Starch Isolation**

The pellets obtained from the centrifugation step during the mucilage separation was re-suspended in 500 ml of sodium metabisulphite (0.075 %) solution, homogenated and passed through a 150 µm sieve. The residue was washed with sodium metabisulphite (0.075 %). The resulting slurry was left to stand overnight at 4 ^{0}C and then centrifuged (14,000 x g; 20 min). The supernatant was discarded and the colored layer manually scraped off of the starch. This centrifugation step was repeated until the supernatant layer becomes almost colorless. After the

last centrifugation, the supernatant was decanted and 10 ml sodium hydroxide solution (0.1 M) added to the remaining sediment (starch). This was followed by addition of deionized water to wash the pellets until its pH became neutral. The recovered starch was dried using an air oven at 40 ^{o}C for 30 h, ground, and sieved using a 500 µm sieve. The yield of starch based on the weight of its respective flour (100 g) was determined. The resulting starch was stored in an air tight container under dry conditions**.**

3.2.5 **Modification of Starches**

3.2.5.1 ***Acid modification***

In the production of acid modified starch, 450 g of an aqueous suspension of starch (36 % w/w starch) was poured into a stainless steel vessel. To this suspension, 28 ml, 6N HCl was added drop wise with stirring and subsequently, the reaction was conducted for 6 h at 54 ^{0}C. After cooling, the acid modified starch was separated from the reaction medium by filtration. On the filter, the separated starch was washed 1:1 with water. The starch was then suspended in 250 ml water and the pH adjusted to 7 with NaOH. The starch was separated by means of filtration with water and dried in an oven at 40 ^{0}C to a moisture content of < 10 %, then ground into a powder and passed through a 500 µm sieve.

3.2.5.2 ***Pregelatinization***

In the production of partially pregelatinized starch, native starch 39.6 g was added to 70 ml of distilled water and the suspension stirred for 10 min at room temperature. The suspension was heated on a water bath (DKZ-2, Uniscope, Shangai, China) thermostatically maintained at a temperature of 55 ^{0}C (i.e. below the gelatinization temperature) for 15 min, the resultant paste was dried in a hot air oven at temperature of 40 ^{0}C to a moisture content of <10 %, then ground into a powder and passed through a 500 μm sieve.

3.2.6 **Preliminary Confirmatory Tests**

3.2.6.1 ***Molish's Test***

Molish's test was carried out as follows; 100 mg dried mucilage powder and 5 mls of Molish's reagent was introduced into a test tube. Conc. H_2S0_4 (2 ml) was added to the side of the test tube and the color at the junction of the two layers was observed.

3.2.6.2 ***Ruthenium Test***

Fifty milligrams of dried mucilage powder was mounted on a slide with 2 drops of ruthenium red solution and observed under a microscope. The colour change was noted.

3.2.6.3 ***Iodine Test***

The BP (2010) starch identification test was adopted. A 1 g quantity of starch was boiled with 15 ml of water. After cooling, 2 drops of 0.1 N iodine solution was added to 1 ml of the mucilage and the colour change noted.

3.2.6.4 ***Enzyme Test***

Enzyme test was carried out as follows: 100 mg of dried mucilage powder was dissolved in 20 ml of distilled water and 0.5 ml of benzedrine in alcohol (90 %) was added. The mixture was shaken and allowed to stand for few minutes and the colour change noted.

3.2.7 **Proximate Analysis**

The methods for the proximate analysis were carried out according to the standard procedure *(*Association of Analytical Chemist, 1990*)*.

3.2.7.1 ***Moisture content***

The moisture content was determined by the oven method. A 2 g quantity of fresh sample was weighed and dried in the oven at 105 °C for 24 h. The dried sample was weighed again until constant weight was achieved, and the percentage moisture was calculated.

3.2.7.2 ***Ash Value***

The ash value was determined by incineration of 2 g of sample in a muffle furnace (6100, Jenway, UK) at 600 °C for 3 h. The sample ash obtained was weighed and the percentage ash was calculated.

3.2.7.3 ***Crude Lipid***

Crude lipid was determined as follows: Two grams of the sample was added to 50 ml of petroleum ether and stirred. When the sample particles settled at the bottom of the container, the mixture was decanted and the liquid portion was placed in a crucible and evaporated in an oven at 60 ^{0}C. The lipid residue that remained in the crucible was weighed and expressed as a

percentage.

3.2.7.4 ***Crude Protein***

Crude protein was determined by the Kjeldahl method. Nitrogen was first determined before the determination of protein. To determine nitrogen, 2 g of the sample was weighed into a beaker and 20 ml of concentrated H_2SO_4 was added with digestion tablets and mixed. Distilled water was added into the beaker until it reached 50 m1and the solution digested for 10 min. After digestion, 10 ml of the solution was taken and added to 20 m1 NaOH and 30 ml distilled water. 20 ml boric acid indicator was measured and put in a separate beaker. The prepared sample was taken to the Macrojelder apparatus and set for distillation. During distillation, the condensed vapour is allowed to drop into boric acid indicator in a separate container, which was set at the lower part of the Macrojelder apparatus. The process continued until the boric acid indicator changed from pink to green colour. The green-coloured sample was titrated using 0.01 N H_2SO_4 until it became pink colour again. The titre value was recorded which was of nitrogen. The percentage nitrogen was calculated and the crude protein was obtained by multiplying the percentage nitrogen by the conversion factor of protein (% N x 6.25).

3.2.7.5 ***Crude Fiber***

Crude fiber was determined by acid-base digestion. The residue from the determination of lipid was used for this determination. To the residue, 20 ml of 10 % H_2SO4 solution and 50 ml of distilled water was added and heated for 30 min and filtered. To the residue, 20 ml of 10 % NaOH solution and 50 ml of distilled water was added and heated for another 30 min and filtered. The residue was transferred into the crucible and taken into the furnace to dry. The

weight of the dry ash obtained was weighed and the percentage fiber was calculated.

3.2.7.6 ***Total Carbohydrates***

The total carbohydrate was determined by the difference between 100 and the sum of the percentage of ash, crude lipid, crude protein and crude fiber as follows;

Total carbohydrate = 100 – (% ash + % crude lipid + % crude protein + % crude fiber)…… (8)

3.2.8 **Starch and Mucilage Dispersions**

Production of mucilage/native starch, mucilage/pregelatinized starch and mucilage/acid hydrolyzed starch dispersions in a ratio 5:100, 10:100, 20:100, 30:100 and 40:100 respectively was carried out as follows:

Ipomoea batatas mucilage was slowly added to distilled water (150 ml) with stirring until dissolution was effected. Starch (native, pregelatinized or acid modified) was then added to the mucilage solutions, and the dispersion stirred for one hour at room temperature. The whole dispersion was then transferred into a glass dish and dried at 45 ^{0}C in an oven to a moisture content of < 10 %, milled and passed through a 500 µm sieve.

3.2.9 **pH Determination**

This was carried out by shaking 2 g of the powder material with 100 ml of distilled water for 5 min and the pH of the supernatant liquid determined using a pH meter (pH 211, Hanna Instrument, UK). Determination was carried out trice.

3.2.10 **Amylose and Amylopectin Fractions**

This was determined by the method of William *et al*. (1958) with little modification. A 0.1 g quantity of the test sample was weighed into a 100 ml volumetric flask and 1 ml of 99-100 % (v/v) ethanol and 9 ml 1N NaOH were carefully added. The mouth of flask was covered with paraffin and the content mixed well. The sample was heated for 10 min in boiling water to gelatinize the starch. The sample was removed from the water bath and allowed to cool very well, then made up to the mark with distilled water and shaken thoroughly. Next, 5 ml was pipetted into another 100 ml volumetric flask and 1.0 ml of 1N acetic acid and 2.0 ml of iodine solution were added. The flask was topped up to the mark with distilled water. Absorbance (A) of the solution was read using a spectrophotometer at 620 nm wavelength. The blank contains 1 ml of ethanol and 9 ml of NaOH boiled and up to the mark with distilled water. Afterwards, 5 ml of the blank was pipetted into a 100 ml volumetric flask and 1.0 ml of 1M acetic acid and 2 ml of iodine solution were added and made up to volume with distilled water. The amylose content was calculated as follow:

Amylose content (%) = 3.06 x absorbance x 20 ……. (9)

Amylopectin (%) = 100 - % amylose content ……... (10)

3.2.11 **Water Solubility Index (WSI)**

The water solubility indices of the starches were determined as described by Anderson and Sefa-dedeh (2001). The starches (2.5 g each) and water (to 100 ml) were vigorously mixed in a 100 ml centrifuge tube incubated in a 37 ^{o}C water bath (Stirred water bath, Medica Instrument Mfg. Co, Mumbai India) for 30 min and then centrifuged (4000 x g for 10 min). The supernatant was collected in a pre-weighed beaker and the residue was weighted after the water was evaporated

below 105 ^{o}C. The percentage of residue with respect to the amount of starch used was taken as the water solubility index.

3.2.12 **Compatibility Studies**

Fourier transform infra red (FT-IR) spectra matching approach was used for detection of any possible chemical interaction between the starch and mucilage and between the model drug and excipient. A 1 mg quantity of the individual and physical mixture (1:1) of drug and mucilage powder was prepared and mixed with 49 mg potassium bromide. The mixture (50 mg) was compressed to form a transparent pellet using a hydraulic press at 5 tons pressure, and then scanned from 4000 – 400 cm^{-1} in a FTIR spectrophotometer (FT-IR, Nexus, USA). The IR spectrum of the physical mixture was compared with those of pure starch and matching done to detect any appearance or disappearance of peak.

3.2.13 **Moisture Sorption Capacity**

Two grams of the starch material was accurately weighed and evenly distributed over the surface of a 70 mm tarred Petri dish. The samples were placed in large desiccators containing distilled water (RH=100 %) and saturated sodium chloride solution (RH=75 %) at room temperature and the weight gained by the sample at the end of a five day period was recorded and the amount of water sobbed calculated from the weight differences.

3.2.14 **True Density**

The true density (D_1) of the starch was determined by the liquid displacement method using xylene as the immersion fluid as described by Ohwoauvorhua *et al* (2004) and computed according to the following equation.

$$D_1 = W/ [(a+w) – b] \times SG \text{ ……. (11)}$$

Where w is the weight of the powder, SG is specific gravity of liquid, a, is Weight of bottle + liquid and b is weight of bottle + solvent + powder.

3.2.15 **Granular Morphology and Particle Size**

Scanning electron micrographs (SEM) were obtained using a scanning electron microscope (EVO/MA 10, Carl Zeiss NTS Ltd, England). Starch samples were applied onto aluminum stubs using double-sided adhesive tape. The samples were coated with gold-palladium. An accelerated potential of 15 Kv was used during the electron micrograph. Particle size was determined using a laser diffraction analyzer (Mastersizer-S, MSS, Malvern instrument Ltd, UK) at room temperature.

3.2.16 **Bulk Density**

A 10 g quantity of the powder sample was placed in 50 ml clean, dry measuring cylinder and the volume V□ occupied by the sample without tapping was determined. The bulk density was calculated as the ratio of the weight of powder and volume (V_o).

3.2.17 **Tapped Density**

A 10 g quantity of the powder sample was placed in 50 ml clean, dry measuring cylinder and the volume occupied after 500 manual taps (V_{500}) was determined. The tapped density was calculated as the ratio of the weight of powder and volume (V_{500}).

3.2.18 **Carr's Index**

The Carr's index was determined using the following equation (Swartz *et al*, 1975).

$$CI = (TD - BD)/TD \times 100\ \% \ldots\ldots\ldots (12)$$

Where CI = Carr's index, TD = tapped density and BD = bulk density.

3.2.19 **Hausner's Quotient**

Hausner's quotient was determined using the following formula:

$$TD/BD \ldots\ldots\ldots (13)$$

Where, TD= tapped density and BD = bulk density

3.2.20 **Angle of Repose**

The static angle of repose, (a) was measured according to the fixed funnel and free standing cone method and the tangent of the angle of repose calculated using the equation

$$\text{Tan } a = 2h/D \ldots\ldots\ldots (14)$$

Where h is the height of the heap of powder and D is the diameter of the base of the heap of powder.

3.2.21 **Powder Porosity**

This was determined from the values of true and bulk densities when fitted into the equation according to the method of Ohwoauvorhua *et al (*2004):

$$e = 1\text{-}BD/D_t \times 10 \ldots\ldots\ldots (15)$$

Where BЬ, is the bulk density, D, is the true density and e is the porosity

3.2.22 **Hydration Capacity**

The method of Kornblum and Stoopak (1973) was used. A 1 g sample was placed in each of four 15 ml plastic centrifuge tubes and 10 ml distilled water added from a 10 ml measuring cylinder and then stoppered. The contents were mixed on a vortex mixer for 2 min. The mixture was then allowed to stand for 10 min and immediately centrifuged. The supernatant was carefully decanted and the sediment weighed. The hydration capacity was taken as the ratio of the weight of the sediment to the dry sample weight.

3.2.23 **Swelling Capacity**

This was determined at the same time as the hydration determination using the method of Okhamafe *et al* (1991) and computed according to the following equation:

$$S = (V_2 - V_1)/V_1 \times 100\% \ldots\ldots\ldots (16)$$

Where S is the % swelling capacity, V_2 is the volume of the hydration or swollen material and V_1 is the tapped volume of the material prior to hydration.

3.2.24 **Pasting Properties**

The pasting properties (ICC standard Method 162) of native starch, modified starches and their dispersions in mucilage were investigated with a Rapid Visco-Analyze (RVA-4, Newport Scientific, Australia). All samples were weighted and the water to be added was corrected for sample moisture content (within normal moisture basis of 14 %). All samples were treated with a heating– cooling cycle. The starch suspensions were equilibrated at 50 ^{o}C for 1 min, heated from 50 ^{o}C to 95 ^{o}C at heating rate of 12 ^{o}C/min, then held at 95 ^{o}C for 3 min. Afterwards the paste was cooled to 50° C at 12 ^{o}C/min and kept at 50 ^{o}C for 2 min. Paddle speed was set at 960 rpm for the first 10 s, then 160 rpm for the remaining time of the experiment. The viscoamylogram described the various characteristics of the starch including peak temperature, peak viscosity, time to peak, and final viscosity at the end of a 50 ^{o}C holding period. Other parameters, including setback and breakdown, were calculated from the viscoamylogram characteristics. The unit of pasting properties of the various starch samples was expressed as RVU, where RVU is the unit of viscosity from the Rapid Visco-Analyzer. Three replicates of each sample were analyzed.

3.2.25 **Thermal Properties**

The thermal properties of the mixed flour were measured using a differential scanning calorimeter (Pyris 6 DSC, Perkin Elmer, USA). Native and modified starches with their dispersions in mucilage (3 mg) and distilled water (12 mg) were loaded into an aluminum pan and hermetically sealed. The sample pans were allowed to stand for 2 h at room temperature in order to attain an even distribution of water before heating the calorimeter. An empty aluminum

pan was used as reference and the calorimeter was calibrated with indium. The scanning temperature range was 20 ^{o}C – 120 ^{o}C at a heating rate of 10 ^{o}C/min. The onset (To), peak (Tp), and conclusion (Tc) temperatures, as well as the enthalpy (ΔH) of gelatinization of the dry starch and mucilage were calculated automatically.

3.2.26 **Syneresis**

Starch retrogradation measured by syneresis was carried out according to the method described by Kuar *et al* (2002) with little modification. A 2 % w/v starch suspension was heated at 85 ^{o}C for 30 min in a temperature controlled water bath and then cooled to room temperature in an ice water bath. The starch samples were stored for 1, 2, 4 and 7 days at 4 ^{o}C. Syneresis was measured as the amount of water (%) released after centrifugation at 3000 x g for 15 min.

3.3 **Tablets Compacts (Placebo)**

Tablets compacts (placebo) were produced using 400 mg of native starch, modified starches and dispersions of native and modified starches at different compression pressures using a tableting machine (Manesty BB, Single Press Tableting Machine, UK) fitted with a 10 mm punch and die and subsequently evaluated for weight variation, relative density, crushing strength, tensile strength, friability and disintegration.

3.3.1 **Uniformity of Weight**

Ten tablets were weighted individually and collectively from each batch using analytical balance, and the mean weight computed. The percent coefficient of tablet weight variation (% CV) was calculated according to the formula.

% CV = standard deviation / mean weight x 100 ……. (17)

3.3.2 Tablet Thickness & Diameter

Tablet thickness and diameter was measured using a micrometer screw gauge 24 h after the tablets is been compressed. Five tablets were used for each determination and the mean calculated.

3.3.3 Relative Densities of Tablet

Relative densities of tablets at corresponding pressure loads were used to evaluate compressibility. Tablet density was obtained from the weight of compact and its volume as follows:

Relative densities (g/ml) = weight of tablet (g) / tablet volume (ml) x ρ ……. (18)

The volume of tablet was calculated from the relationship:

Volume of tablet = $\pi r^2 t$ ……. (19)

Where r = radius of tablet

t = tablet thickness

ρ = particle density of the granule

3.3.4 Crushing Strength

Five tablets were taken and the crushing strength was determined using tablet hardness tester (YD-2, Vanguard Pharmaceutical Machinery INC, UK). Each tablet is placed between two

anvils and the force that just causes the tablet to break was recorded. Crushing strengths recorded are averages of five tablets.

3.3.5 **Tablet Tensile Strength**

The radial tensile strength was calculated using the data obtained from crushing strength determination, diameter, and thickness of the tablets using the equation.

$$Ts = 2F/\pi dt \quad \ldots\ldots\ldots (20)$$

Where Ts is the tensile strength, F is the load needed to break the tablet, d is the diameter of the tablet and t is the tablet thickness.

3.3.6 **Friability Determination**

Ten tablets from each batch were weighed and placed in the friability tester (Erweka TA3R friabilator, Erweka apparatebau GmbH, Western Germany) and subjected to combined effects of abrasion and shock. The apparatus was set to revolve at 25 rpm for 4 min. The tablets were dusted and weighed. The percent loss in weight was calculated as friability.

3.3.7 **Disintegration Time (DT)**

DT test was carried out according to BP (2010) specification, six tablets were placed in a disintegration tester (Disintegration machine 78X Shanghai, China) filled with distilled water at 37 ± 0.2 °C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh. Disintegration times recorded are mean of six determinations.

3.4 **Compaction Studies**

3.4.1 **Preparation of Tablets**

Quantities (500 mg) of each starch powder, were compressed for 30 sec with predetermined loads (4.98 – 34.24 KN) on a Carver hydraulic hand press (Model C, Wisconsin, USA) using a 10.0 mm die and flat-faced punches lubricated with a 2 % w/v dispersion of magnesium stearate in ethanol. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening, and prevent falsely low yield values. Their weights (w) and dimensions were then determined to within ± 1mg and ± 0.01 mm respectively, and their relative densities (D) were calculated using equation (11) above. Heckel plots of ln (1/1-D) versus applied pressure (P) and Kawakita plots of P/C versus P were constructed for all the starches.

3.5 **Elastic Recovery**

Elastic recovery (ER) was determined based on the difference between the out-of-die (after 24 h) and in-die relative densities (D) of the tablets compressed at various pressures according to the equation:

$$ER\ \% = D\ (\text{out of die}) - D\ (\text{in-die}) / D\ (\text{out of die}) \times 100 \quad \ldots\ldots\ldots (21)$$

3.6 **Brittle Fracture Index (BFI)**

The tensile strengths of the normal tablets (T) and apparent tensile strengths of those containing a hole (To) were determined at room temperature by diametral compression. Results were taken only from tablets which split cleanly into two halves without any sign of lamination. All measurements were made in triplicate and the results given are the means of several determinations. The Brittle Fracture Index (BFI) of the tablets was calculated using the following equation.

$$BFI = 0.5\ [(T / To) - 1] \quad \ldots\ldots\ldots (22)$$

3.7 **Dilution Capacity**

Ascorbic acid was added to each starch samples at various concentrations (0, 20, 40, 60 and 80 % w/w). The mixtures was mixed for 10 min and tablets (500 mg) were compressed using hydraulic hand press (Carver hydraulic hand press Model C, Wisconsin, USA) at compression pressure ranging from 2.49 – 19.93 KN. Dilution potential was determined by using dilution capacity index (DCI) according to Habib *et al*. (1996). Tensile strength (Ts) was calculated using equation (20). The tensile strength of the binary mixtures was plotted against compaction pressures and the points were fitted into a quadratic polynomial equation of the order:

$Ts = aP^2 + bP + c$ …… (23)

Were P is the compression force in KN and a, b and c are constants.

Integrating equation (22) in the limit of compression force P_1 to P_2, the area under the tensile strength-compression force curve (AUC) was determined as follows

$AUC = [aP_2^3/3 + bP_2^2/2 + cP_2 + d] – [aP_1^3/3 + bP_1^2/2 + cP_1 + d]$ ……. (24)

Were P_1 and P_2 are the lowest and highest compression forces.

The AUC of each mixture was divided by the AUC of the 0% w/w mixture of the corresponding starch samples to give a ratio known as work potential or area ratio as defined by Minchom and Armstrong (1987). The area ratio was then plotted against the percentage w/w ascorbic acid for each starch samples. Linear regression and back extrapolation to zero area ratios gave the value reflecting the dilution capacity or MA index. The dilution capacity index (DCI) was determined by multiplying the MA index by AUC of the drug free blend.

3.8 **Lubricant Sensitivity Ratio (LSR)**

Starch samples (500 mg) were lubricated with magnesium stearate at 0, 0.25 and 0.5 % and compressed using a hydraulic hand press at a pressure range of 2.49 – 19.93 KN. The LSR was determined based on the difference between the tensile strength with and without lubricant of the tablets compressed at various pressures according to the equation below

LSR = Ts (without lub.) – Ts (with lub.) / Ts (without lub.) ……. (25)

3.9 **Formulation of Ascorbic acid Chewable Tablets**

Ascorbic acid chewable tablets were formulated by the direct compression method using single station tablet press (Manesty BB, Single Press Tableting Machine, UK) fitted with 8 mm punch and die assembly (batch size of 100 tablets) according to the following formulae (Table 3.1 – 3.4) at compression pressure of 6.0 metric tones

Table 3.1: Tablet Formulae for Ascorbic Acid Chewable Tablet using Modified Starch and Mucilage Dispersions

Parameters (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ascorbic acid	100	100	100	100	100	100
30-MSPS	120	-		120	-	-
30-MPPS	-	120		-	120	-
30-MAPS	-	-	120	-	-	120
Sodium saccharine	-	-	-	0.25	0.25	0.25
Crosspovidone	-	-	-	1.20	1.20	1.20
Magnesium stearate	0.55	0.55	0.55	0.55	0.55	0.55

30-MSPS, 30-MPPS and 30-MAPS represents 30 g of mucilage incorporated into 100 g of native, pregelatinized and acid modified starch respectively

Table 3.2: Tablet Formulae for Ascorbic Acid Chewable Tablet using Binary Mixtures of Modified Starch and Mucilage Dispersion with Mannitol

Parameters (mg)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Ascorbic acid	100	100	100	100	100	100
30-MSPS	100	-	-	80	-	-
30-MPPS	-	100	-	-	80	-
30-MAPS	-	-	100	-	-	80
Mannitol	20	20	20	40	40	40
Crosspovidone	3.50	3.50	3.50	3.50	3.50	3.50
Magnesium stearate	0.55	0.55	0.55	0.55	0.55	0.55

30-MSPS, 30-MPPS and 30-MAPS represents 30 g of mucilage incorporated into 100 g of native, pregelatinized and acid modified starch respectively

Table 3.3: Tablet Formulae for Ascorbic Acid Chewable Tablet using Binary Mixtures of Modified Starch and Mucilage Dispersion with Maltitol

Parameters (mg)	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Ascorbic acid	100	100	100	100	100	100
30-MSPS	100	-	-	80	-	-
30-MPPS	-	100	-	-	80	-
30-MAPS	-	-	100	-	-	80
Maltitol	20	20	20	40	40	40
Crosspovidone	3.50	3.50	3.50	3.50	3.50	3.50
Magnesium stearate	0.55	0.55	0.55	0.55	0.55	0.55

30-MSPS, 30-MPPS and 30-MAPS represents 30 g of mucilage incorporated into 100 g of native, pregelatinized and acid modified starch respectively

Table 3.4: Tablet Formulae for Ascorbic Acid Chewable Tablet using mannitol and Avicel HFE

Parameters (mg)	**F19**	**F20**
Ascorbic acid	100	100
Mannitol	120	
Avicel HFE		120
Sodium saccharine	0.25	0.25
Crosspovidone	3.50	3.50
Magnesium stearate	0.55	0.55

The tablets were evaluated for weight variation, relative density, crushing strength, tensile strength, friability and disintegration time.

3.9.1 **Dissolution Test**

The dissolution test of ascorbic acid tablets were carried out according to the USP (2010) specification using dissolution apparatus Type II (Variant VK 7000 Dissolution Apparatus, NC, USA), with 900 ml of 0.1 N HCl as the dissolution medium at 37 ± 0.5 ^{o}C which was stirred at a rate of 100 rpm. Ascorbic acid was determined using spectrophotometer at wavelength of 244 nm.

3.10 **Panel Assessment Test**

The sensory panel test was performed as described by Shishu and Kapoor (2010) with little modification. Twenty volunteers, 20–24 years in age (both male and female), were selected to

evaluate the taste of the chewable tablets. The volunteers were given the tablets to chew for 10 sec and then mouth rinsed out with water. Tablets were rated from 0 to 5 points for their appearance, aroma, hardness, taste, mouth feel sensation and aftertaste. The criteria for scoring were as follows

1 = very poor
2 = poor
3 = acceptable
4 = good
5 = excellent

Overall tablets qualities were calculated as a sum of all recorded sensory properties.

3.11 **Stability Studies**

Accelerated stability studies to observe the effect of temperature and relative humidity on optimized formulation were carried out as described by Ashok *et al*. (2008). Optimized formulations were kept at 40 ± 2 °C, in airtight container for three months, at RH 75±5 %. Physical evaluation and *in-vitro* drug release was carried out after every one month.

CHAPTER FOUR

4.0 RESULTS

4.1 Physico-Chemical and Material Properties

The physic-chemical and material properties obtained from the analysis performed in chapter three are presented below:

Table 4.1: Proximate Analysis of Native Starch, Modified Starches and Mucilage obtained from *Ipomoea batatas*

Parameters	**SPS**	**PPS**	**APS**	***Ipomoea batatas* mucilage**
Molisch's test	Positive	Positive	Positive	Positive
Ruthenium test	Negative	Negative	Negative	Positive
Iodine test	Positive	Positive	Positive	Negative
Enzyme test	Negative	Negative	Negative	Negative
Moisture content (%)	12.0	5.00	7.50	6.50
Ash value (%)	0.51	0.58	0.53	0.68
Lipid (%)	0.30	0.20	0.25	0.10
Fiber (%)	0.50	0.50	0.50	0.35
Crude protein (%)	0.35	0.38	0.39	3.33

Total carbohydrate (%)	98.34	98.34	98.33	85.54
Amylose (%)	34.90	37.60	35.40	Nd
Amylopectin (%)	65.10	62.40	64.60	Nd

Nd = not determined, SPS, PPS and APS represents native, pregelatinized and acid modified starches obtained from *Ipomoea batatas* respectively

From the Table 4.1 above, positive Molish's test confirmed the presence of carbohydrate, positive ruthenium test confirmed the presence of mucilage, iodine test confirmed the absence of starch in the mucilage and generally, absence of enzymes was recorded in all samples. The moisture content and ash values for native and modified starches were within the specification of the British Pharmacopoeia (2012). There were no significant differences between the crude fiber, crude protein and total carbohydrate for the native and modified starches. There was an increased crude protein content in the mucilage as compared to the native and modified starches. The amylose content was in the order PPS > APS > SPS.

Table 4.2: Organoleptic Properties of Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

Parameters	Colour	Taste	Odour	WSI
SPS	Off white	Characteristic	Characteristic	0.88
5-MSPS	Off white	Characteristic	Characteristic	4.91
10-MSPS	Off white	Characteristic	Characteristic	8.40
20-MSPS	Brown	Slightly sweet	Characteristic	14.49
30-MSPS	Brown	Slightly sweet	Characteristic	19.62
40-MSPS	Brown	Sweet	Characteristic	23.61
PPS	Off white	Characteristic	Characteristic	2.90
5-MPPS	Off white	Characteristic	Characteristic	6.97
10-MPPS	Off white	Characteristic	Characteristic	10.13
20-MPPS	Brown	Slightly sweet	Characteristic	14.95
30-MPPS	Brown	Slightly sweet	Characteristic	20.86
40-MPPS	Brown	Sweet	Characteristic	25.22
APS	Off white	Characteristic	Characteristic	1.00
5-MAPS	Off white	Characteristic	Characteristic	5.05
10-MAPS	Off white	Characteristic	Characteristic	8.37

20-MAPS	Brown	Slightly sweet	Characteristic	14.11
30-MAPS	Brown	Slightly sweet	Characteristic	19.76
40-MAPS	Brown	Sweet	Characteristic	24.02

SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch). 5-MSPS, 10-MSPS, 20-MSPS, 30-MSPS and 40-MSPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of sweet potato starch respectively). 5-MPPS, 10-MPPS, 20-MPPS, 30-MPPS and 40-MPPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of pregelatinized sweet potato starch respectively). 5-MAPS, 10-MAPS, 20-MAPS, 30-MAPS and 40-MAPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of acid modified sweet potato starch respectively), WSI (water solubility index)

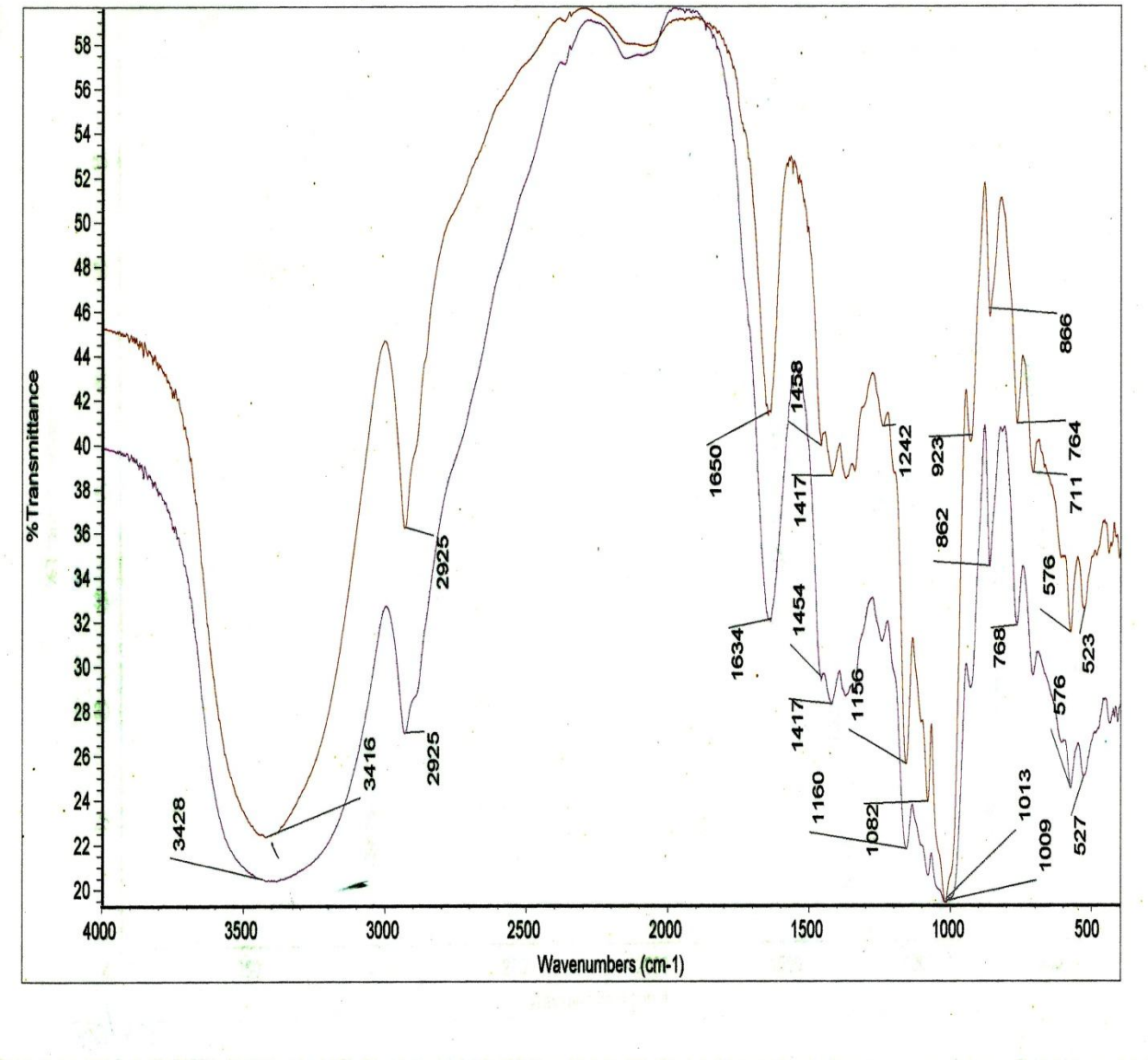


Fig.4.1: FTIR Spectra of SPS and MSPS

The result of FTIR spectra determination of SPS and MSPS as presented in Fig. 4.1 shows that there was no appearance or disappearance of peaks

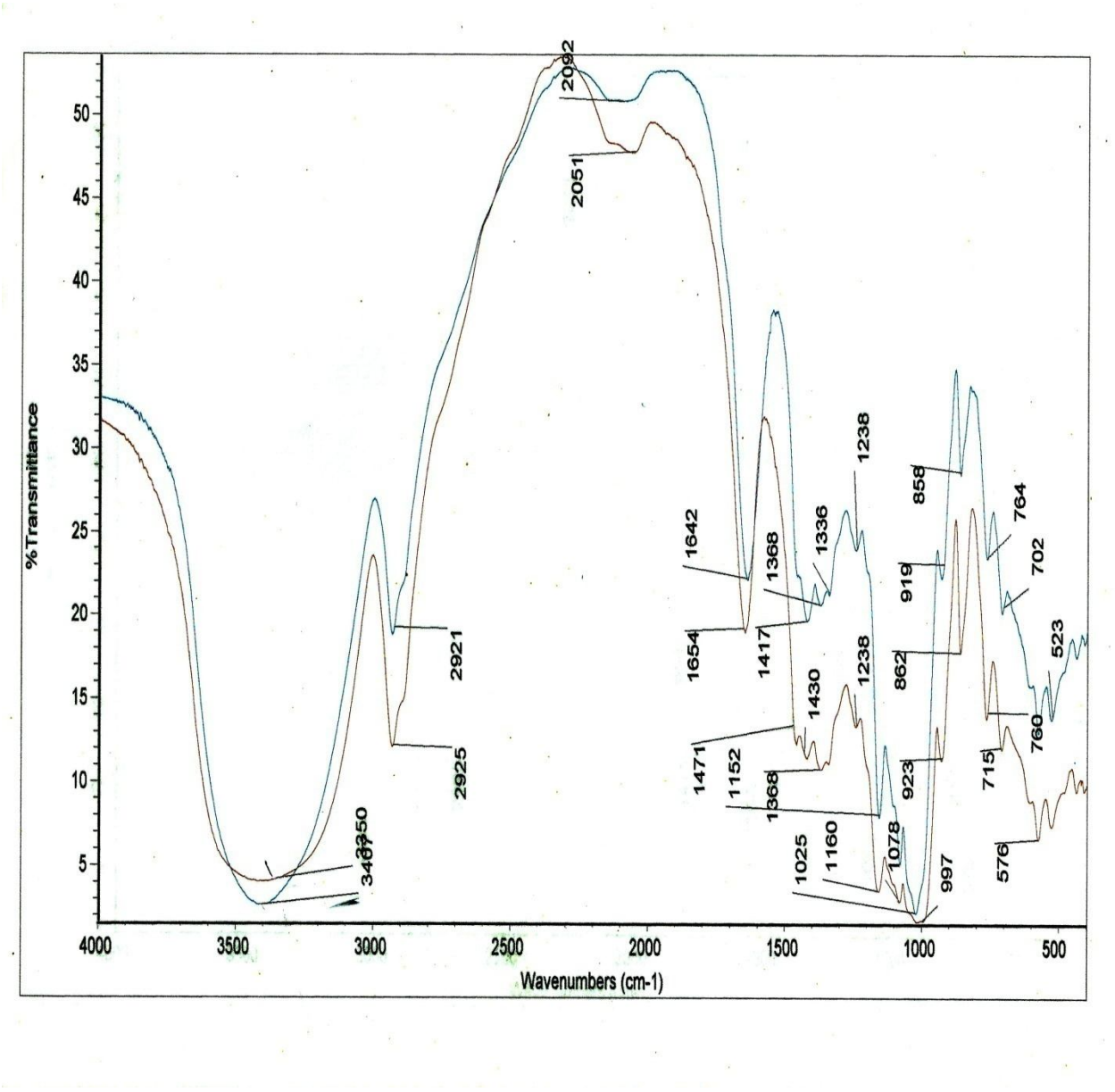


Fig. 4.2: FTIR Spectra of PPS and MPPS

The result of FTIR spectra determination of PPS and MPPS as presented in Fig. 4.2 shows that there was no appearance or disappearance of peaks

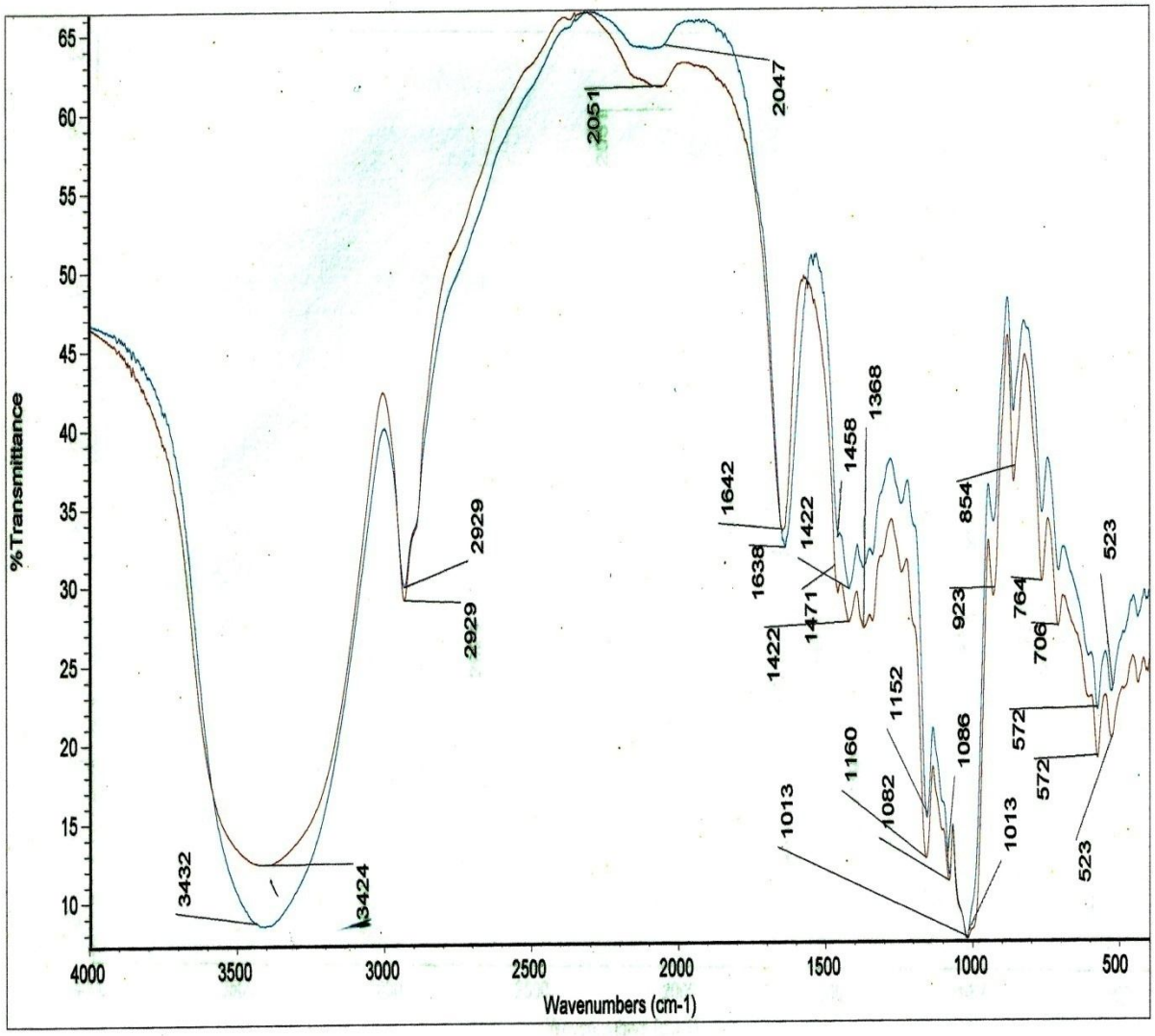


Fig. 4.3: FTIR Spectra of APS and MAPS

The result of FTIR spectra determination of APS and MAPS as presented in Fig. 4.3 shows that there was no appearance or disappearance of peaks

Table 4.3: Micromeritic Properties of Native Starch, Modified Starch and Dispersions of Modified Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	Moisture content (%)	Moisture sorption capacity (%)		True density (g/cm^2)	Ash value (%)	pH
		RH=75%	RH= 100%			
SPS	12.0 (0.5)	2.5 (0.5)	24.5 (0.3)	1.32 (0.12)	0.51 (0.02)	6.85
5-MSPS	6.0 (0.9)	4.5 (0.3)	34.5 (0.2)	1.41 (0.20)	0.50 (0.11)	6.69
10-MSPS	6.5 (1.2)	5.0 (0.3)	33.5 (0.2)	1.48 (0.08)	0.58 (0.08)	6.29
20-MSPS	5.0 (1.1)	6.5 (0.3)	43.5 (0.2)	1.54 (0.12)	0.56 (0.12)	6.26
30-MSPS	5.0 (0.9)	7.0 (0.2)	54.5 (0.3)	1.56 (0.06)	0.56 (0.02)	6.30
40-MSPS	5.0 (0.9)	9.0 (0.3)	59.5 (0.2)	1.56 (0.08)	0.59 (0.04)	6.21
PPS	5.0 (0.2)	7.0 (0.1)	30.0 (0.3)	1.48 (0.11)	0.58 (0.10)	6.82
5-MPPS	5.0 (0.4)	5.5 (0.2)	33.0 (0.2)	1.54 (0.12)	0.50 (0.08)	6.21
10-MPPS	5.0 (0.2)	5.0 (0.2)	34.5 (0.4)	1.54 (0.08)	0.51 (0.12)	6.14
20-MPPS	5.0 (0.6)	7.0 (0.2)	46.5 (0.3)	1.54 (0.14)	0.47 (0.06)	5.93
30-MPPS	5.0 (0.1)	8.0 (0.1)	56.0 (0.3)	1.59 (0.02)	0.54 (0.11)	5.79
40-MPPS	5.0 (0.3)	10.0 (0.1)	61.5 (0.2)	1.59 (0.10)	0.45 (0.14)	5.37
APS	7.5 (0.2)	6.5 (0.1)	25.5 (0.3)	1.56 (0.10)	0.53 (0.08)	6.85
5-MAPS	5.5 (0.2)	6.0 (0.5)	31.0 (0.2)	1.65 (0.14)	0.50 (0.12)	6.66
10-MAPS	5.5 (0.2)	6.0 (0.6)	35.5 (0.2)	1.65 (0.08)	0.50 (0.10)	6.29

20-MAPS	6.0	(0.2)	7.5 (0.5)	43.5 (0.2)	1.72 (0.12)	0.48 (0.14)	6.00
30-MAPS	6.0	(0.5)	9.5 (0.2)	54.0 (0.3)	1.79 (0.20)	0.49 (0.08)	5.81
40-MAPS	5.5	(0.2)	10.5 (0.4)	60.0 (0.1)	1.79 (0.02)	0.52 (0.11)	5.70

Value is mean and standard deviation is in parenthesis, number of replicate = 3, SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch). 5-MSPS, 10-MSPS, 20-MSPS, 30-MSPS and 40-MSPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of sweet potato starch respectively). 5-MPPS, 10-MPPS, 20-MPPS, 30-MPPS and 40-MPPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of pregelatinized sweet potato starch respectively). 5-MAPS, 10-MAPS, 20-MAPS, 30-MAPS and 40-MAPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of acid modified sweet potato starch respectively)

As seen in Table 4.3 There was an increase in moisture sorption capacity and true density with a decrease in moisture content and pH with increased mucilage concentration. Moisture content and ash value were all below 15 % and 0.6 % as stipulated for starches in the British Pharmacopoeia (2012)

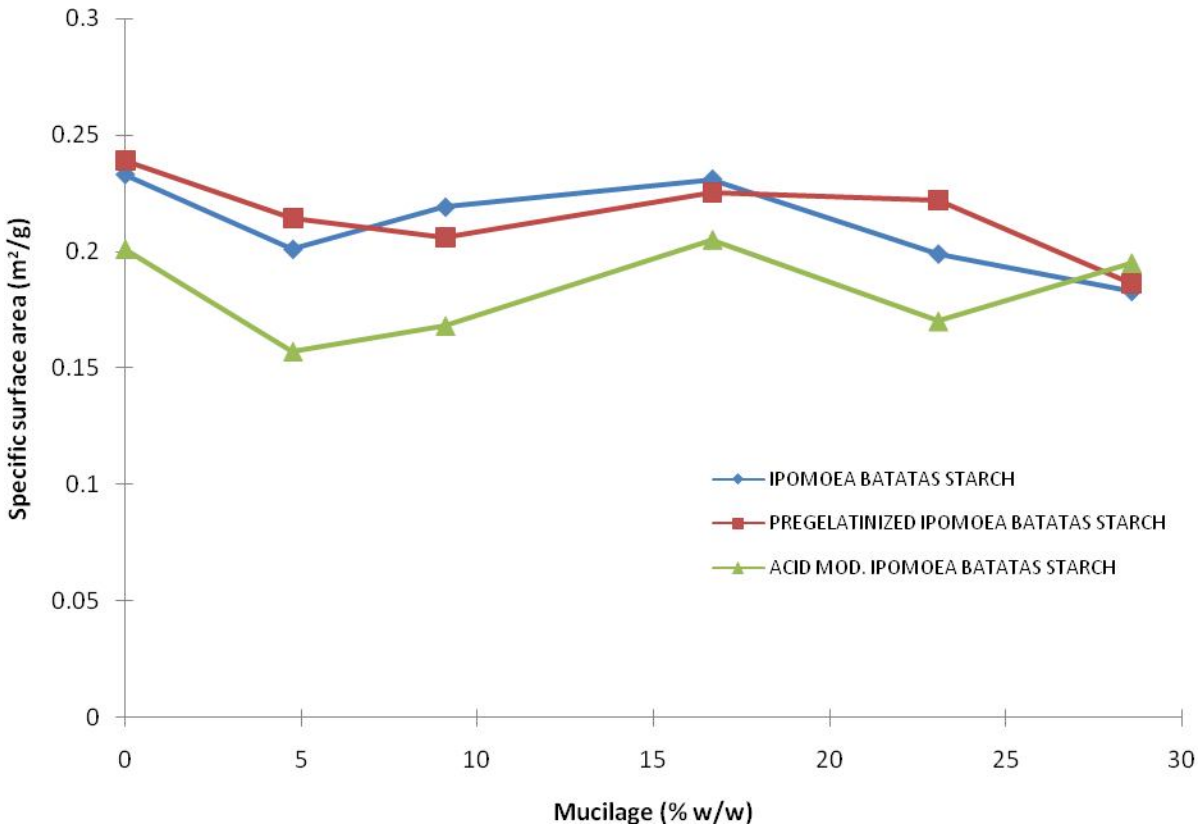


Fig. 4.4: Graph of Specific Surface Area (m^2/g) Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

Native and pregelatinized starches had higher specific surface area as compared to acid modified starch. Dispersions of all starches in mucilage showed an initial decrease in specific surface area followed by an increment as the mucilage concentration increases.

Table 4.4: Particle Properties of Starch and Dispersions of Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	SPS	5-MSPS	10-MSPS	20-MSPS	30-MSPS	40-MSPS
D[4,3] (μm)	53.45[a] (1.23)	105.37[b] (4.22)	82.65[c] (6.13)	103.31[b] (2.03)	138.84[d] (7.70)	160.80[d] (13.92)
D[3,2] (μm)	19.45[a] (0.13)	21.21[b] (0.28)	18.52[a] (0.29)	16.86[c] (0.18)	19.32[a] (0.54)	21.02[b] (0.72)
D[v, 0.1] (μm)	11.55[a] (0.05)	11.78[a] (0.06)	11.11[a] (0.07)	9.81[b] (0.04)	10.34[b] (0.12)	10.88[b] (0.29)
D[v, 0.5] (μm)	28.31[a] (0.23)	33.00b (0.84)	26.08[c] (0.40)	25.96[c] (0.28)	36.90[d] (2.58)	55.74[e] (12.20)
D[v, 0.9] (μm)	137.69[a] (3.52)	314.39[b] (14.99)	262.22[c] (21.81)	333.71[b] (7.13)	407.88[d] (19.54)	448.07[d] (32.46)

Value is mean and standard deviation is in parenthesis, number of replicate = 3, a–e Means with different letters within the same row differed significantly ($p < 0.05$)

Table 4.5: Particle Properties of Pregelatinized Starch and Dispersions of Pregelatinized Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	PPS	5-MPPS	10-MPPS	20-MPPS	30-MPPS	40-MPPS
D[4,3] (μm)	80.19[a] (0.25)	103.33[b] (4.60)	103.05[b] (0.96)	111.67 (8.35)	110.09 (12.20)	156.80 (3.43)
D[3,2] (μm)	17.01[a] (0.45)	18.23[a] (0.48)	18.87[a] (0.19)	17.36[a] (0.45)	17.05[a] (0.46)	20.29 (0.21)
D[v, 0.1] (μm)	10.26[a] (0.08)	10.41[a] (0.08)	10.96[a] (0.03)	9.86[a] (0.13)	9.27[a] (0.10)	10.12[a] (0.10)
D[v, 0.5] (μm)	26.24[a] (0.61)	28.36[a] (0.55)	27.83[a] (0.43)	28.10[a] (1.16)	32.40[b] (1.81)	77.68[c] (4.69)
D[v, 0.9] (μm)	253.30[a]	317.75[b]	321.92[b]	344.82[b]	326.54[b]	417.63[c]

(26.61)	(11.31)	(3.95)	(25.10)	(35.76)	(7.95)

Value is mean and standard deviation is in parenthesis, number of replicate = 3, a–d Means with different letters within the same row differed significantly ($p < 0.05$)

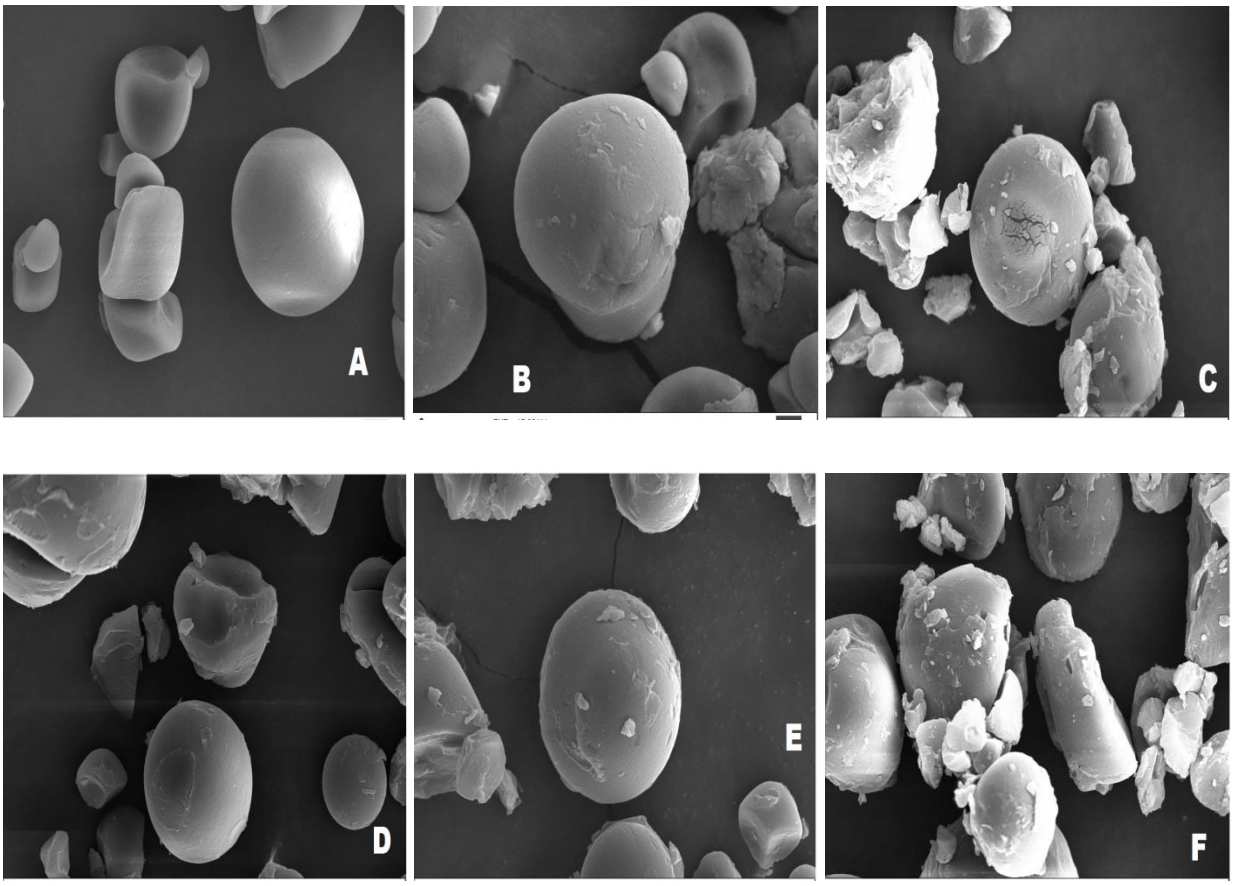
Table 4.6: Particle Properties of Acid Modified Starch and Dispersions of Acid Modified Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	APS	5-MAPS	10-MAPS	20-MAPS	30-MAPS	40-MAPS
D[4,3] (μm)	77.08^{a} (7.62)	152.20^{b} (6.01)	153.71^{b} (9.91)	108.09 (0.69)	142.65^{b} (9.20)	123.35 (6.65)
D[3,2] (μm)	19.15^{a} (0.23)	23.15^{b} (0.44)	21.68^{b} (0.81)	17.02^{a} (0.10)	19.80^{a} (0.57)	17.17^{a} (0.18)
D[v, 0.1] (μm)	11.37^{a} (0.05)	11.48^{a} (0.13)	10.88^{a} (0.21)	9.53^{b} (0.03)	10.04^{a} (0.16)	9.09^{b} (0.03)
D[v, 0.5] (μm)	27.30^{a} (0.42)	55.72^{b} (3.40)	50.03^{b} (9.30)	30.78^{a} (0.66)	55.78^{b} (6.63)	39.35^{c} (1.46)
D[v, 0.9] (μm)	232.87^{a} (25.37)	421.72^{b} (18.07)	435.63^{b} (22.73)	323.61^{c} (3.25)	391.86^{c} (24.24)	354.98^{c} (19.91)

Value is mean and standard deviation is in parenthesis, number of replicate = 3, a–d Means with different letters within the same row differed significantly ($p < 0.05$)

Particle size analysis showed that the surface area mean diameter, D [3,2], mass median diameter D [v, 0.5] and particles less than 10 % D [v, 0.1] for native, pregelatinized and acid modified starches were in the order, native starch > acid modified starch > pregelatinized starch while the volume mean diameter D [4,3], and particles less than 90 % D [v, 0.9] were in the order pregelatinized starch > acid modified starch > native starch. Generally, there was a slight

increase in D [4,3], D [v, 0.5] and D [v, 0.9] with a decrease in D [v, 0.1] as the mucilage ratio increased with all samples as seen in Table 4.4 - 4.6



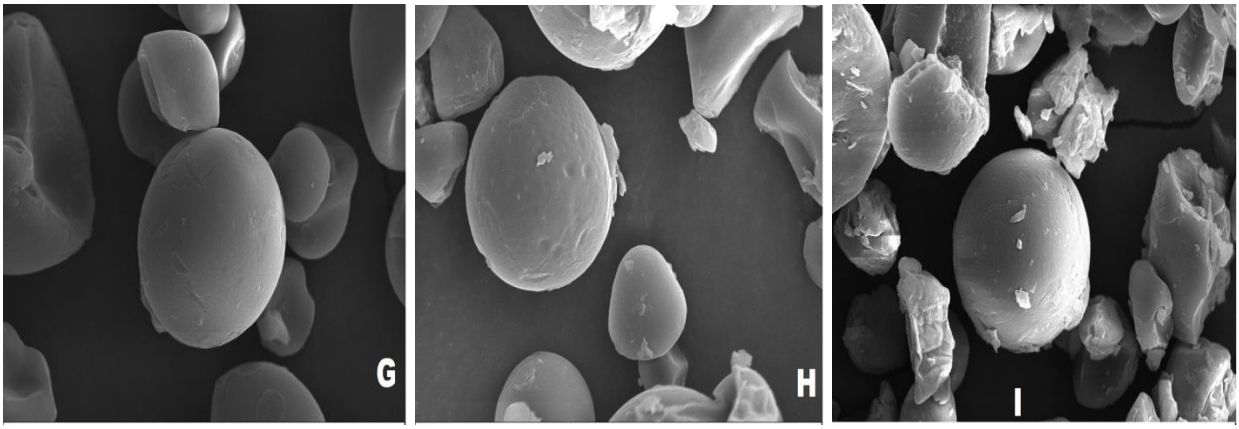


Fig. 4.5: Scanning Electron Micrographs of SPS (A), 10-MSPS (B), 30-MSPS (C), PPS (D), 10 MPPS (E), 30-MPPS (F), APS (G), 10-MAPS (H) and 30-MAPS (I). [Magnification = 2.00 KX]

All starch samples appeared round, spherical or irregular in shape and also increased in mucilage aggregate as the mucilage concentration increased (Fig. 4.5).

Table 4.7: Micromeritic Properties of Starch, Modified Starches and Dispersions of Native and Modified Starch in Mucilage obtained from *Ipomoea batatas*

Parameters	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's index
SPS	0.51 (0.04)	0.73 (0.01)	30.40	1.44
5-MSPS	0.52 (0.03)	0.75 (0.01)	30.67	1.44
10-MSPS	0.54 (0.04)	0.77 (0.02)	29.87	1.43
20-MSPS	0.57 (0.02)	0.80 (0.01)	28.75	1.40
30-MSPS	0.61 (0.03)	0.83 (0.02)	26.51	1.36
40-MSPS	0.61 (0.02)	0.83 (0.01)	26.51	1.36
PPS	0.56 (0.02)	0.77 (0.01)	27.27	1.38
5-MPPS	0.63 (0.01)	0.83 (0.01)	24.10	1.32
10-MPPS	0.63 (0.01)	0.83 (0.01)	24.10	1.32

20-MPPS	0.63 (0.01)	0.83 (0.01)	24.10	1.32
30-MPPS	0.67 (0.01)	0.83 (0.01)	19.93	1.25
40-MPPS	0.67 (0.01)	0.83 (0.01)	19.93	1.25
APS	0.54 (0.01)	0.72 (0.01)	25.00	1.33
5-MAPS	0.59 (0.01)	0.77 (0.01)	23.38	1.31
10-MAPS	0.59 (0.01)	0.77 (0.01)	23.38	1.31
20-MAPS	0.61 (0.01)	0.78 (0.01)	21.80	1.28
30-MAPS	0.63 (0.01)	0.80 (0.01)	21.25	1.27
40-MAPS	0.63 (0.01)	0.80 (0.01)	21.25	1.27

Value is mean and standard deviation is in parenthesis, number of replicate = 3

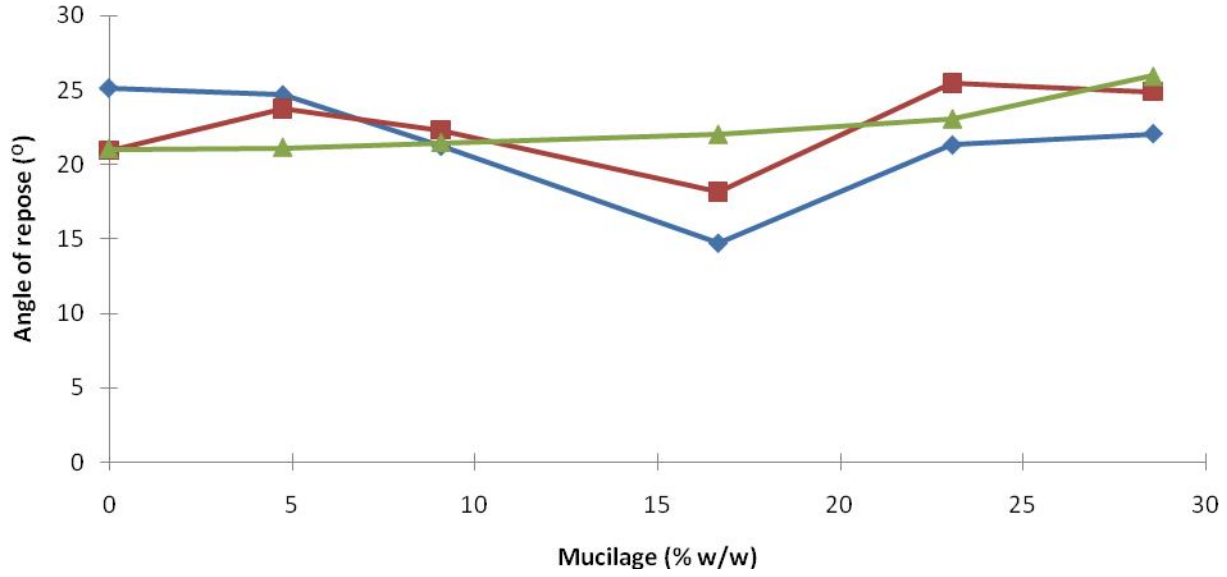


Fig.4.6: Graph of Angle of Repose (^{O}) Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

The angle of repose for native starch, pregelatinized starch and acid modified starch were in the order native starch > pregelatinized starch > acid modified starch. This trend was also reflected with their dispersions in mucilage. At higher mucilage concentration, there was no significant difference in the angle of repose. Generally, angle of repose decreases with increase mucilage concentration

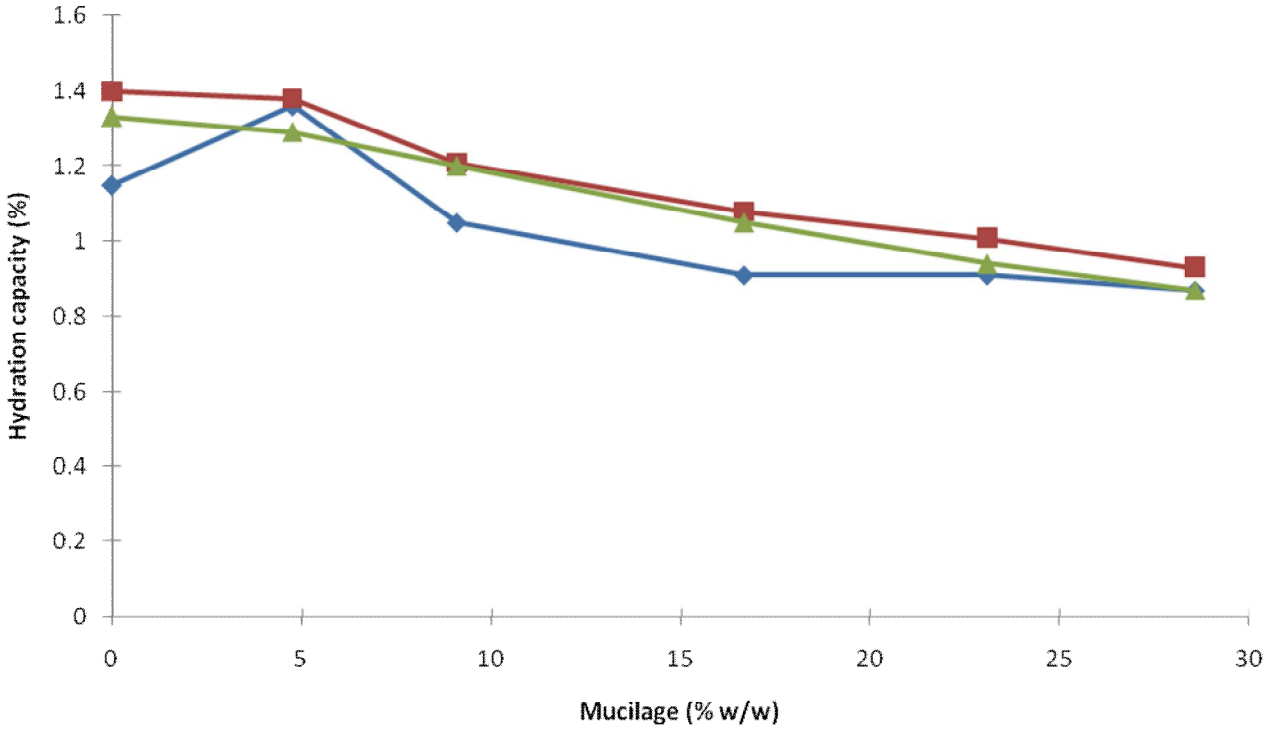


Fig.4.7: Graph of Hydration Capacity (%) Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

The hydration capacity for native starch, pregelatinized starch and acid modified starch were in the order pregelatinized starch > acid modified starch > native starch. This trend was also reflected with their dispersions in mucilage. At higher mucilage concentration, there was no

significant difference in the hydration capacity. Hydration capacity decreased with increase in mucilage concentration

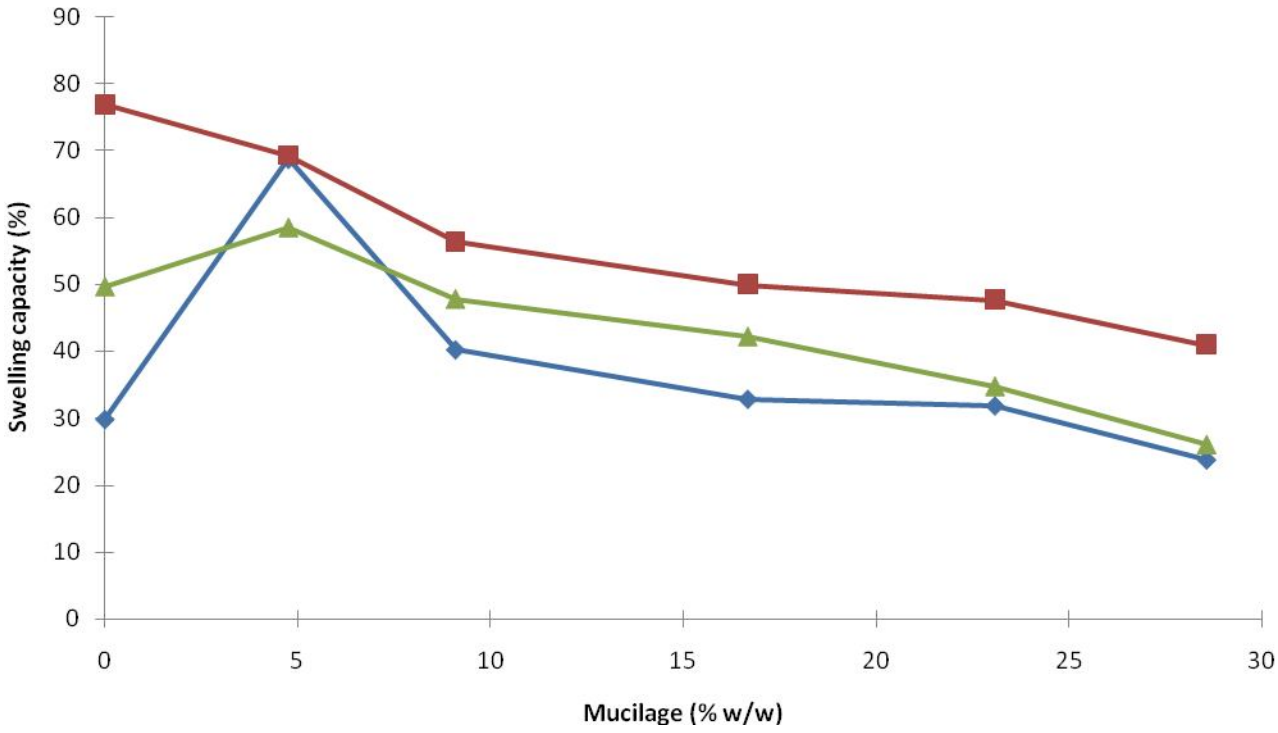


Fig. 4.8: Graph of Swelling Capacity (%) Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

The swelling capacity for native starch, pregelatinized starch and acid modified starch were in the order pregelatinized starch > acid modified starch > native starch. This trend was also reflected with their dispersions in mucilage. Swelling capacity decreased with increase in mucilage concentration

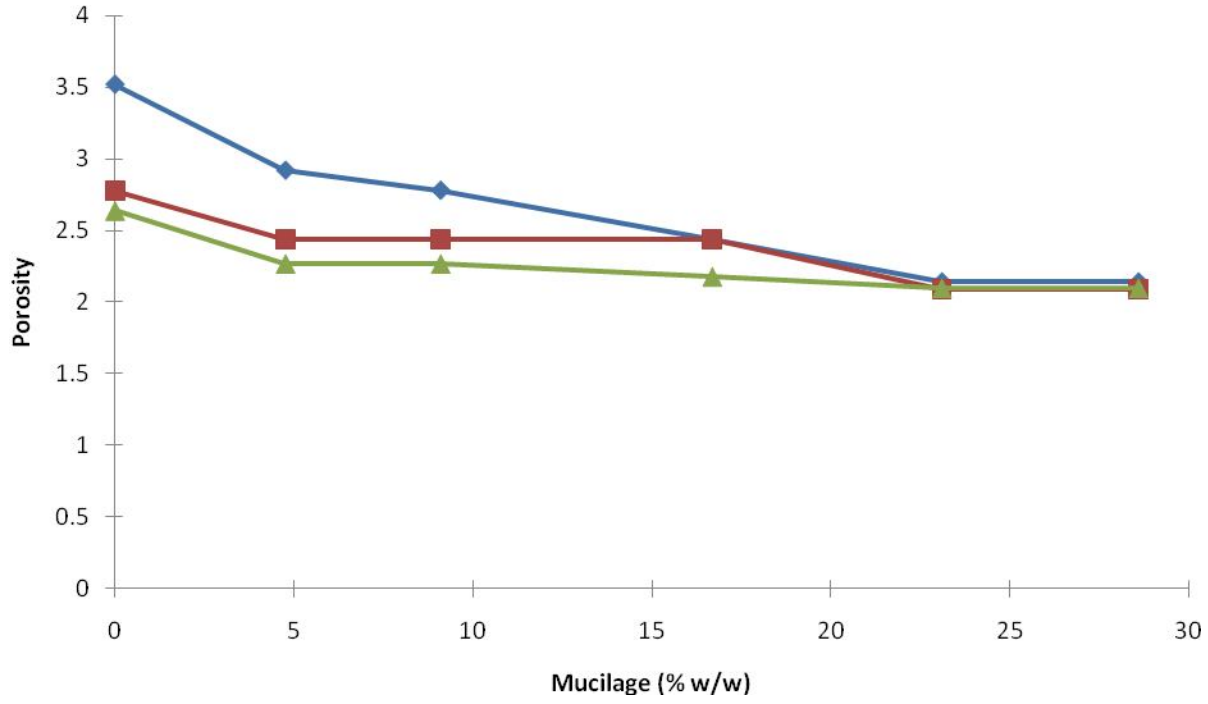


Fig. 4.9: Graph of Porosity Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

The porosity for native starch, pregelatinized starch and acid modified starch were in the order native starch > pregelatinized starch > acid modified starch. This trend was also reflected with their dispersions in mucilage. At higher mucilage concentration, there was no significant difference in the porosity of the starches. Generally, porosity decreased with increased percentage mucilage up to 20 % then remained constant after ward

Table 4.8: Pasting Properties of Native Starch and Dispersions of Native Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	SPS	5-MSPS	10-MSPS	20-MSPS	30-MSPS	40-MSPS
Trough 1	204.33^{a}	137.17^{b}	119.5^{c}	97.5^{d}	85.33^{e}	70.17^{f}
Breakdown	103.5^{a}	39.58^{b}	33.58^{c}	20.00^{d}	8.67^{e}	4.83^{f}
Final viscosity	277.33^{a}	175.33^{b}	142.5^{c}	119.5^{d}	104.0^{e}	82.08^{f}
Setback	73.0^{a}	38.17^{b}	23.0^{c}	22.0^{c}	18.67^{d}	11.92^{e}
Peak time	4.72^{a}	5.18^{b}	5.38^{b}	5.52^{b}	5.78^{b}	6.12^{c}
Pasting temperature	78.95^{a}	84.75^{b}	85.55^{b}	85.80^{b}	86.35^{b}	89.55^{c}

Value is mean, number of replicate = 3, a–f Means with different letters within the same row differed significantly ($p < 0.05$)

Table 4.9: Pasting Properties of Pregelatinized Starch and Dispersions of Pregelatinized Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	PPS	5-MPPS	10-MPPS	20-MPPS	30-MPPS	40-MPPS

Trough 1	185.08[a]	133.75[b]	110.42[c]	86.92[d]	64.25[e]	49.58[f]
Breakdown	43.42[a]	16.75[b]	13.92[c]	9.08[d]	2.5[e]	1.92[f]
Final viscosity	276.5[a]	171.08[b]	140.25[c]	104.83[d]	75.67[e]	60.0[f]
Setback	91.42[a]	37.33[b]	29.83[c]	17.92[d]	11.42[e]	10.42[f]
Peak time	5.25[a]	5.58[a]	5.72[b]	5.92[b]	6.32[c]	6.92[c]
Pasting temperature	82.30[a]	84.00[b]	84.75[b]	84.80[b]	84.80[b]	87.95[c]

Value is mean, number of replicate = 3, a–f Means with different letters within the same row differed significantly ($p < 0.05$)

Table 4.10: Pasting Properties of Acid Modified Starch and Dispersions of Acid Modified Starch and Mucilage obtained from *Ipomoea batatas*

Parameters	APS	5-MAPS	10-MAPS	20-MAPS	30-MAPS	40-MAPS
Trough 1	8.67[a]	8.67[a]	7.42[b]	6.17[c]	5.83[d]	5.08[d]
Breakdown	10.83[a]	9.92[b]	9.42[b]	7.67[c]	5.08[d]	3.58[e]
Final viscosity	111.58[a]	12.08[b]	10.25[c]	8.75[d]	7.17[e]	7.33[e]
Setback	2.92[a]	3.42[b]	2.83[a]	2.58[a]	1.33[c]	2.25[a]
Peak time	4.45[a]	4.58[a]	4.52[a]	4.58[a]	4.45[a]	4.38[a]
Pasting temperature	87.15[a]	87.95[a]	88.80[a]	88.05[a]	88.00[a]	88.00[a]

Value is mean, number of replicate = 3, a–f Means with different letters within the same row differed significantly ($p < 0.05$)

The RVA results as seen in Table 4.8 – 4.10 shows that SPS have a trough, breakdown and final viscosity as compared to pregelatinized and acid modified starch in the order SPS > PPS > APS. This trend was also seen with the various dispersions in mucilage with a decrease in trough, breakdown and final viscosity as the mucilage concentration increased. The pasting temperature was higher with acid modification as compared with native and pregelatinized starch in the order: acid modified > pregelatinized starch > native starch. Similar trends were seen with their various dispersions which increased with increase in mucilage concentration. The set back and peak time were in the order: pregelatinized starch > native starch > acid modified starch, and also with their dispersions which decreased with increase in mucilage concentration and increased with increased mucilage concentration respectively in the same order.

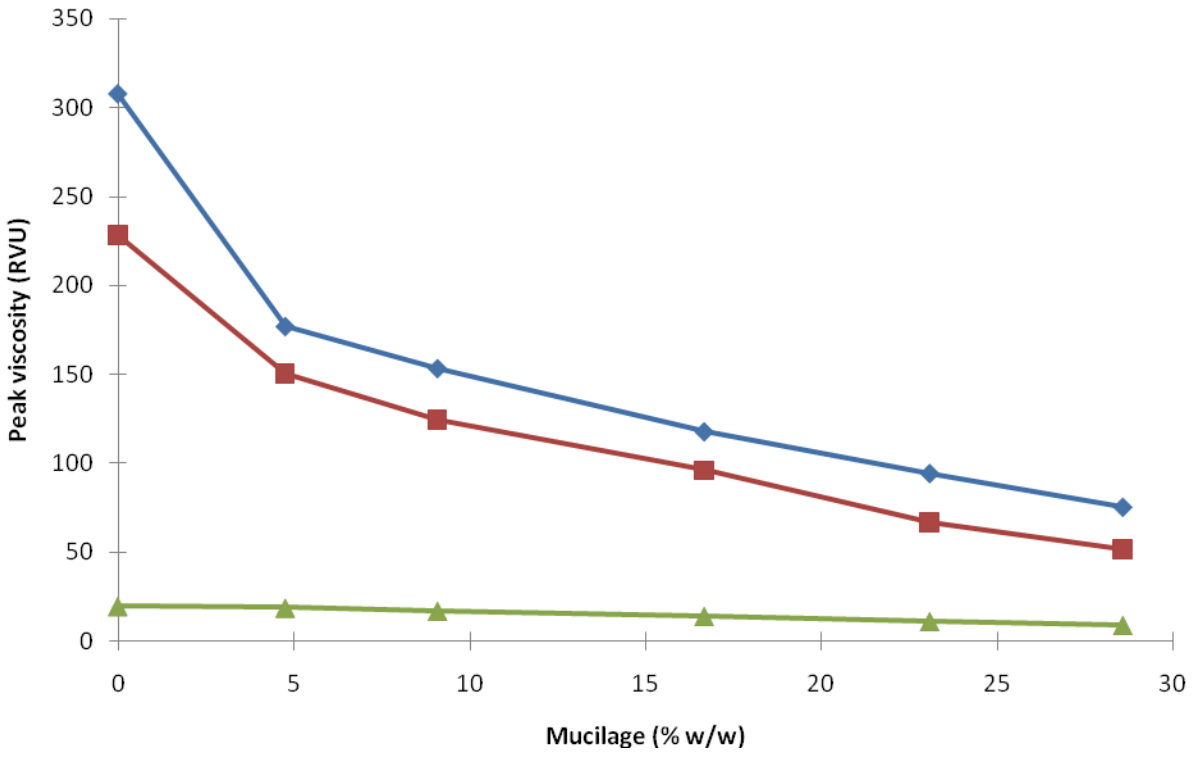


Fig.4.10: Graph of Peak Viscosity (RVU) Vs % w/w Mucilage of Native and Modified Starches with their Dispersions obtained from *Ipomoea batatas*

The peak viscosities of native starch, pregelatinized starch and acid modified starch are in the order: native starch > pregelatinized starch > acid modified starch. This trend was also reflected with their dispersions in mucilage with decrease viscosity as the mucilage concentration increased.

Table 4.11: Effect of Mucilage on the Thermal Properties of Starch and Modified Starches obtained from *Ipomoea batatas*

Parameters	To	Tp	Tc	Tc - To	ΔH (J/g)
SPS	67.81 (1.23)	77.37 (0.67)	83.45 (1.22)	15.64	6.79 (0.68)
5-MSPS	70.16 (0.46)	78.51 (0.34)	85.65 (0.82)	15.49	6.81 (1.01)
10-MSPS	72.90 (0.86)	84.65 (1.06)	88.40 (0.56)	15.50	6.86 (0.86)
20-MSPS	71.02 (0.45)	81.66 (0.86)	86.55 (0.76)	15.53	8.10 (0.14)
30-MSPS	63.06 (1.08)	78.91 (0.24)	77.67 (0.54)	14.61	9.31 (0.88)
40-MSPS	55.82 (0.66)	66.45 (1.68)	69.36 (1.06)	13.54	9.35 (2.06)
PPS	75.45 (0.56)	80.49 (1.08)	84.15 (0.67)	8.70	5.53 (0.45)
5-MPPS	77.67 (2.07)	82.62 (2.08)	86.07 (0.88)	8.40	6.78 (0.33)
10-MPPS	77.20 (1.86)	82.21 (1.88)	85.25 (0.82)	8.05	6.81 (1.08)
20-MPPS	76.25 (0.64)	81.94 (0.82)	85.99 (1.52)	9.74	6.93 (1.55)
30-MPPS	74.36 (0.66)	77.25 (2.98)	80.52 (0.16)	6.16	6.84 (0.42)
40-MPPS	71.94 (0.89)	71.74 (0.46)	74.76 (1.22)	2.82	9.01 (0.81)
APS	80.83 (0.92)	81.63 (2.02)	84.43 (0.65)	3.60	5.21 (0.22)
5-MAPS	78.97 (0.45)	85.29 (1.08)	89.15 (0.82)	10.18	6.55 (0.67)
10-MAPS	78.89 (1.08)	85.81 (2.74)	91.89 (0.92)	13.00	6.73 (0.92)
20-MAPS	77.68 (1.22)	82.38 (1.22)	84.82 (1.86)	7.14	8.39 (1.86)
30-MAPS	77.46 (1.69)	84.53 (0.12)	85.45 (2.28)	7.99	8.42 (0.74)
40-MAPS	81.18 (0.92)	85.99 (1.66)	88.53 (0.18)	7.35	8.92 (1.36)

To, Tp, Tc, and DH are onset temperature, peak temperature, conclusion temperature, and enthalpy change, respectively. Value is mean and standard deviation is in parenthesis, number of replicate = 3, SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch). 5-MSPS, 10-MSPS, 20-MSPS, 30-MSPS and 40-MSPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of sweet potato starch respectively). 5-MPPS, 10-MPPS, 20-MPPS, 30-MPPS and 40-MPPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of pregelatinized sweet potato starch respectively). 5-MAPS, 10-MAPS, 20-MAPS, 30-MAPS and 40-

MAPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of acid modified sweet potato starch respectively)

The thermal properties shown in Table 4.11 shows that the addition of mucilage caused marked increase in the onset temperature for the tested starches. The enthalpy changes for native and modified starches were in the order: SPS > PPS > APS. This trend was also seen with their dispersion in mucilage with an increase in ΔH as the mucilage concentration increased. The onset of temperature, peak temperature, conclusion temperature and temperature range were in the order: APS > PPS > SPS. For both native and pregelatinized starches, there was an initial increase in the onset temperature, peak temperature and conclusion temperature at lower concentrations of mucilage followed by a reduction at higher concentrations as compared to acid modification, which showed a decrease in the onset temperature with increase in mucilage concentrations.

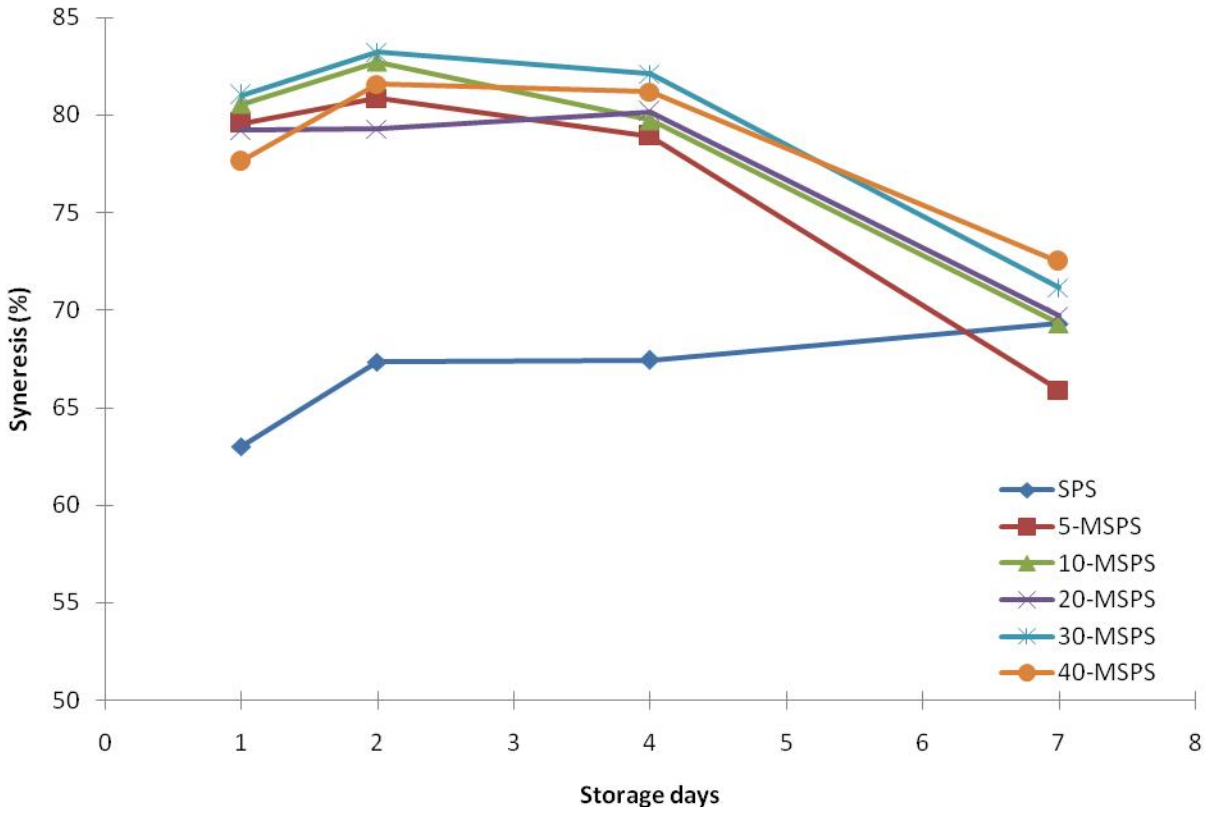


Fig. 4.11: Graph of Syneresis (%) Vs Storage Days on the Retrogradative Property of Native Starches and their Dispersions in Mucilage obtained from *Ipomoea batatas*

The result of syneresis determination as presented in Fig. 4.11 shows that syneresis for the native starch increased with storage days, while native starch dispersions increased up to day 2, and then decreased with storage days. Generally, there was an increase in syneresis with increase in mucilage concentration

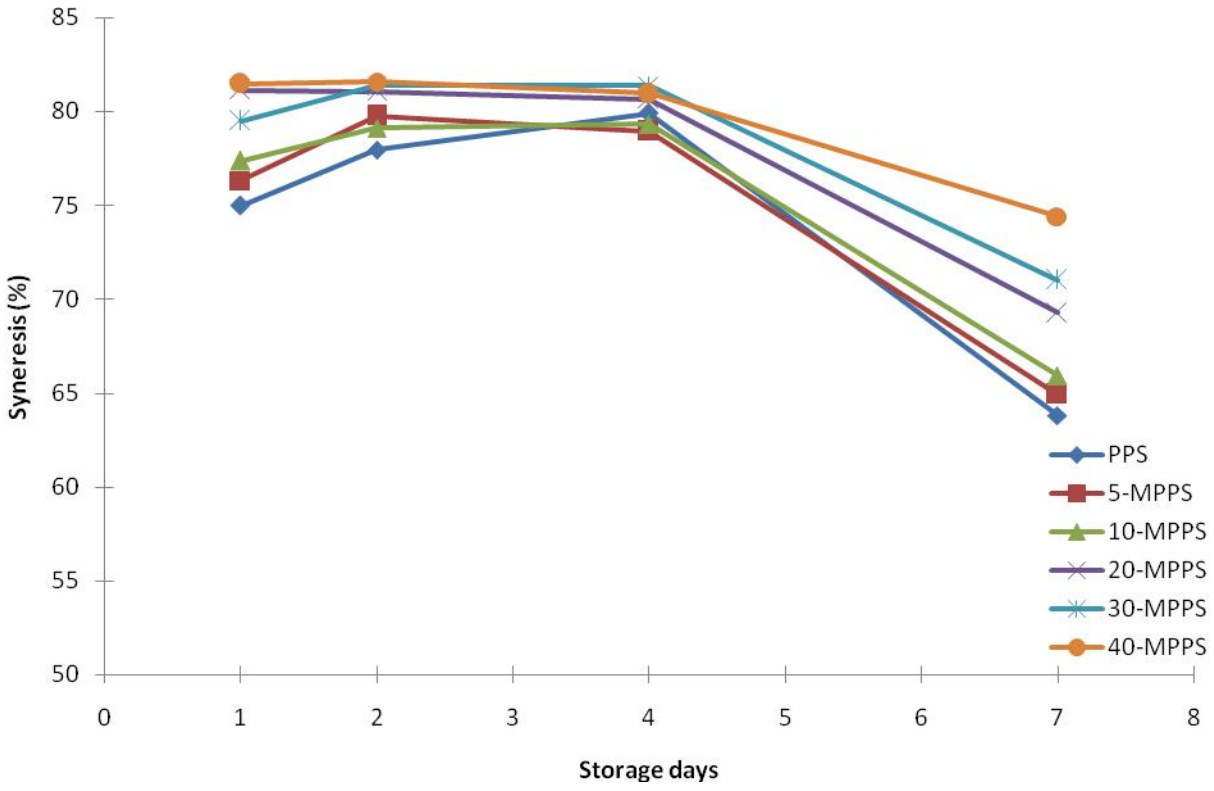


Fig. 4.12: Graph of Syneresis (%) Vs Storage Days on the Retrogradative Property of Pregelatinized Starches and their Dispersions in Mucilage obtained from *Ipomoea batatas*

The result of syneresis determination as presented in Fig. 4.12 shows that syneresis for pregelatinized starch and its dispersions decreased with storage days. Generally, there was an increase in syneresis with increase in mucilage concentration

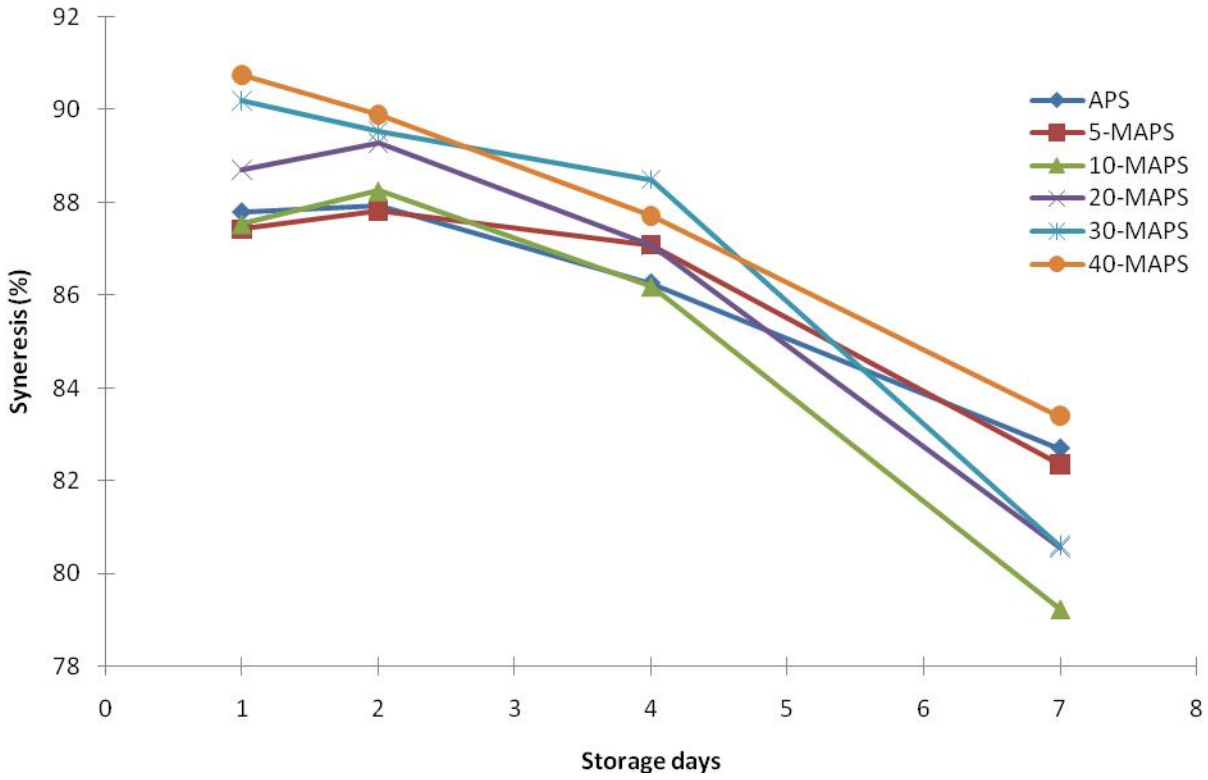


Fig. 4.13: Graph of Syneresis (%) Vs Storage Days on the Retrogradative Property of Acid Modified Starches and their Dispersions in Mucilage obtained from *Ipomoea batatas*

The result of syneresis determination as presented in Fig. 4.13 shows that syneresis for acid modified starch and its dispersions decreased with storage days. Generally, there was an increase in syneresis with increase in mucilage concentration

Table 4.12: Tableting Properties of Compacts (Placeboes) of Native Starch and Dispersions of Native Starch and Mucilage obtained from *Ipomoea batatas*

Description	Pressure (M/Ton)	Wt.uniformity (%coefficient)	Relative density (g/cm^3)	Crushing strength (kg/F)	Disintegration (min.)	Friability (%)	Tensile strength (Kg/cm^2)
SPS	6	2.00	0.600	0.79 (0.11)	0.42 (0.70)	91.04 (1.26)	0.82 (0.11)
5-MSPS	4	2.00	0.531	0.36 (0.11)	0.69 (0.72)	90.32 (1.20)	0.35 (0.11)
	5	2.00	0.587	2.45 (0.17)	0.95 (0.74)	4.38 (0.86)	2.60 (0.17)
10-MSPS	4	5.00	0.504	0.29 (0.16)	0.91 (0.33)	90.14 (2.18)	0.28 (0.16)
	5	2.00	0.559	1.75 (0.23)	1.19 (0.05)	4.14 (1.81)	1.86 (0.23)
20-MSPS	3	5.00	0.477	1.05 (0.34)	3.30 (0.70)	6.40 (1.65)	1.03 (0.34)
	4	5.00	0.535	4.47 (0.66)	4.04 (0.69)	1.02 (0.65)	4.93 (0.66)
30-MSPS	3	7.00	0.501	1.77 (0.14)	6.42 (0.13)	0.98 (0.46)	1.80 (0.14)
	4	5.00	0.562	7.35 (1.09)	7.18 (1.24)	0.25 (0.34)	8.34 (1.09)

40-MSPS	3	7.00	0.501	1.44 (0.15)	8.31 (0.57)	17.77 (1.57)	1.43 (0.15)
	4	5.00	0.561	8.24 (0.33)	10.04 (0.78)	0.25 (0.64)	9.33 (0.33)

Value is mean and standard deviation is in parenthesis, number of replicate = 3, SPS (sweet potato starch), 5-MSPS, 10-MSPS, 20-MSPS, 30-MSPS and 40-MSPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of sweet potato starch respectively).

Table 4.13: Tableting Properties of Compacts (Placeboes) of Pregelatinized Starch and Dispersions of Pregelatinized Starch and Mucilage obtained from *Ipomoea batatas*

Description	Pressure (M/Tone)	Wt.uniformity (%coefficient)	Relative density (g/cm^3)	Crushing strength (kg/F)	Disintegration (min.)	Friability (%)	Tensile strength (Kg/cm^2)
PPS	3	4.22	0.479	0.63 (0.15)	0.95 (0.48)	100 (0.00)	0.78 (0.15)
	4	3.44	0.563	3.50 (0.37)	1.25 (0.06)	2.22 (1.45)	3.69 (0.37)
5-MPPS	3	1.49	0.533	4.05 (0.64)	2.64 (0.31)	1.01 (0.55)	4.52 (0.64)
	4	2.97	0.588	11.14 (0.49)	4.30 (0.08)	0.26 (0.12)	11.34 (0.49)
10-MPPS	3	3.05	0.522	2.49 (0.55)	3.80 (0.36)	0.95 (0.54)	2.86 (0.55)
	4	2.97	0.592	13.43 (1.02)	5.28 (0.62)	0.12 (0.32)	13.57 (1.02)
20-MPPS	3	3.42	0.531	2.33 (0.45)	6.49 (0.39)	0.48 (0.24)	2.62 (0.45)
	4	4.15	0.580	15.33 (0.85)	7.47 (0.28)	0.24 (0.11)	15.79 (0.85)
30-MPPS	3	4.78	0.503	3.85 (0.28)	11.86 (0.56)	0.25 (0.11)	4.57 (0.28)

	4	4.15	0.569	19.99	12.95	0.001	21.05
				(0.00)	(0.38)	(0.01)	(0.00)
40-MPPS	3	7.97	0.503	3.76	15.33	0.27	4.45
				(0.53)	(2.39)	(0.10)	(0.53)
	4	7.87	0.566	18.95	17.47	0.12	19.95
				0.38	(1.02)	(0.01)	0.38

Value is mean and standard deviation is in parenthesis, number of replicate = 3, PPS (pregelatinized sweet potato starch), 5-MPPS, 10-MPPS, 20-MPPS, 30-MPPS and 40-MPPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of pregelatinized sweet potato starch respectively).

Table 4.14: Tableting Properties of Compacts (Placeboes) of Acid Modified Starch and Dispersions of Acid Modified Starch and Mucilage obtained from *Ipomoea batatas*

Description	Pressure (M/Tone)	Wt.uniformity (%coefficient)	Relative density (g/cm^3)	Crushing strength (kg/F)	Disintegration (min.)	Friability (%)	Tensile strength (Kg/cm^2)
APS	4	2.14	0.491	1.08 (0.13)	0.63 (0.92)	76.02 (2.65)	1.30 (0.13)
5-MAPS	3	2.44	0.465	1.36 (0.18)	1.60 (0.33)	1.21 (1.36)	1.74 (0.18)
	4	2.44	0.528	9.67 (0.70)	3.93 (0.73)	0.99 (0.86)	10.90 (0.70)
10-MAPS	3	4.76	0.471	1.63 (0.29)	2.30 (0.08)	13.69 (1.12)	2.04 (0.29)
	4	1.95	0.528	8.57 (0.88)	4.48 (0.06)	0.98 (0.64)	9.64 (0.88)
20-MAPS	3	4.88	0.455	2.51 (0.40)	5.72 (0.68)	1.25 (0.84)	3.29 (0.40)
	4	2.44	0.526	15.42 (0.48)	8.21 (0.22)	0.25 (0.22)	17.57 (0.48)

30-MAPS	3	2.38	0.443	3.38 (0.28)	11.04 (0.47)	0.49 (0.12)	4.56 (0.28)
	4	5.00	0.499	19.99 (0.00)	11.45 (0.14)	0.02 (0.01)	23.91 (0.00)
40-MAPS	3	4.88	0.447	4.14 (0.44)	13.38 (0.68)	0.25 (0.14)	5.53 (0.44)
	4	4.88	0.503	19.99 (0.00)	14.71 (0.81)	0.02 (0.01)	23.88 (0.00)

Value is mean and standard deviation is in parenthesis, number of replicate = 3, APS (acid modified sweet potato starch), 5-MAPS, 10-MAPS, 20-MAPS, 30-MAPS and 40-MAPS (represents 5,10,20,30 and 40 grams of mucilage incorporated into 100 grams of acid modified sweet potato starch respectively)

Table 4.15: Tableting Properties of Compacts (Placeboes) of Mannitol and Microcrystalline cellulose

Description	Pressure (M/Tone)	Wt.uniformity (%coefficient)	Relative density (g/cm^3)	Crushing strength (kg/F)	Disintegration (min.)	Friability (%)	Tensile strength (Kg/cm^2)
Mannitol	4	4.21	0.543	0.55 (0.01)	0.33 (0.62)	81.41 (2.14)	0.60 (0.01)
MCC (PH 101)	9	2.35	0.450	3.57 (0.47)	2.23 (1.36)	0.26 (1.02)	3.05 (0.45)
	10	2.23	0.625	8.28 (0.56)	16.76 (10.36)	0.13 (0.54)	9.63 (0.50)

Value is mean and standard deviation is in parenthesis, number of replicate = 3

The results of tableting properties of compacts as seen in Table 4.12 – 4.15 shows that there was an improvement in crushing and tensile strength with starch modification in the order: PPS > APS > SPS, and decrease in disintegration time in the same order. Generally, native and modified starches dispersions showed an increase in disintegration time, crushing and tensile strength with a decrease in friability as the mucilage concentration increased. All batches of native and modified starches and their dispersions passed the disintegration test as stipulated by BP (2010) except 40-MPPS. All modified starches dispersions showed good crushing strength (above 4 KgF) and friability (below 1 %), while native starch dispersions showed good crushing strength and friability for batches 30-MSPS and 40-MSPS. In comparison to mannitol and microcrystalline cellulose, modified starches dispersions showed a better tableting property.

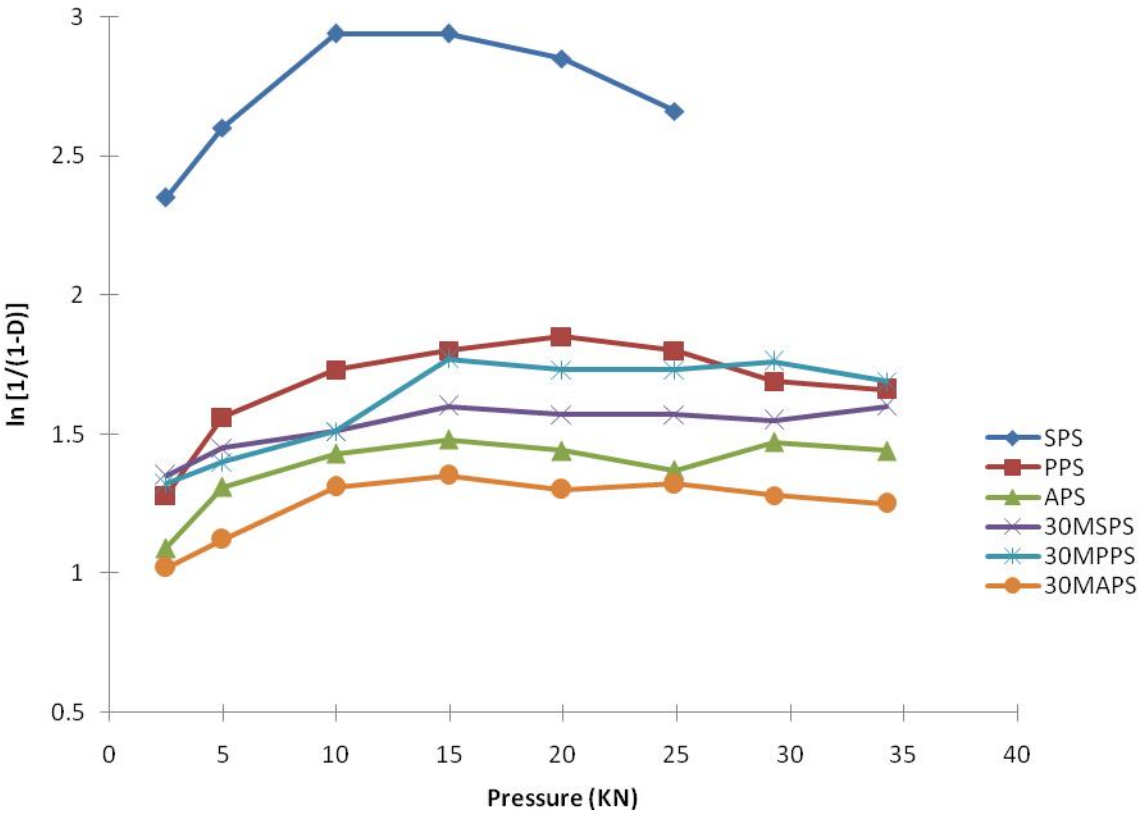


Fig. 4.14: Heckel Plots of ln [1/(1-D)] Vs Pressure (KN) for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

The result of Heckel plot as presented in Fig. 4.14 shows the effect of compaction pressures on the relative densities of optimized native and modified starches dispersions in mucilage in comparison to their parent forms. The order of reduction in relative density was SPS > PPS > APS. This trend was also seen with their dispersions.

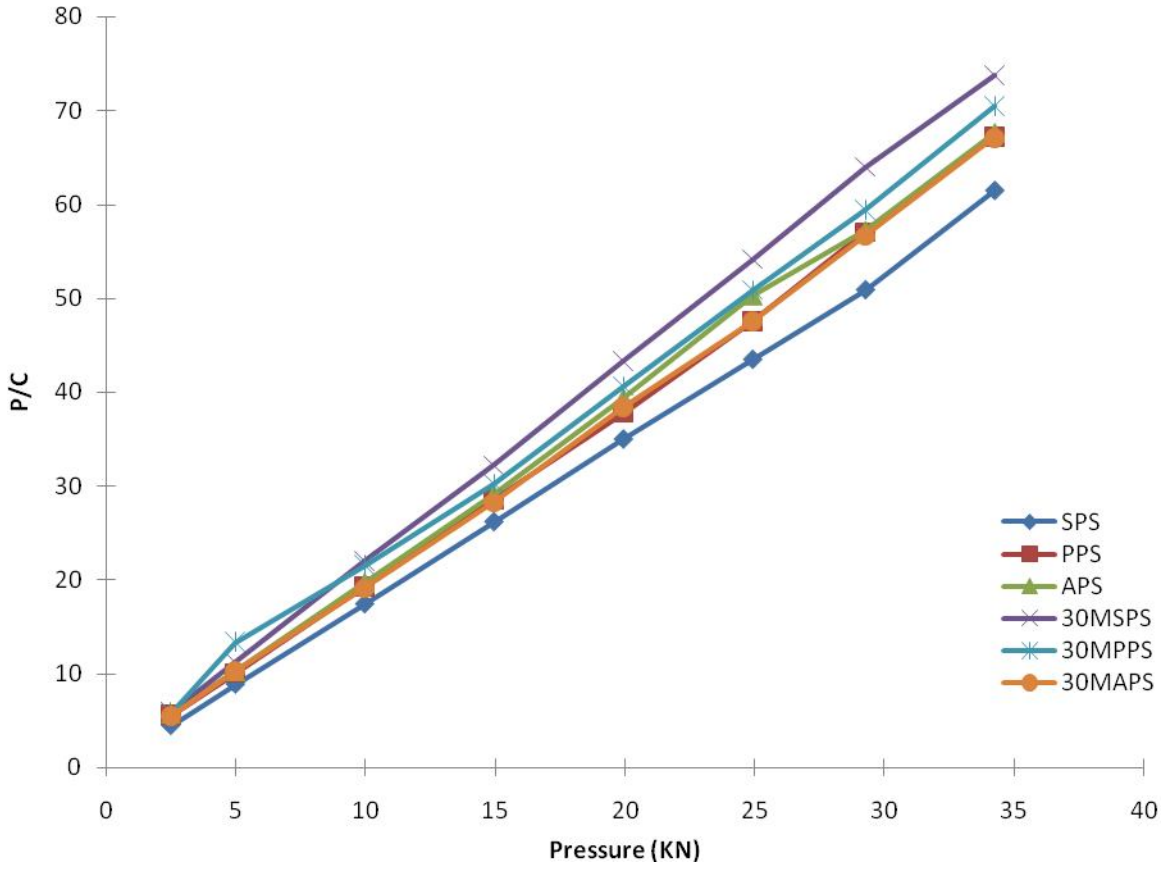


Fig. 4.15: Kawakita Plots of P/C Vs Pressure (KN) for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

The result of Kawakita plot as presented in Fig. 4.15 shows the effect of compaction pressures on volume reduction of optimized native and modified starches dispersions in mucilage in

comparison to their parent forms. The order of reduction in volume was: PPS =APS > SPS, while for the dispersions, the order was: 30-MSPS > 30-MPPS > 30-MAPS.

Table 4.16: Heckel Parameters for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

Parameters	K	P_y (KN^{-1})	A	e^{-A}	D_o	D_A	D_B
SPS	0.0775	12.9	2.180	0.113	0.409	0.887	0.478
PPS	0.024	41.49	1.457	0.233	0.399	0.767	0.368
APS	0.017	58.48	1.237	0.290	0.378	0.710	0.332
30-MSPS	0.0186	53.76	1.327	0.265	0.430	0.735	0.305
30-MPPS	0.035	28.65	1.218	0.296	0.421	0.704	0.283
30-MAPS	0.039	25.84	0.925	0.397	0.352	0.603	0.251

SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch), 30-MSPS, 30-MPPS and 30-MAPS (represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively).

The result of Heckel parameters as presented in Table 4.16 shows that modification of the native starch increased the mean yield pressure (P_y) in the order: APS > PPS > SPS, while for the dispersions; the mean yield pressure was in the order: 30-MSPS > 30-MPPS > 30-MAPS. The relative density (D_A), the relative density at zero pressure (D_O) and the relative density at low

pressure (D_B) were in the order: SPS > PPS > APS. This trend was also seen with their dispersions in mucilage

Table 4.17: Kawakita Parameters for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

Parameters	1/a	1/ab	a	D_i (1-a)	b	P_K (KN)
SPS	1.775	0.310	0.563	0.437	5.714	0.175
PPS	1.952	0.330	0.512	0.488	5.917	0.169
APS	1.968	0.270	0.508	0.492	7.300	0.137
30-MSPS	2.152	0.480	0.465	0.535	4.484	0.223
30-MPPS	2.020	0.480	0.495	0.505	4.219	0.237
30-MAPS	1.900	0.490	0.526	0.474	3.876	0.258

SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch), 30-MSPS, 30-MPPS and 30-MAPS (represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively).

The result of Kawakita parameters as presented in Table 4.17 shows that modification of the native starch decreased the minimum porosity (a) in the order: SPS > PPS > APS, while for the dispersions, the minimum porosity was in the order: 30-MSPS < 30-MPPS < 30-MAPS. The constant (b) which relates to the plasticity of the material were in the order: APS > PPS > SPS, while for the dispersions, the order was 30-MSPS > 30-MPPS > 30-MAPS.

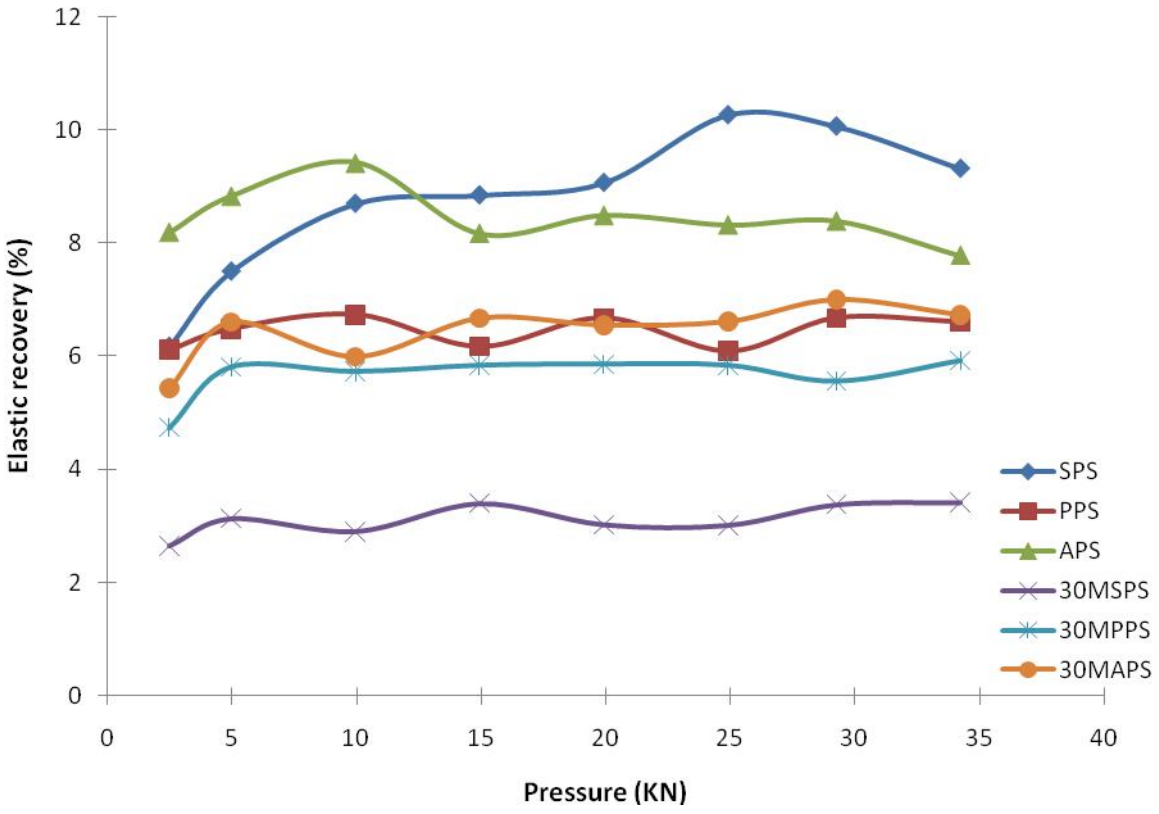


Fig. 4.16: Graph of Elastic Recovery (%) Vs Pressure (KN) for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

The result of elastic recovery as presented in Fig. 4.16 shows that modification of starch reduced the elastic recovery in the order: SPS > APS > PPS. For the dispersions, the elastic recovery was in the order: 30-MAPS > 30-MPPS > 30-MSPS.

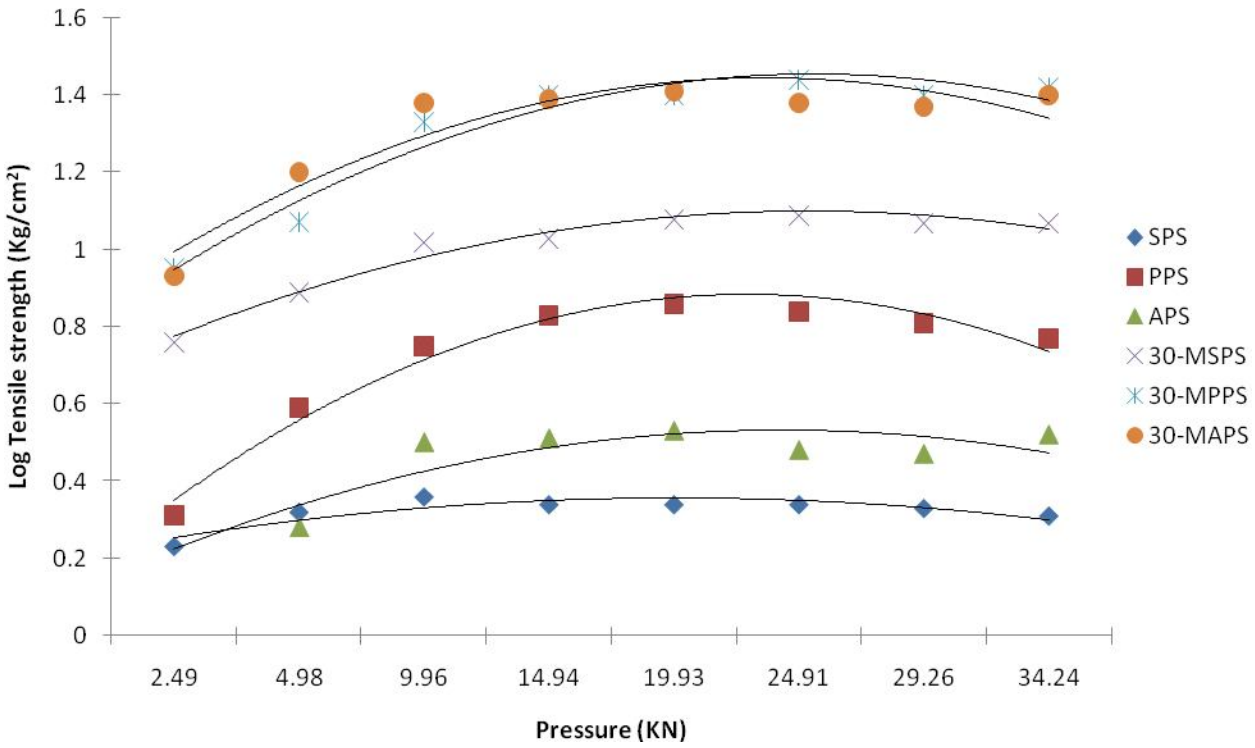


Fig. 4.17: Graph of Log Tensile Strength (Kg/cm^2) Vs Pressure (KN) for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

The result of log tensile strength as presented in Fig. 4.17 shows that the log tensile strength of the native starch improved with modification in the order: SPS > PPS > APS. These trends were also seen with their dispersions in mucilage in the order: 30-MSPS > 30-MPPS > 30-MAPS.

Table 4.18: Brittle Fracture Index (BFI) Parameters for Native Starch, Modified Starches and Dispersions of Native and Modified Starches in Mucilage obtained from *Ipomoea batatas*

S/No	Parameters	T	T_O	BFI
1	SPS	0.41 (0.34)	0.05 (0.36)	3.60
2	PPS	5.01 (1.23)	3.67 (0.55)	0.18
3	APS	5.48 (0.86)	3.47 (0.73)	0.29
4	30-MSPS	8.54 (0.34)	7.16 (0.14)	0.10

5	30-MPPS	12.55 (1.04)	6.48 (0.56)	0.47
6	30-MAPS	14.45 (0.46)	7.44 (0.24)	0.47

Value is mean and standard deviation is in parenthesis, number of replicate = 3, T= Tensile strengths of the normal tablets and T_O = Tensile strengths of tablet with a hole at the center. SPS (sweet potato starch), PPS (pregelatinized sweet potato starch), APS (acid modified sweet potato starch), 30-MSPS, 30-MPPS and 30-MAPS (represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively).

The result of BFI parameters as presented in Table 4.18 shows that modification of the native starch decreased the BFI in the order: SPS > APS > PPS while for the dispersions; the BFI was in the order 30-MPPS = 30-MAPS > 30-MSPS.

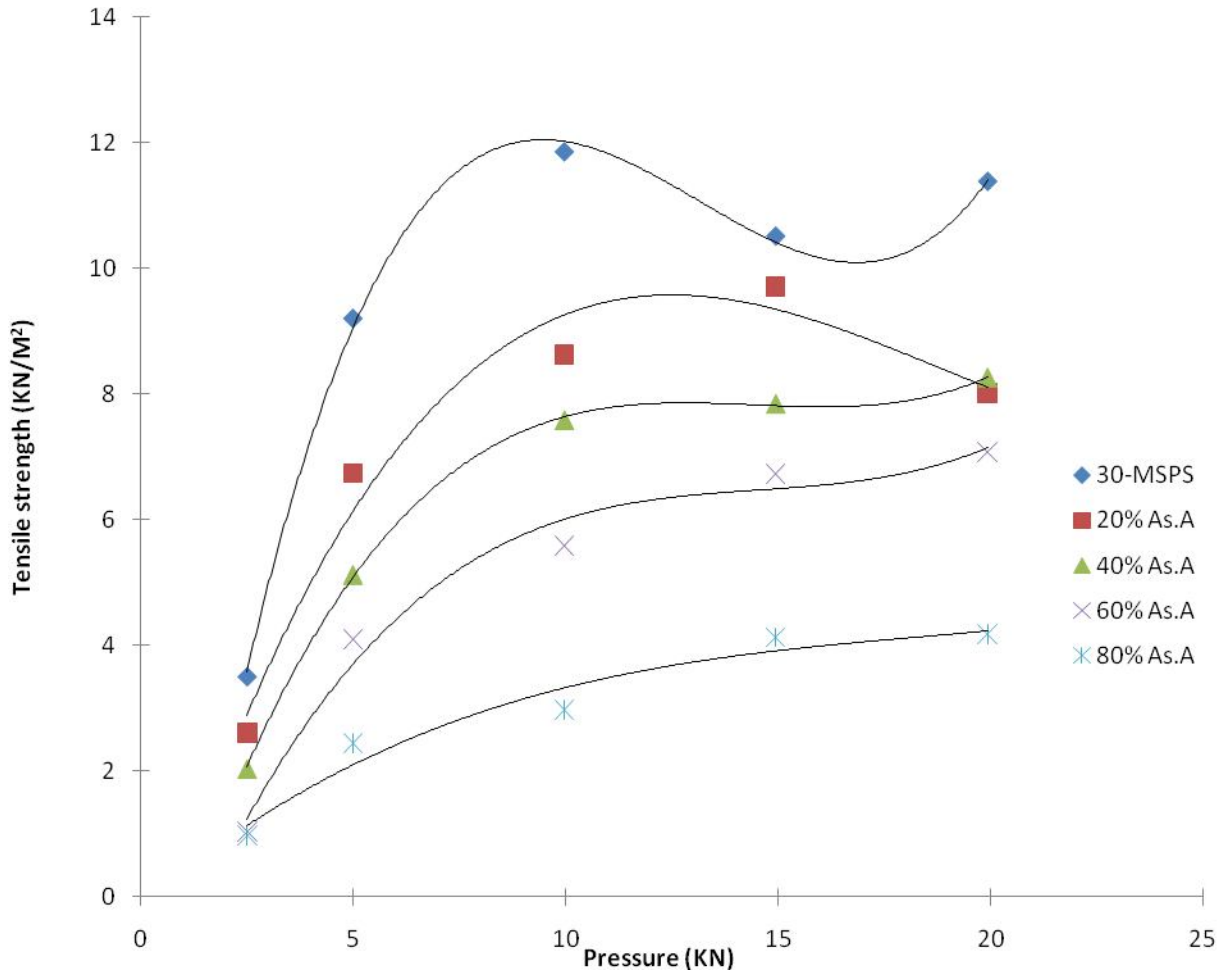


Fig. 4.18: Graph of Tensile Strength (KN/M^2) Vs Pressure (KN) of Binary Mixture of Ascorbic acid and 30-MSPS Tablets

The result of tensile strength against pressure as presented in Fig. 4.18 shows the effect of compression pressures on the tensile strength of ascorbic acid tablets. There was a gradual

reduction in tensile strength with increased ascorbic acid concentration using 30-MSPS as excipient.

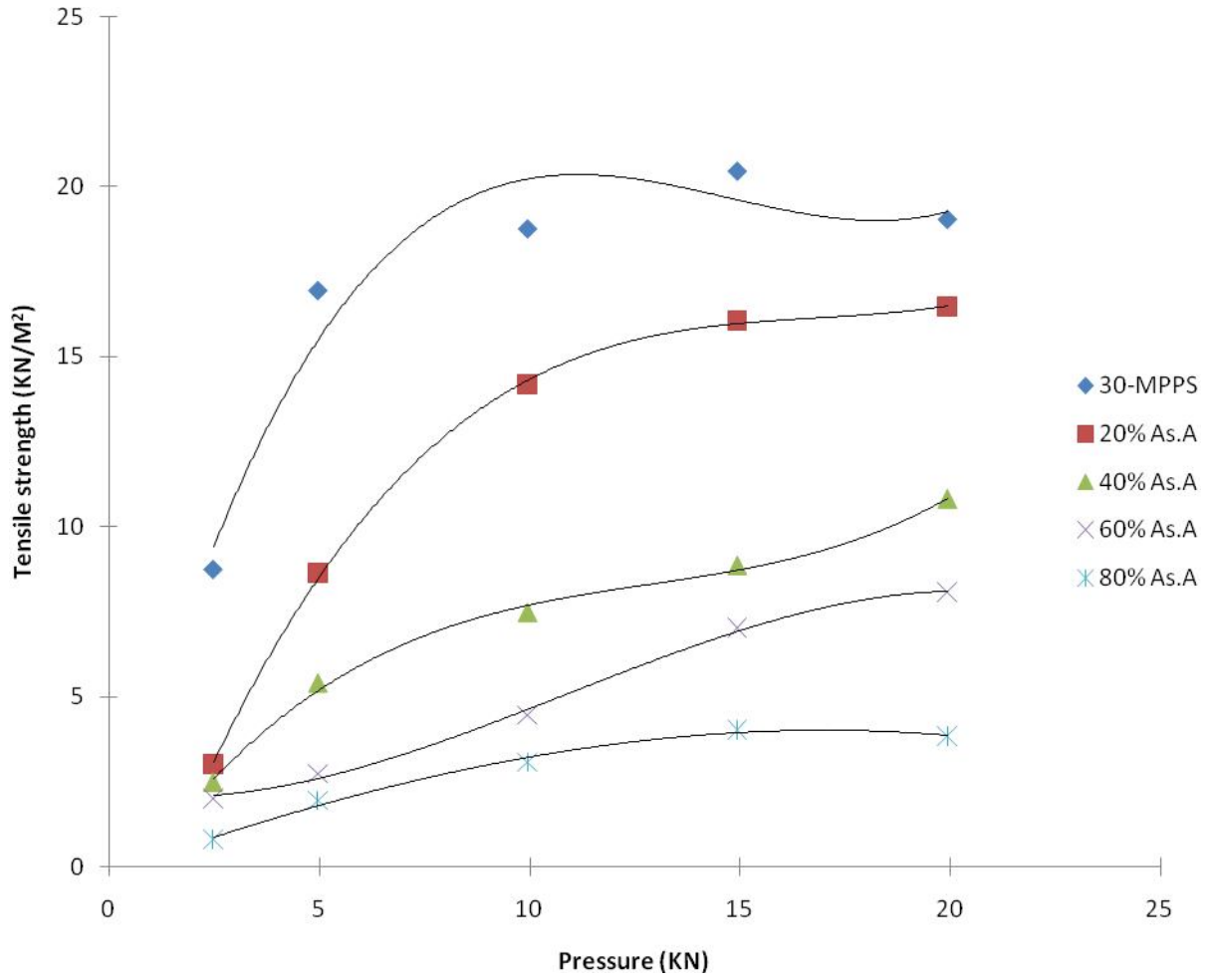


Fig. 4.19: Graph of Tensile Strength (KN/M^2) Vs Pressure (KN) of Binary Mixture of Ascorbic acid and 30-MPPS Tablet

The result of tensile strength against pressure as presented in Fig. 4.19 shows the effect of compression pressures on the tensile strength of ascorbic acid tablets. There was a gradual reduction in tensile strength with increased ascorbic acid concentration using 30-MPPS as excipient.

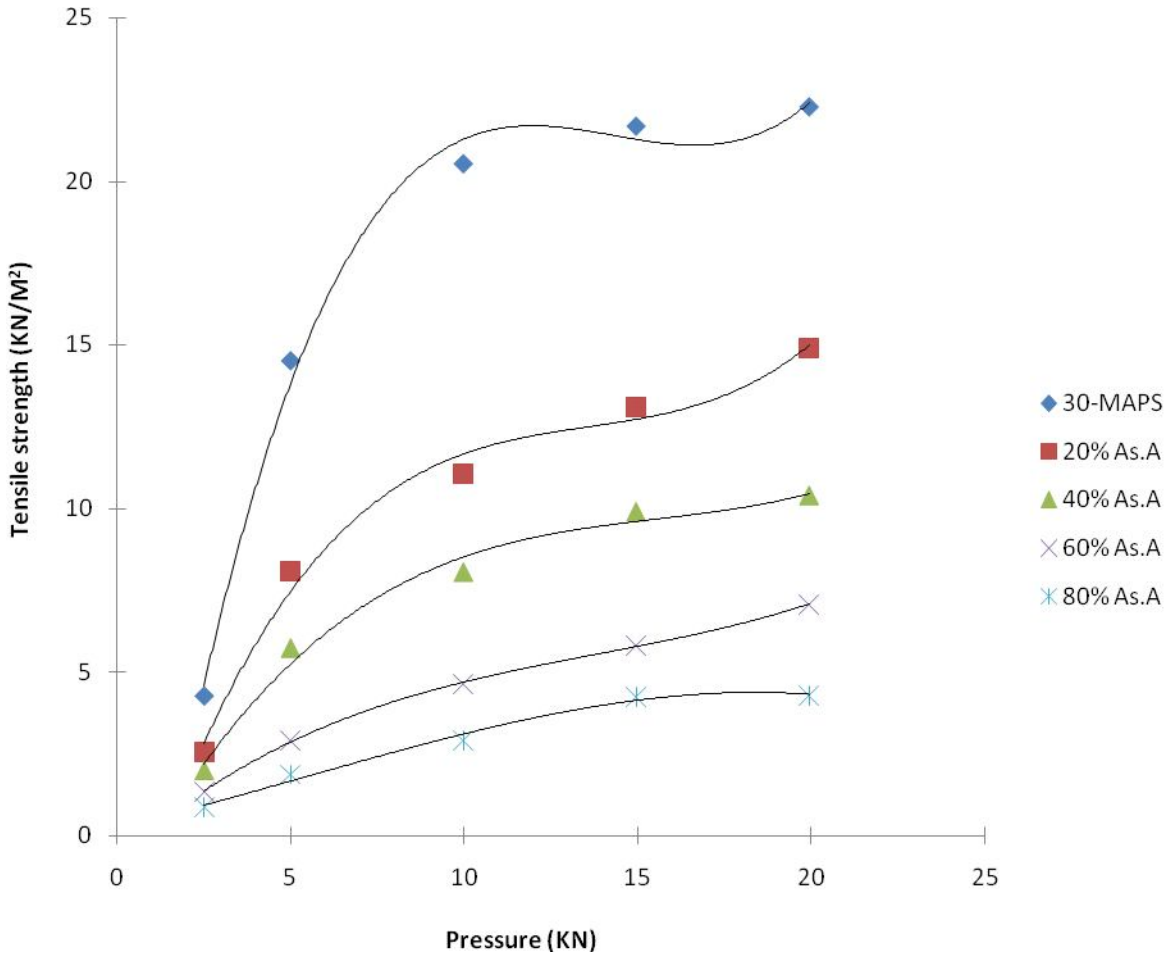


Fig. 4.20: Graph of Tensile Strength (KN/M^2) Vs Pressure (KN) of Binary Mixture of Ascorbic acid and 30-MAPS Tablet

The result of tensile strength against pressure as presented in Fig. 4.20 shows the effect of compression pressures on the tensile strength of ascorbic acid tablets. There was a gradual reduction in tensile strength with increased ascorbic acid concentration using 30-MAPS as excipient.

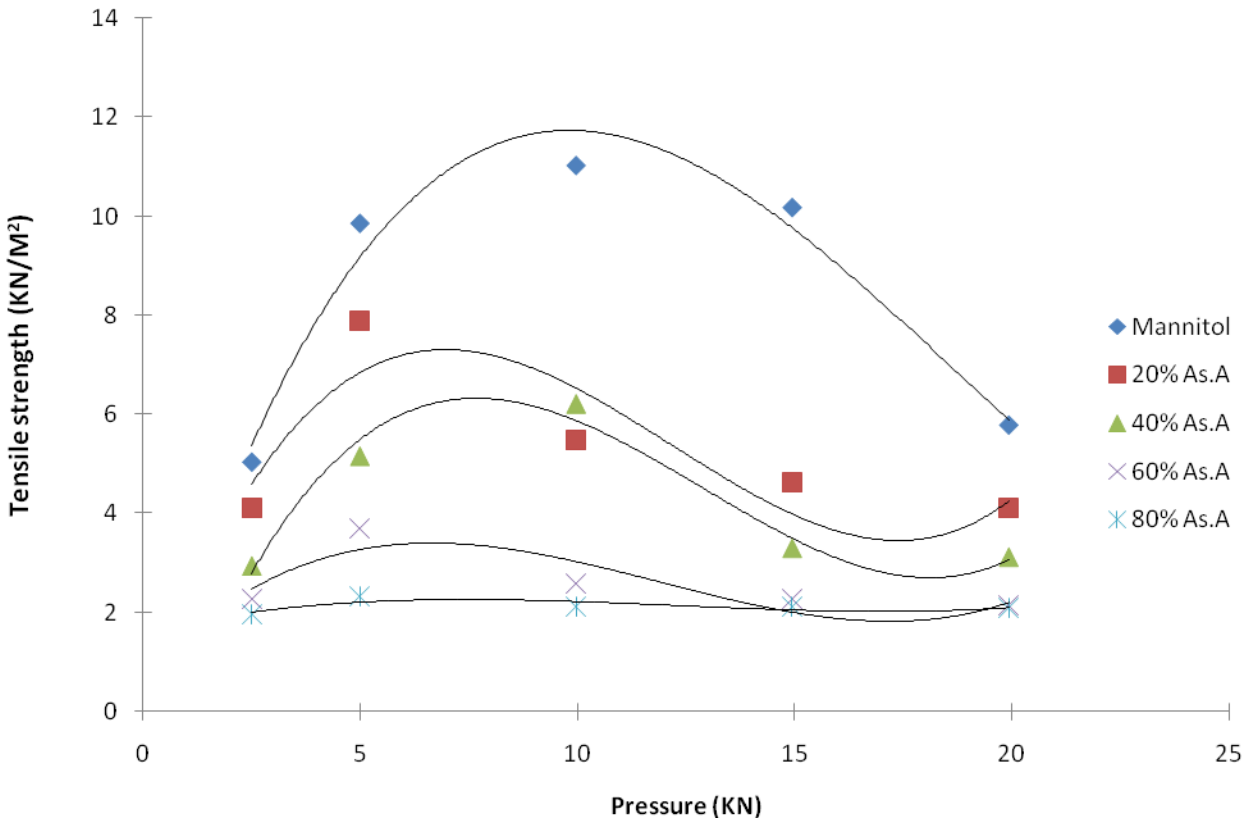


Fig. 4.21: Graph of Tensile Strength (KN/M^2) Vs Pressure (KN) of Binary Mixture of Ascorbic acid and Mannitol Tablet

The result of tensile strength against pressure as presented in Fig. 4.21 shows the effect of compression pressures on the tensile strength of ascorbic acid tablets. There was a gradual reduction in tensile strength with increased ascorbic acid concentration using mannitol as excipient

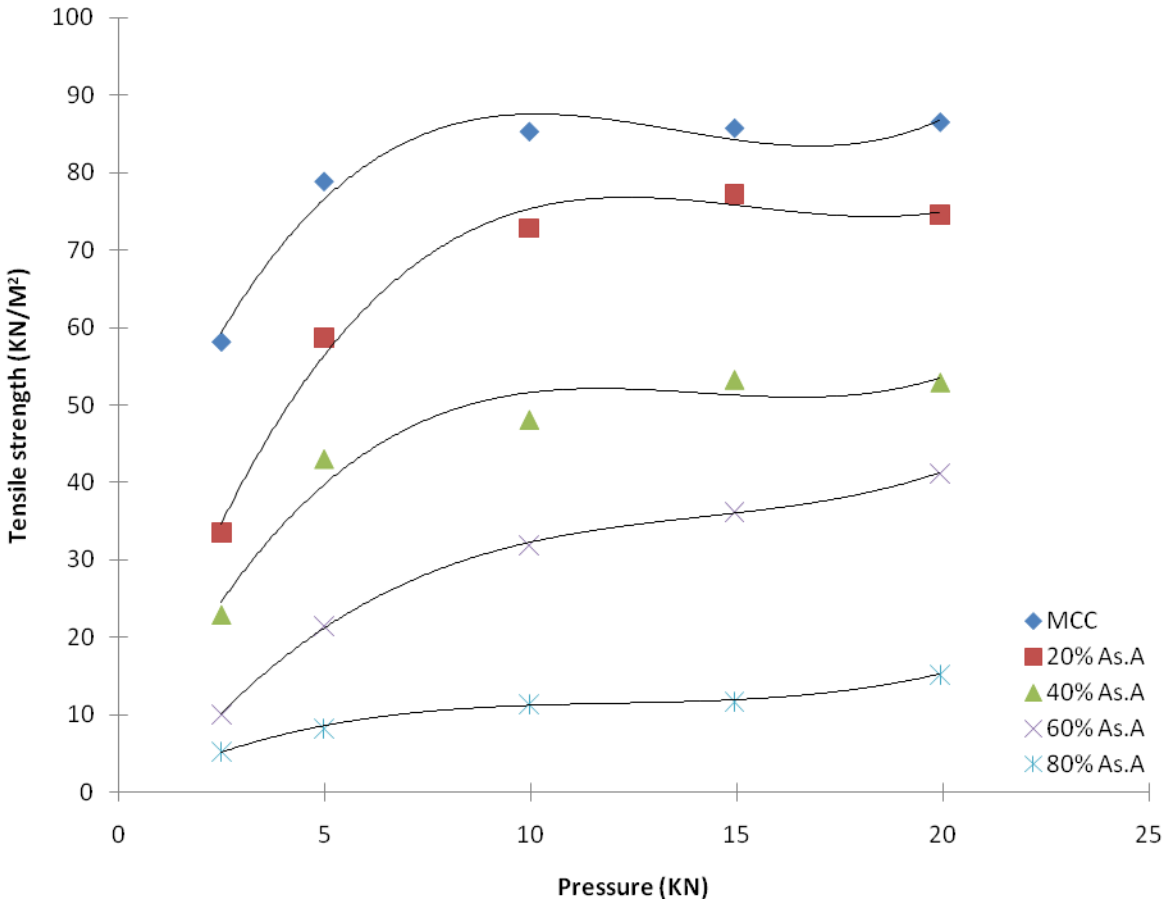


Fig. 4.22: Graph of Tensile Strength (KN/M^2) Vs Pressure (KN) of Binary Mixture of Ascorbic acid and Microcrystalline Cellulose Tablet

The result of tensile strength against pressure as presented in Fig. 4.22 shows the effect of compression pressures on the tensile strength of ascorbic acid tablets. There was a gradual reduction in tensile strength with increased ascorbic acid concentration using microcrystalline cellulose as excipient.

Table 4.19: Work Potentials of Native and Modified Starches Dispersion in Mucilage obtained from *Ipomoea batatas,* Mannitol and Microcrystalline Cellulose

S/NO	Parameters	% Ascorbic acid	AUC (m^2)	Work potential
1	30-MSPS	0	179.02	1.000
		20	130.52	0.729
		40	99.09	0.554
		60	70.13	0.392
		80	19.73	0.117
2	30-MPPS	0	321.19	1.000
		20	232.18	0.723
		40	129.83	0.404
		60	92.29	0.287
		80	56.06	0.175
3	30-MAPS	0	330.62	1.000
		20	192.95	0.584
		40	139.69	0.423
		60	82.78	0.250
		80	54.25	0.164
4	MANNITOL	0	165.06	1.000
		20	65.40	0.396
		40	63.23	0.383
		60	19.18	0.118
		80	15.99	0.098
5	MCC PH 101	0	1427.64	1.000

20	1173.00	0.821
40	800.54	0.560
60	511.93	0.358
80	189.87	0.133

30-MSPS, 30-MPPS and 30-MAPS represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively. MCC (microcrystalline cellulose)

Table 4.20: Dilution Capacity Index of Native and Modified Starch Dispersion in Mucilage obtained from *Ipomoea batatas*, Mannitol and Microcrystalline Cellulose

S/NO	Parameters	MA Index (% w/w As. A)	Dilution capacity index (x 1000)
1	30-MSPS	91	16.29
2	30-MPPS	87	27.94
3	30-MAPS	84	27.77
4	Mannitol	78	12.87
5	MCC PH 101	93	132.77

30-MSPS, 30-MPPS and 30-MAPS represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively. MCC (microcrystalline cellulose)

The result of dilution capacity index as presented in Table 4.19 shows that increase in ascorbic acid concentration resulted in decreased area under the pressure–tensile strength curve of the

various excipients. Table 4.20 shows the dilution capacity index of the dispersions compared to mannitol and microcrystalline cellulose as reference. The order of magnitude was MCC > 30-MPPS > 30-MAPS > 30-MSPS > mannitol

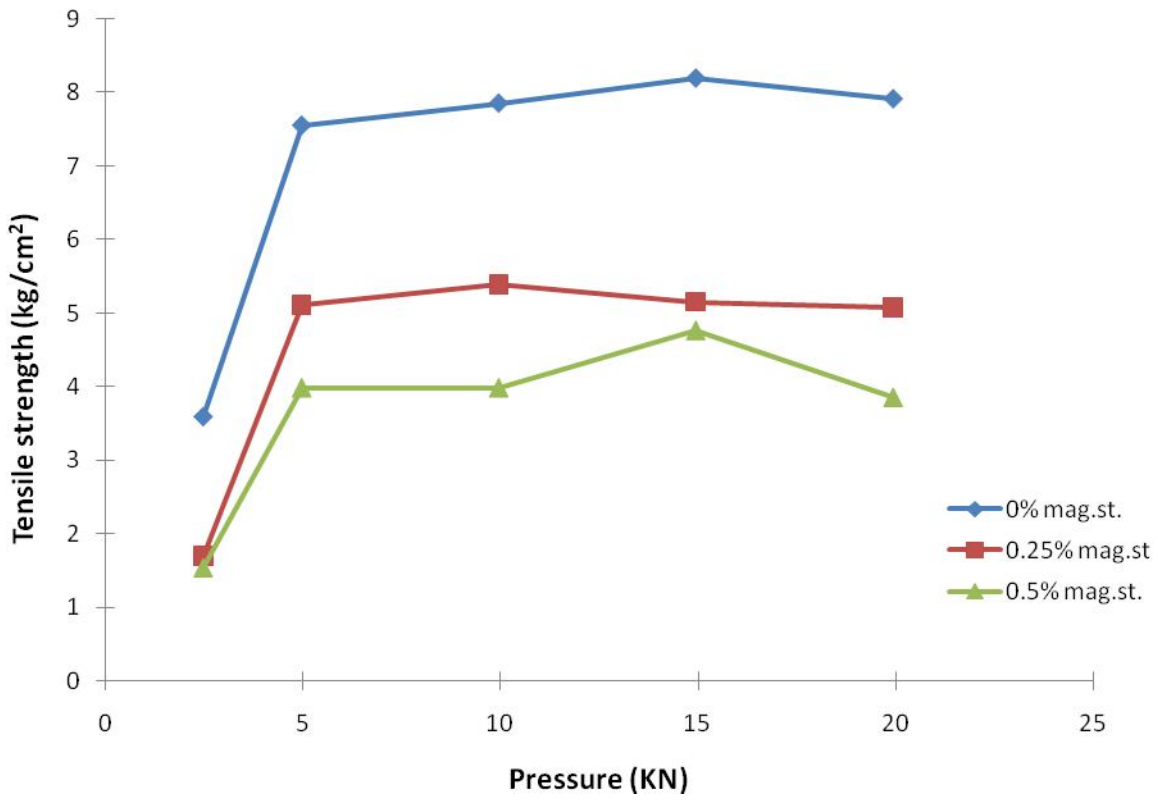


Fig. 4.23: Graph of Tensile Strength (Kg/cm^2) Vs Pressure (KN) of Starch and Mucilage Dispersion obtained from *Ipomoea batatas* (30-MSPS)

The result of lubricant sensitivity as presented in Fig. 4.23 shows the effect of lubricant (magnesium stearate) on the tensile strength of 30-MSPS. There was a gradual reduction in tensile strength with increased magnesium stearate concentration.

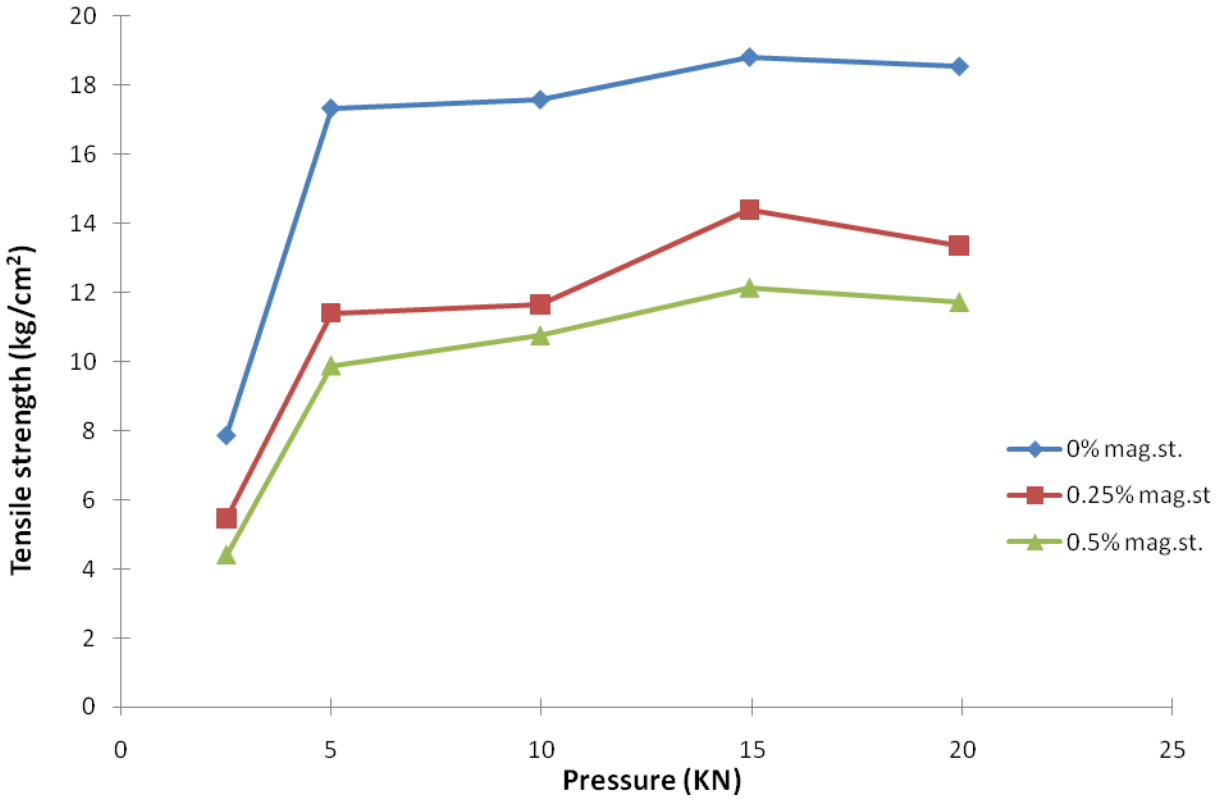


Fig. 4.24: Graph of Tensile Strength (Kg/cm^2) Vs Pressure (KN) of Pregelatinized Starch and Mucilage Dispersion obtained from *Ipomoea batatas* (30-MPPS)

The result of lubricant sensitivity as presented in Fig. 4.24 shows the effect of lubricant (magnesium stearate) on the tensile strength of 30-MPPS. There was a gradual reduction in tensile strength with increased magnesium stearate concentration.

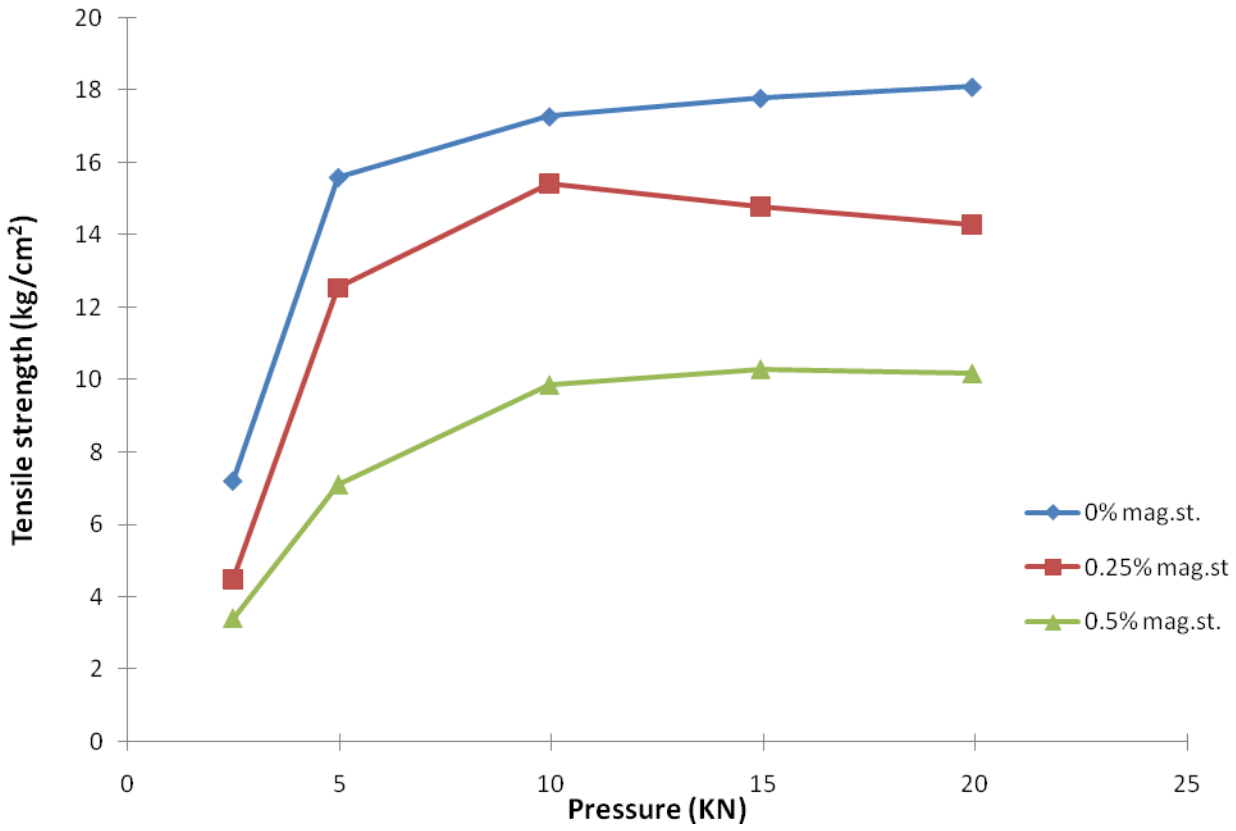


Fig. 4.25: Graph of Tensile Strength (Kg/cm^2) Vs Pressure (KN) of Acid Modified Starch and Mucilage Dispersion obtained from *Ipomoea batatas* (30-MAPS)

The result of lubricant sensitivity as presented in Fig. 4.25 shows the effect of lubricant (magnesium stearate) on the tensile strength of 30-MAPS. There was a gradual reduction in tensile strength with increased magnesium stearate concentration.

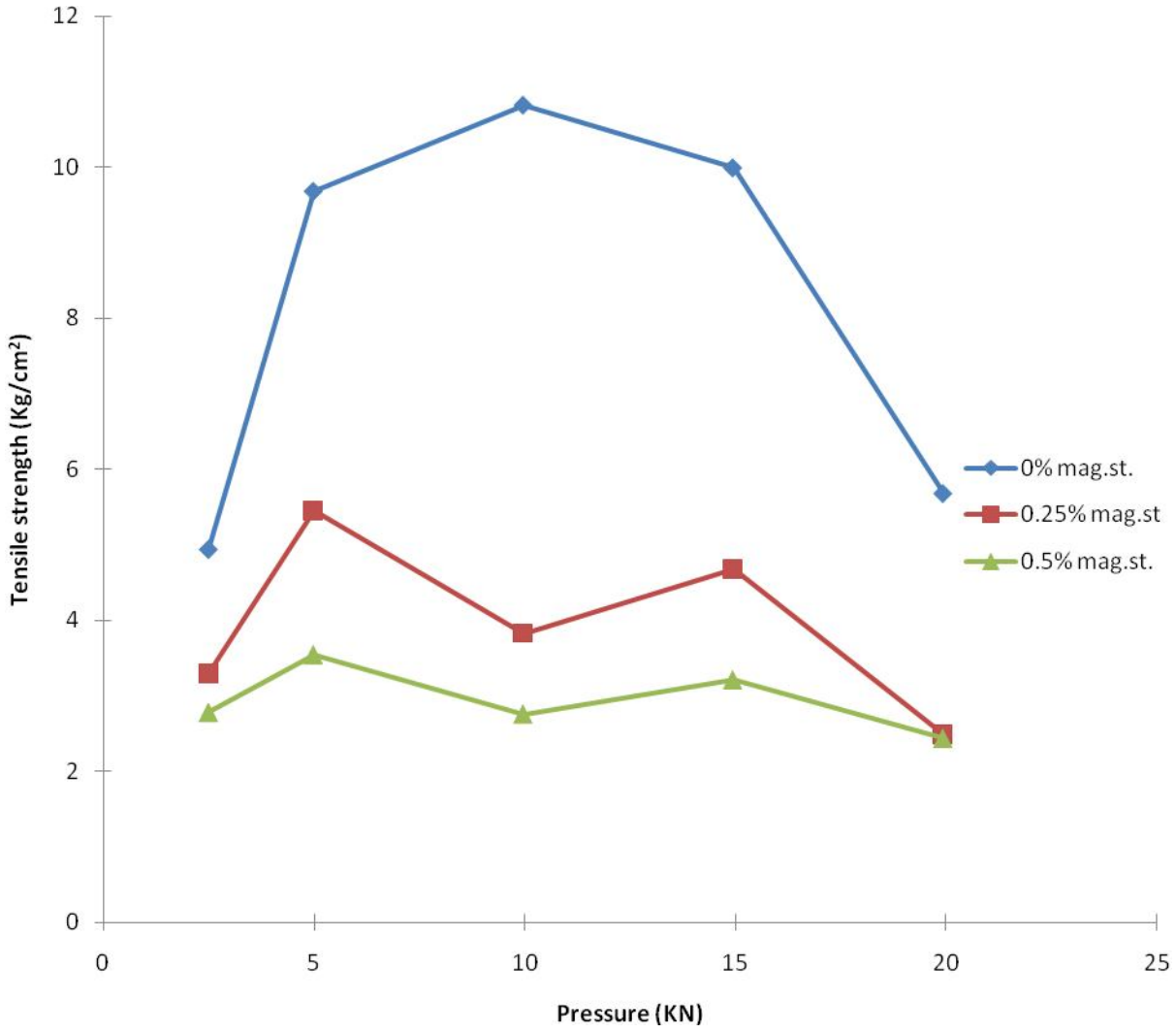


Fig. 4.26: Graph of Tensile Strength (Kg/cm^2) Vs Pressure (KN) of Mannitol

The result of lubricant sensitivity as presented in Fig. 4.26 shows the effect of lubricant (magnesium stearate) on the tensile strength of mannitol. There was a gradual reduction in tensile strength with increased magnesium stearate concentration.

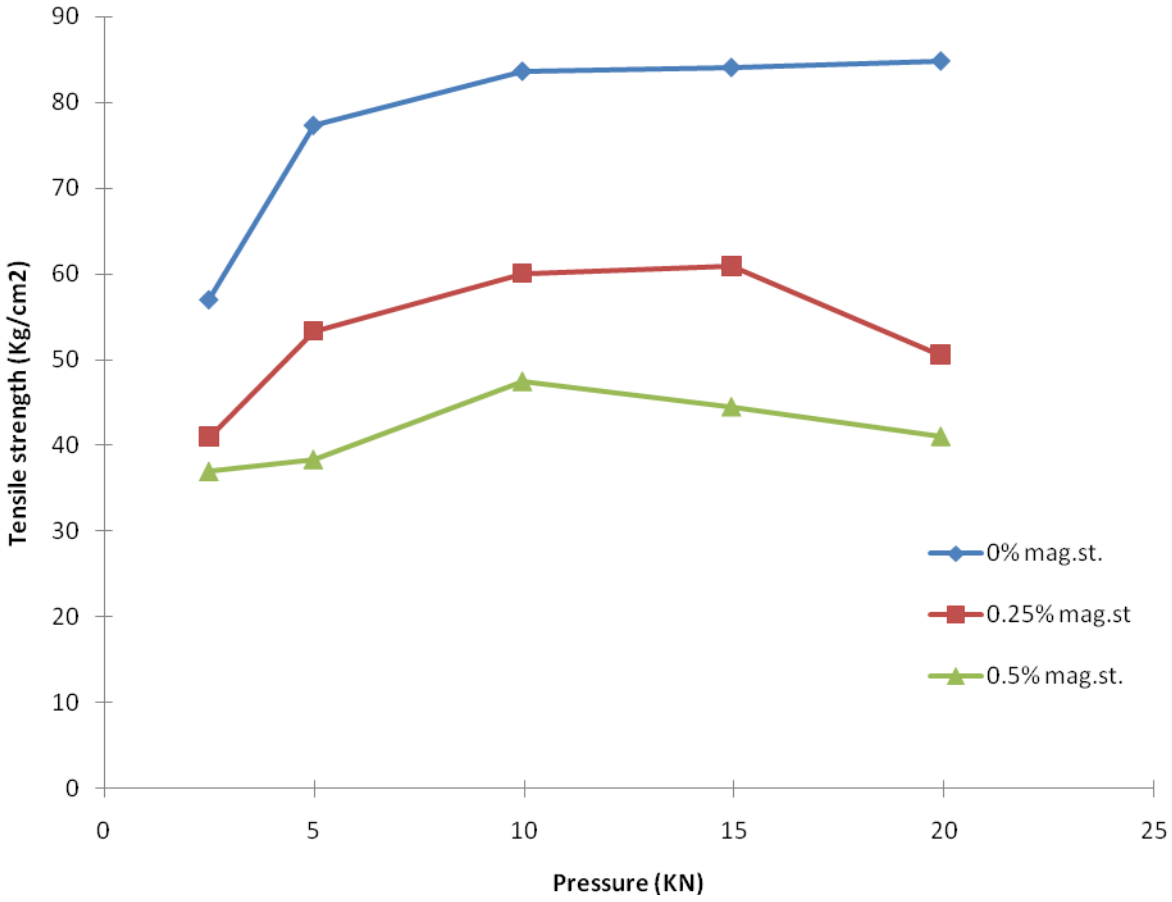


Fig. 4.27: Graph of Tensile Strength (Kg/cm^2) Vs Pressure (KN) of Microcrystalline Cellulose (Avicel PH 101)

The result of lubricant sensitivity as presented in Fig. 4.27 shows the effect of lubricant (magnesium stearate) on the tensile strength of microcrystalline cellulose. There was a gradual reduction in tensile strength with increased magnesium stearate concentration.

Table 4.21: Lubricant Sensitivity Ratios of Native and Modified Starches Dispersion in Mucilage obtained from *Ipomoea batatas*

		LUBRICANT SENSITIVITY RATIO (L.S.R)	
S/NO	Pressure (KN)	0.25% (Mag. Stearate)	0.5% (Mag. Stearate)
30-MSPS			
	2.49	0.53 (0.29)	0.57 (0.28)
	4.98	0.32 (0.15)	0.47 (0.13)
	9.96	0.31 (0.24)	0.49 (0.20)
	14.94	0.37 (0.24)	0.42 (0.11)
	19.93	0.36 (0.28)	0.51 (0.21)
30-MPPS			
	2.49	0.30 (0.30)	0.44 (0.12)
	4.98	0.34 (1.22)	0.43 (0.08)
	9.96	0.34 (0.67)	0.39 (1.04)
	14.94	0.24 (0.96)	0.35 (0.15)
	19.93	0.28 (0.32)	0.37 (0.56)
30-MAPS			
	2.49	0.38 (0.11)	0.53 (0.21)
	4.98	0.20 (0.20)	0.55 (0.37)
	9.96	0.11 (0.23)	0.43 (0.20)
	14.94	0.17 (0.53)	0.42 (0.38)
	19.93	0.21 (0.10)	0.44 (0.41)
Mannitol			
	2.49	0.30 (0.22)	0.44 (0.18)
	4.98	0.44 (0.13)	0.63 (0.90)
	9.96	0.65 (0.04)	0.75 (0.73)
	14.94	0.53 (0.14)	0.68 (0.80)
	19.93	0.56 (0.13)	0.57 (0.04)
MCC			
	2.49	0.28 (0.32)	0.35 (0.08)
	4.98	0.31 (0.22)	0.47 (0.24)
	9.96	0.28 (0.14)	0.43 (0.33)

14.94	0.28 (0.18)	0.47 (0.14)
19.93	0.40 (0.12)	0.52 (0.22)

Value is mean and standard deviation is in parenthesis,(number of replicate = 3), 30-MSPS, 30-MPPS and 30-MAPS represents 30 grams of mucilage incorporated into 100 grams of sweet potato starch, pregelatinized sweet potato starch and acid modified sweet potato starch respectively. MCC (microcrystalline cellulose)

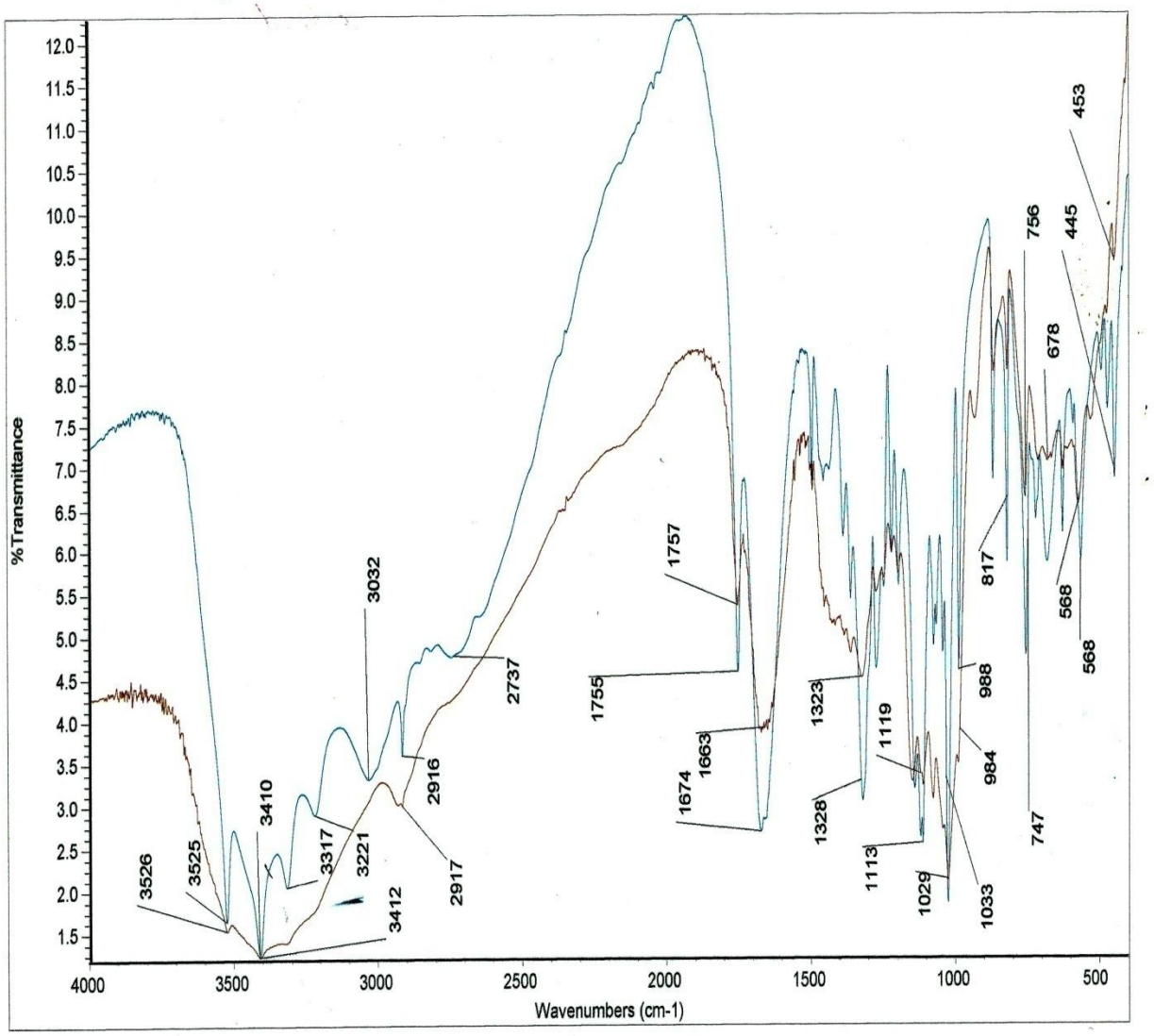


Fig. 4.28: FTIR Spectra of Ascorbic acid and 30-MSPS

The result of FTIR spectra determination of SPS and MSPS as presented in Fig. 4.28 shows that there was no appearance or disappearance of peaks.

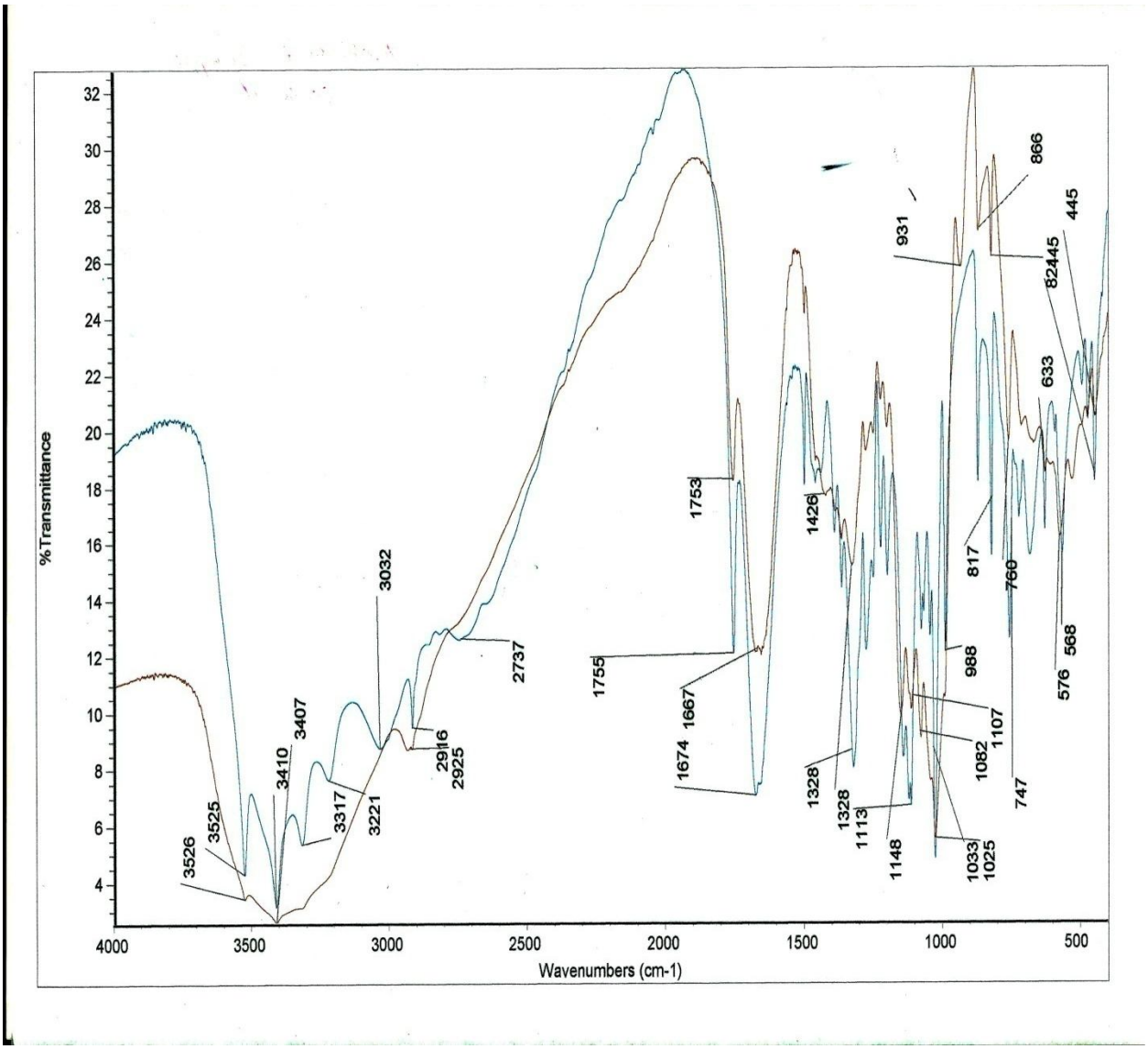


Fig. 4.29: FTIR Spectra of Ascorbic acid and 30-MPPS

The result of FTIR spectra determination of SPS and MSPS as presented in Fig. 4.29 shows that there was no appearance or disappearance of peaks.

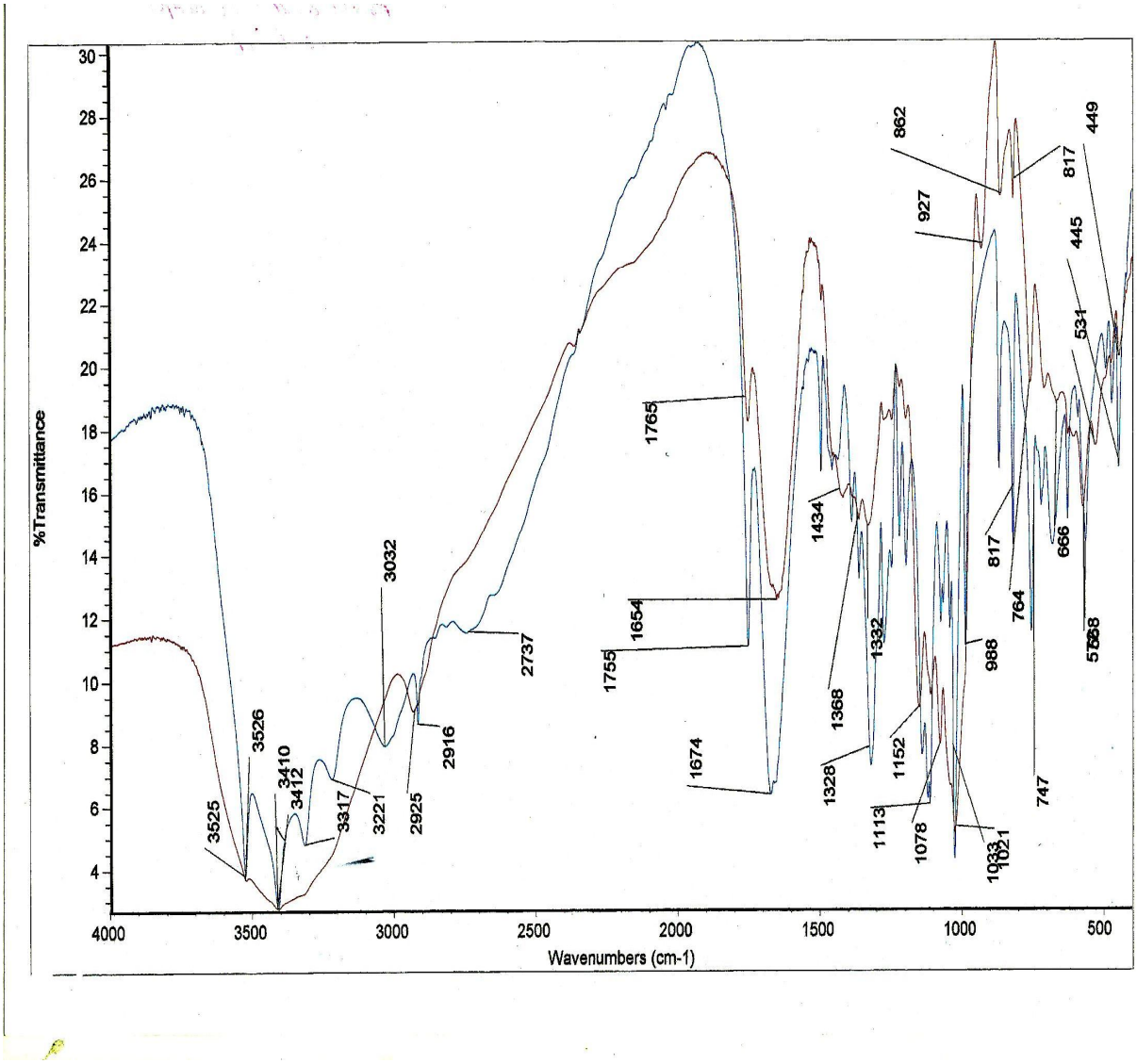


Fig. 4.30: FTIR Spectra of Ascorbic acid and 30-MAPS

The result of FTIR spectra determination of SPS and MSPS as presented in Fig. 4.30 shows that there was no appearance or disappearance of peaks.

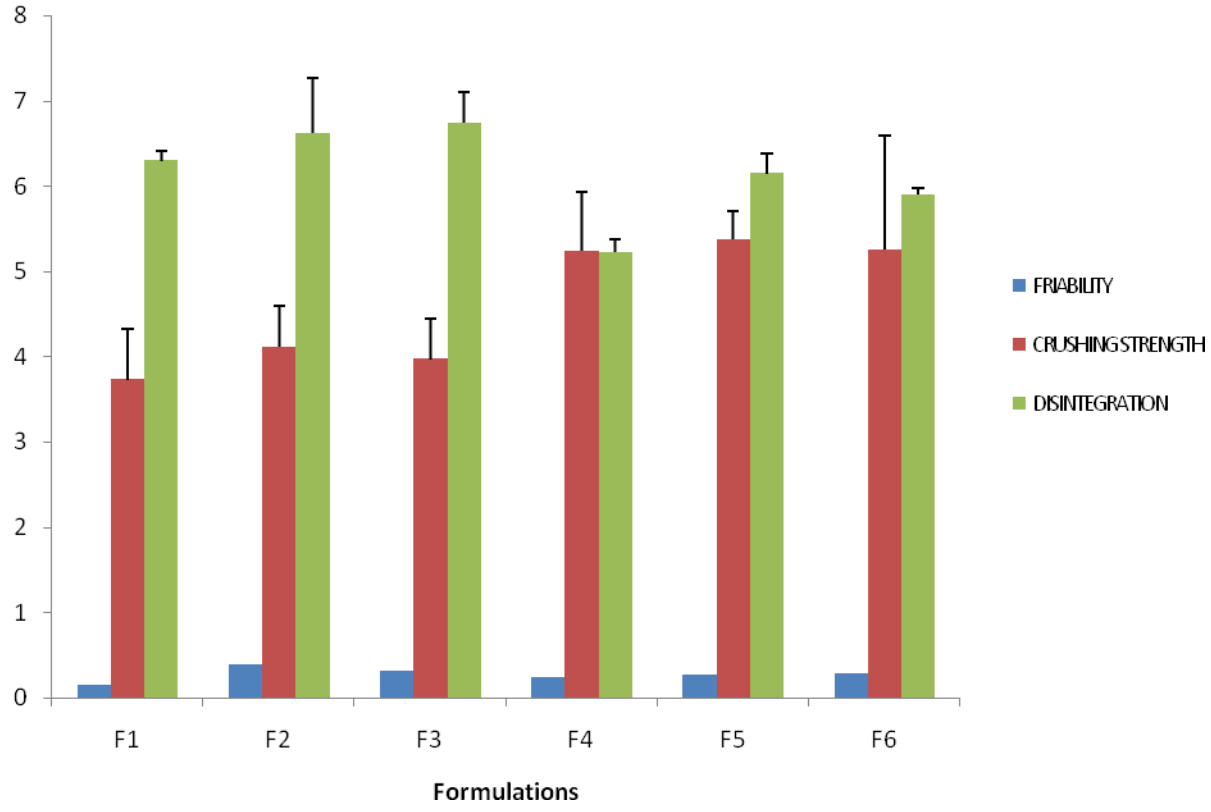


Fig. 4.31: Chart of Friability, Crushing Strength and Disintegration Time of Ascorbic acid Chewable Tablets using 30-MSPS, 30-MPPS and 30-MAPS as Excipient

The result of friability, crushing strength and disintegration time as presented in Fig. 4.31 shows that all the formulations had friability value less than 1 %, crushing strengths between 3.5 – 5.5

kgF and disintegration time less than 7 min. Formulations F4 – F6 had higher crushing strengths as compare to formulation F1 – F3.

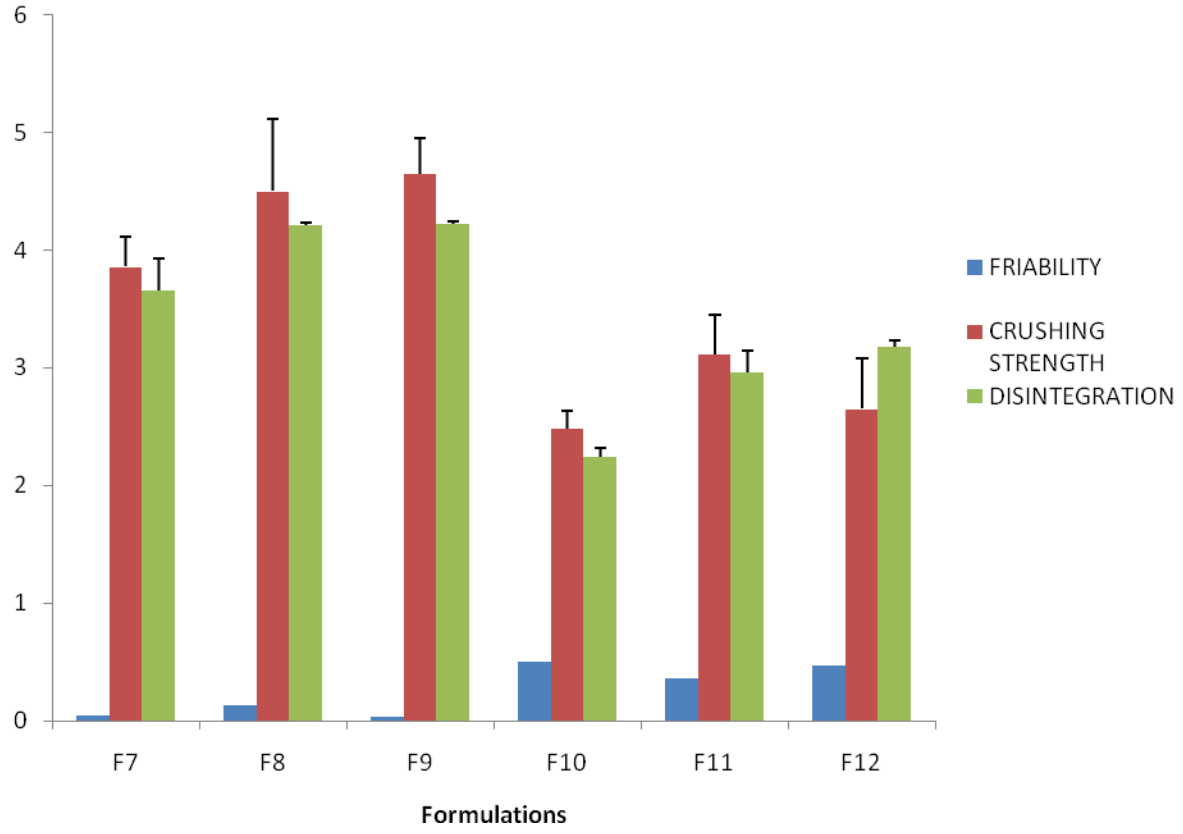


Fig. 4.32: Chart of Friability, Crushing Strength and Disintegration Time of Ascorbic acid Chewable Tablet using 30-MSPS, 30-MPPS and 30-MAPS in Binary Mixtures of Mannitol

The result of friability value, crushing strengths and disintegration time as presented in Fig. 4.32 shows that all formulation had friability values less than 1 %, crushing strengths between 2.5 – 5.5 kgF and disintegration time less than 6 min. Formulations F7 – F9 had higher crushing strengths and disintegration time and lower friability values compared to formulations F10 –F12.

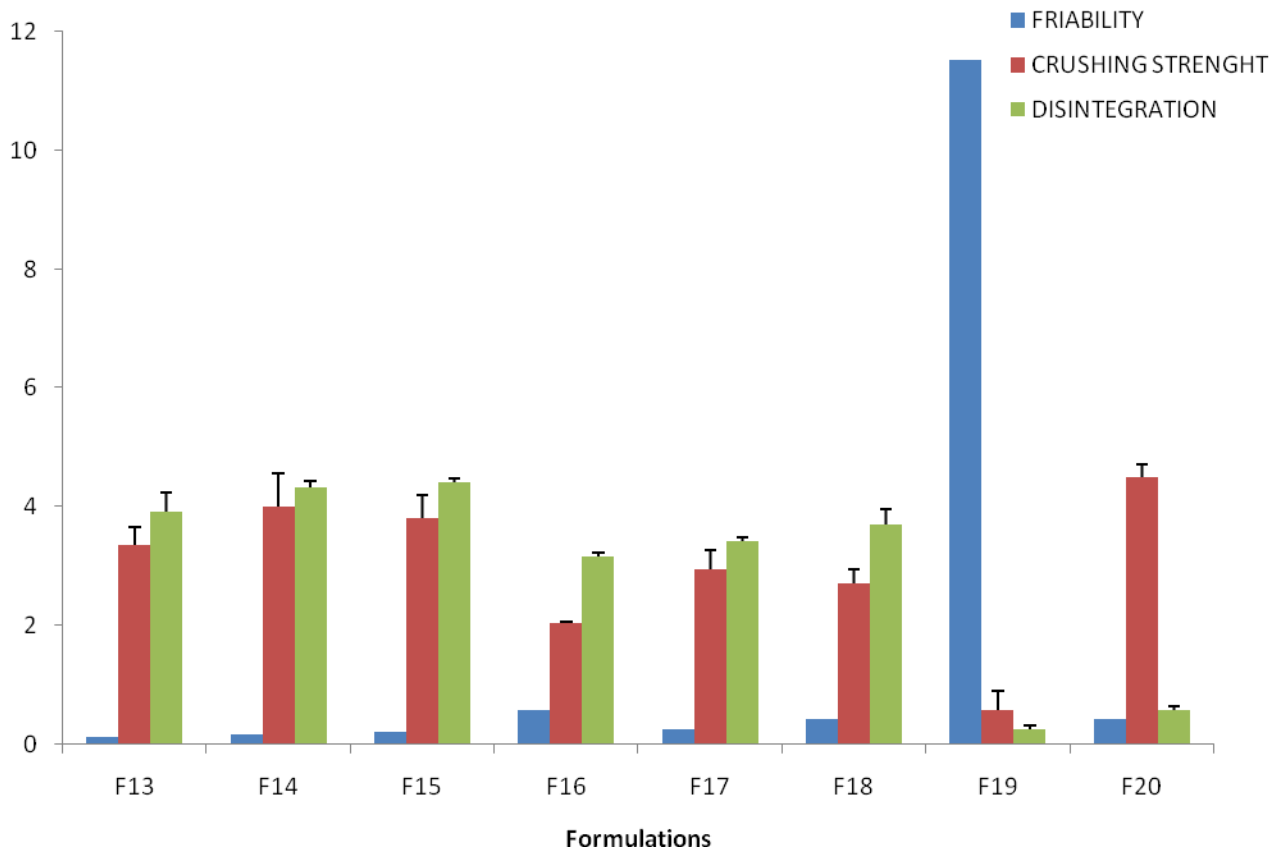


Fig. 4.33: Chart of Friability, Crushing Strength and Disintegration Time of Ascorbic acid Chewable Tablet using Mannitol, Avicel HFE and 30-MSPS, 30-MPPS and 30-MAPS in Binary Mixtures of Maltitol

The result of friability value, crushing strengths and disintegration time as presented in Fig. 4.33 shows that all formulation had friability values less than 1 % (except F19), crushing strengths between 1.0 – 4.5 kgF and disintegration time less than 4.5 min. Formulations F13 – F15 had higher crushing strengths, disintegration time and a lower friability value as compared to formulations F16 –F19 with F20 showing a better crushing strength compared to others.

Table 4.22: Cumulative Drug Release for Optimized Ascorbic acid Chewable Tablet Formulations

FORMULATIONS	TIME (MINUTES)					
	1	2	4	6	10	15
F1	7.80	21.90	44.70	62.10	63.15	83.85
F2	4.35	10.80	25.20	44.10	63.75	81.90
F3	4.80	13.05	31.80	47.40	67.20	78.15
F4	13.05	19.05	35.70	49.35	68.25	86.10
F5	11.25	18.75	35.70	51.45	67.35	87.45
F6	7.50	12.15	26.25	41.40	63.30	82.05
F7	12.90	28.20	46.65	63.75	72.90	76.35
F8	16.50	29.70	49.05	64.80	78.60	78.75
F9	16.20	26.40	46.35	62.10	78.15	80.25
F13	24.30	39.60	71.40	90.15	100.95	101.10
F14	15.45	30.90	57.60	77.25	97.95	100.50

F15	17.10	31.20	54.00	74.25	96.15	100.50
F20	69.75	98.70	101.0	101.0	101.0	101.0

The result of cumulative drug release as presented in Table 4.22 shows that formulation F20 had the highest onset of drug release as compared to formulations F2 and F3 which had the lowest onset of drug release. Formulations F13 – F20 had the highest cumulative drug release within 15 min.

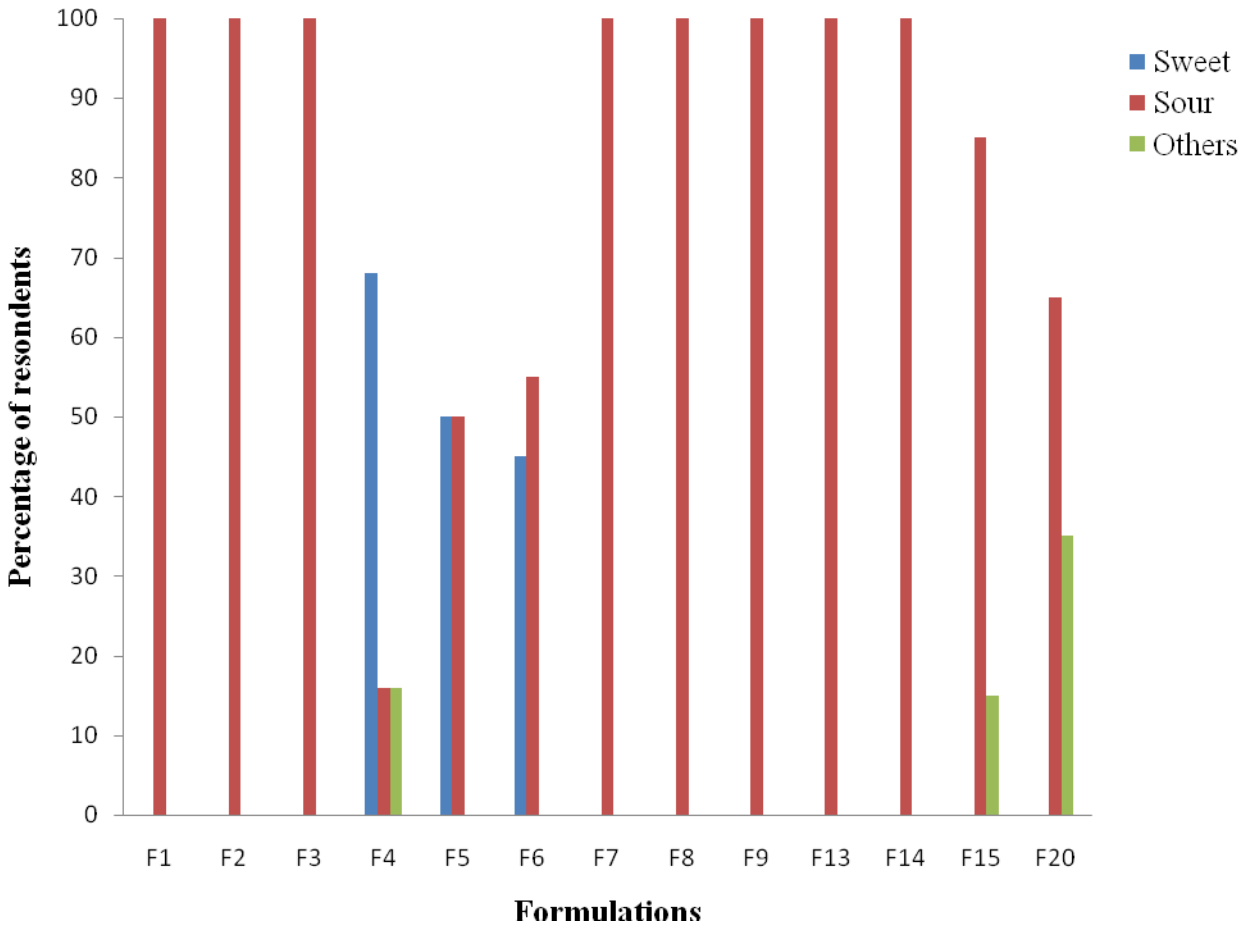


Fig. 4.34: Chart of Percentage Response to Taste of Formulated Ascorbic acid Chewable Tablets

The result of percentage response to taste as presented in Fig. 4.34 shows the response to taste of formulated ascorbic acid chewable tablets. Percentage of response to sweetness between 45 – 70 % were seen for formulations F4, F5 and F6 whereas all other formulations recorded between 70 – 100 % response to sourness.

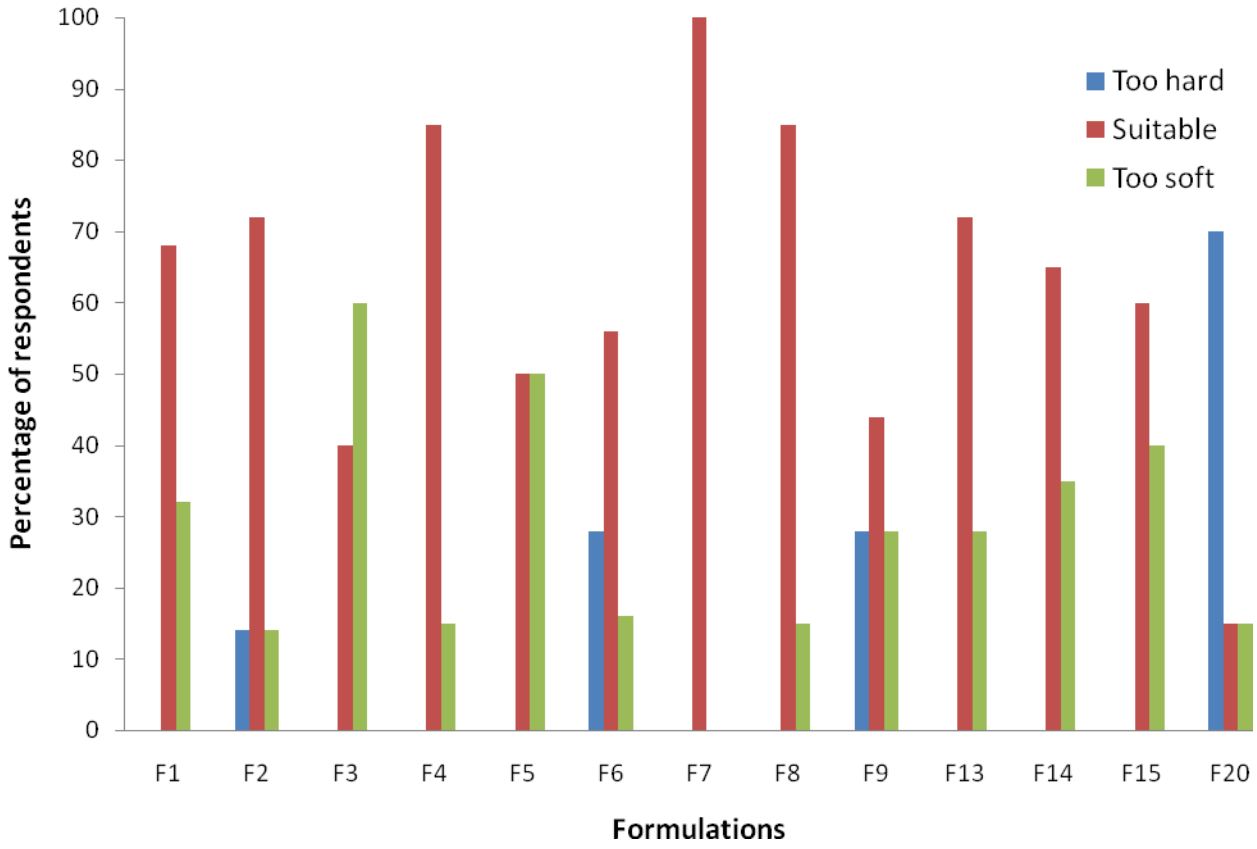


Fig. 4.35: Chart of Percentage Response to Hardness of Formulated Ascorbic acid Chewable Tablets

The result of percentage response to hardness as presented in Fig. 4.35 shows the response to hardness of formulated ascorbic acid chewable tablets. There was 100 % response for formulation F7 as being suitable with formulations F1, F3, F4, F5, F8, F13, F14 and F15 as

either suitable or too soft and all other formulations are either too hard, suitable or too soft by various respondents.

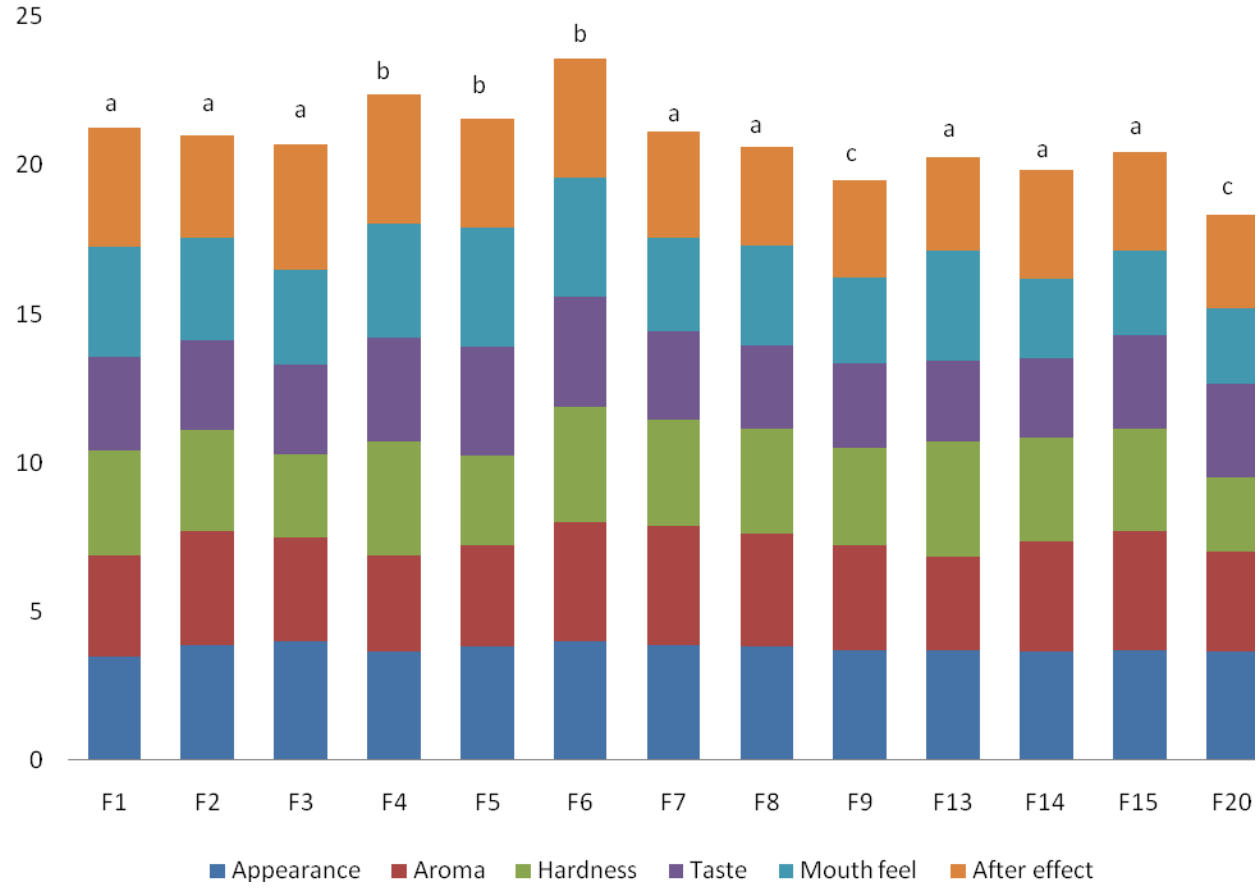


Fig. 4.36: Chart of Degree of Acceptance for Formulated Ascorbic acid Chewable Tablets

Value is mean, number of replicate = 20, a-c means with different letters within the same column differed significantly ($p < 0.05$)

The result of degree of acceptance as presented in Fig. 4.36 shows the degree of acceptance of formulated ascorbic acid chewable tablets. Formulation F6 had the highest acceptance, while

formulation F20 had the lowest. Generally, formulations F4 – F6 had higher acceptance as compared to other formulations.

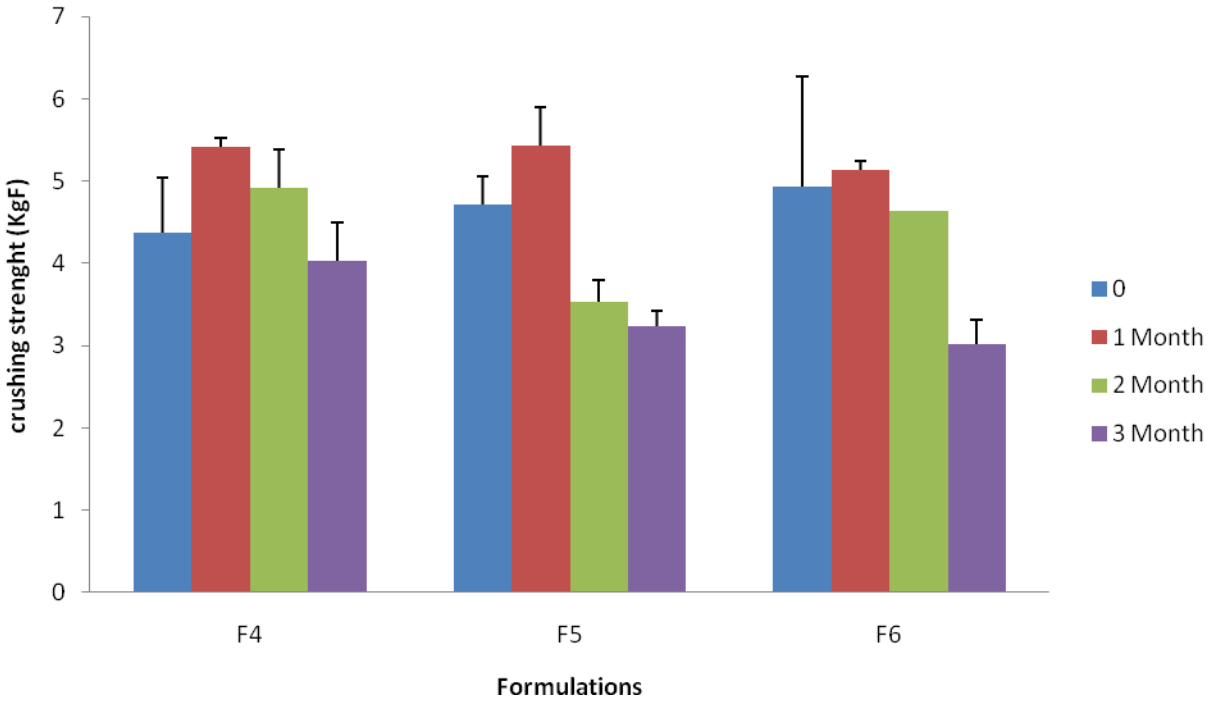


Fig. 4.37: Chart of Crushing Strength Profile of Optimized Formulation during Stability Studies

The result of crushing strength as presented in Fig. 4.37 shows that there was a slight increase in crushing strength within one month of stability studies and subsequently, a reduction for the remaining 2 months for all the formulations.

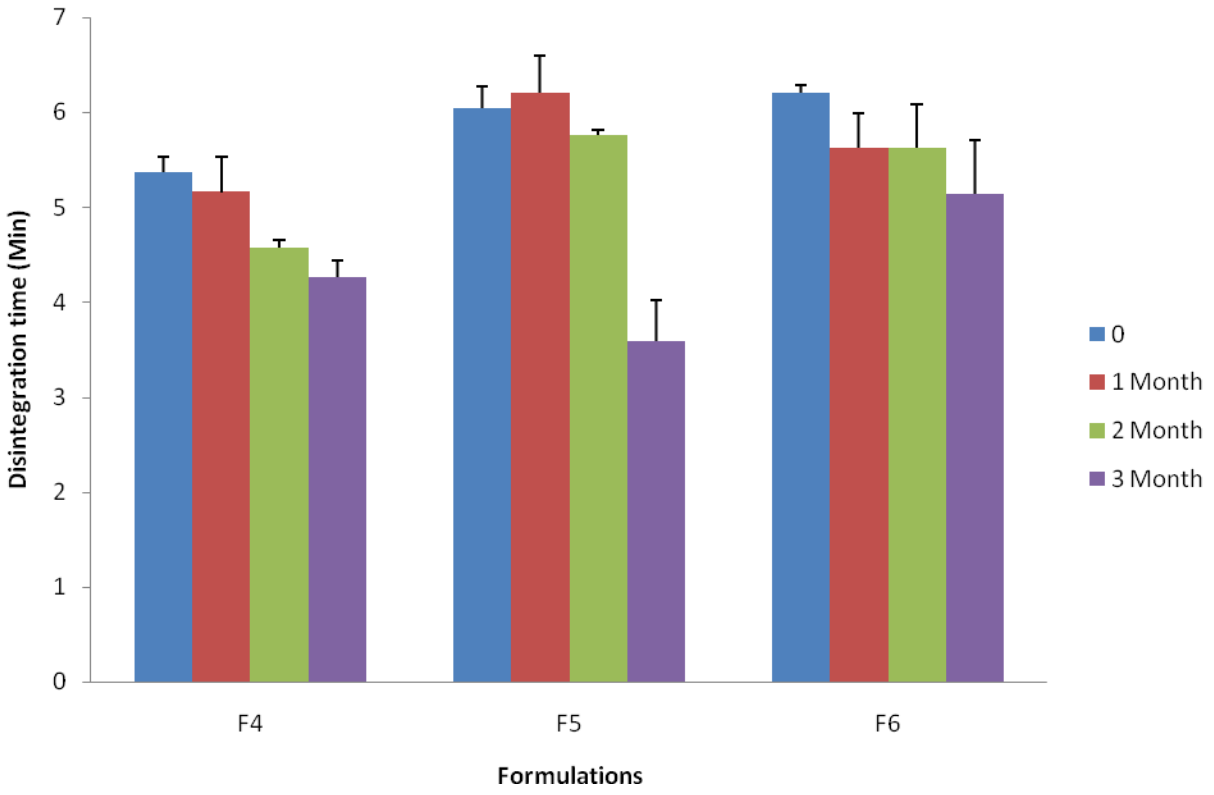


Fig. 4.38: Chart of Disintegration Time Profile of Optimized Formulation during Stability Studies

The result of disintegration time as presented in Fig. 4.38 shows that there was a gradual decrease in disintegration time within the periods of stability testing in all the formulations.

Table 4.23: Stability Studies on Weight Variation and Cumulative Drug Release of Optimized Ascorbic acid Chewable Tablet Formulations

Formulations	0	1 month	2 month	3 month
Weight variation				
F4	0.26 (0.23)	0.26 (0.07)	0.25 (0.08)	0.28 (0.07)
F5	0.25 (0.33)	0.26 (0.06)	0.24 (0.01)	0.28 (0.05)
F6	0.25 (0.12)	0.26 (0.09)	0.25 (0.05)	0.28 (0.10)
Cumulative drug release				
F4	86.10[a]	85.87[a]	85.88[a]	85.24[a]
F5	87.45[a]	87.24[a]	87.22[a]	85.18[b]
F6	82.05[a]	82.08[a]	81.99[a]	81.90[a]

Value is mean, number of replicate = 3, a-b means with different letters within the same row differed significantly ($p < 0.05$)

The result of weight variation and cummulative drug release as presented in Table 4.23 shows that there was no change in weight until the third month of stability test and also, there was no significant difference in the cumulative drug release for the period of test for all the formulations.

h

CHAPTER FIVE

5.0 DSICUSSIONS

5.1 Physico-Chemical Properties of Native and Modified Starch Dispersions

In context of this discussion, "modified starch" refers to pregelatinized and acid modified *Ipomoea batatas* starch. Molisch's and enzyme test confirmed the present and absence of carbohydrate and enzymes respectively in all the samples. The presence of mucilage and absence of starch were confirmed in the non-starch portion of *Ipomoea batatas* using ruthenium and iodine tests respectively. The reaction of starch with iodine is a common identity test for starch. It's believed that the amylose portion complexes with iodine by forming a helix around it to give a blue to bluish red colour (Whistler and Daniel, 1983). This blue colour has been used both as a qualitative and quantitative test for starch in various systems. As seen in Table 4.1, the moisture content and ash values for native and modified starches were within the specification of the

British Pharmacopoeia (2012). There were no significant differences between the crude fiber, crude protein and total carbohydrate for the native and modified starches. There was an increased crude protein content in the mucilage as compared to the native and modified starches. This could be attributed to the glycoprotein complex which is a major component in the mucilage. From Table 4.1, it can also be seen that the amylose content were in the order: PPS > APS > SPS. Increase in amylose content as seen in PPS and APS could be attributed to amylose leaching and early disintegration of the amorphous inter-micellar regions of the amylopectin molecule respectively. The difference in amylose and amylopectin contents contributes to significant differences in the starch properties and functionality (Thomas and Alweell, 1999). The higher the amylose content, the less expansion potential and lower the gel strength for the same starch concentration.

All the starch samples except SPS, PPS and APS possessed slight characteristic sweet taste and aroma which increased as the ratio of the mucilage increased. The aroma produced by the dispersions is as a result of the several volatile components with the predominant being hexanal, 3-pente-2-ol, isoledene, 2, 4-decadienal and 2-pentyl furan (Dumas and Ortiz, 2006). SPS, 5-MSPS, 10-MSPS, PPS, 5-MPPS, 10-MPPS, APS, 5-MAPS and 10-MAPS were off white while 20-MSPS, 30-MSPS, 40-MSPS, 20-MPPS, 30-MPPS, 40-MPPS, 20-MAPS, 30-MAPS and 40-MAPS were light brown in colour. A number of excellent reviews on the microscopy of starches have been published (Schoch and Maywald, 1984). The granule shape and size are characteristic of the botanical origin and can be used to identify the material. All the starch samples appeared round, spherical or irregular in shape as seen in Fig. 4.5.

Generally, starches are insoluble in water and the water solubility index (Table 4.2) was a reflection of the solubility of the dispersed mucilage in the powder. There was a slight increase in the water solubility index of the modified starches as compared to the native form. This could be attributed to the soluble amylose that leached out during starch modification.

FT-IR spectra matching approach was used for detection of any possible chemical interaction between the native and modified starches with their dispersion. There was no appearance or disappearance of peaks which indicate no interaction between native/modified starch and mucilage. The characteristic peaks and bands for the native and modified starches with their dispersions are presented in Fig. 4.1-4.3. The native and modified starches showed the following absorption bands: the band between 3350 – 3424 cm^{-1} represents O-H stretch; the absorption shoulder at 2925 cm^{-1} represent C-H stretch; aromatic absorption is absent in the diagnostic regions (1600 cm^{-1} and 1500 cm^{-1}) but medium intensity absorption at 1650 cm^{-1} was due to water absorbed in the amorphous region of the starch. 1238 - 1242 cm^{-1} represents CH_2OH. The absorption peak at 1156 - 1160 cm^{-1} represents coupling mode of C-C, C-O stretching vibrations while the band at 1078 - 1082 cm^{-1} represents C-O-H bending vibration. The absorption at 923 cm^{-1} is typical of the system (C-O-C), skeletal mode vibration of α-1,4-glycosidic linkage while 576 cm^{-1} represents the skeletal mode of pyranose ring (See Fig 1).

There was an increase in moisture sorption capacity and true density with a decrease in moisture content and pH as the mucilage concentration increased as seen in Table 4.3. Moisture content and ash value were all below 15 % and 0.6 % as stipulated for starches in the British Pharmacopoeia (2012).

Particle size analysis showed that the surface area mean diameter, mass median diameter and particles less than 10 % [D (v, 0.1)] for native, pregelatinized and acid modified starches were in the order: native starch > acid modified starch > pregelatinized starch, while the volume mean diameter and particles less than 90 % [D (v, 0.9)] were in the order: pregelatinized starch > acid modified starch > native starch. Generally, there was a significant increase in specific surface area, surface area mean diameter, mass median diameter and D [v, 0.9] with a decrease in D [v, 0.1] as the mucilage ratio increased with all the samples as seen in Tables 4.4-4.6 and Fig. 4.4. This could be due to adsorption of mucilage to the surface of starch grains and particle aggregation.

There was an increase in bulk and tapped densities with modification and also dispersion of starch in mucilage as seen in Table 4.7. Bulk powder characteristics are important in understanding the handling properties of an excipient or a granulated product. A number of studies have investigated the bulk powder properties of starch (Newman *et al*., 1996). The starch materials were found to exhibit poor to borderline flow properties, which correlated with the result obtained with starch studied.

The flow properties of a powder are essential in determining its suitability as direct compression excipient. The angle of repose, Hausner's and Carr's indices are considered as indirect measurement of powder flowability (Staniforth, 1996). High angle of repose is indicative of poor flow, while the Hausner's index is indicative of antiparticle friction; the Carr's index shows the tendency of a material to diminish in volume. As the value of this indices increases, the flow of the powder decreases. In general, however, Hausner's ratio greater than 1.25 indicates poor flow; Carr's index below 16 % indicates good flowability, while values above 35 % indicate

cohesiveness (Staniforth, 1996). The angle of repose for native starch, pregelatinized starch and acid modified starch were in the order: native starch > pregelatinized starch > acid modified starch. This trend was also reflected in their dispersions in mucilage. Increase in mucilage concentration generally led to an improvement in flow characteristics as seen with a decrease in angle of repose (Fig. 4.6) and a decrease in Carr's index and Hausner's ratio (Table 4.7.). Characteristics of individual particle, particle shape, surface characteristics, particle, size distribution and packing configuration adopted by the powder during bulk densities determination play an important role in the determination of flow characteristics. The increase in D [v. 0.9] and decrease in D [v. 0.1] as seen in Tables 4.4 - 4.6 justify the increase in flow properties of the starches and dispersions.

Starch has been classified as a moderately hygroscopic material (Faroongsarng and Peck, 1994). The extent of hydration and swelling depends on the accessibility of the hydroxyl groups in the starch to the water, and it has been suggested that the amorphous regions are responsible for the reversible swelling of starch upon the absorption of water (French, 1984). Generally, there was a decrease in hydration capacity, swelling capacity and porosity as seen in Fig. 4.7 – 4.9 respectively with increase in mucilage concentration. Generally, the moisture sorption, hydration and swelling capacities were in the order pregelatinized starch > acid modified starch > native starch and for porosity the order was: native starch > pregelatinized starch > acid modified starch. These trends were also seen with their dispersions in mucilage. Similar findings were reported by Liu *et al*. (2006) that addition of mucilage to starch resulted in a decrease in the swelling power of starch. The increase in moisture sorption capacity was as a result of high affinity for water by hydrocolloids. Increase in the true densities of the starches was as a result of

increase in molecular weight brought about by penetration of mucilage into the interior of the starch granules and also adsorption to its surfaces, which led to decrease in intra and interstitial spaces and subsequently reduction in porosity. The hydration and swelling power of starch determines the degree of water absorption of starch during the starch swelling procedure (Carcea and Acquistucci, 1997). The decrease in hydration and swelling capacity of the native starch and its modified products by mucilage could be as a result of enlarged submicropores of the starch granules (Christianson, 1982), also as a result of hydrocarbon chains of internal lipids, which suppresses hydration of the amorphous regions of starch granules (Tester and Morrison, 1990), antiplastisizing effect of hydrocolloid compared with water, the influence of sugar-starch interaction and effect of sugars on water structures (Fasihuddin and Williams, 1999).

5.2 Pasting Properties of Native and Modified Starch Dispersions

Starch suspensions swell markedly and the viscosity increase dramatically when heated in sufficient water. The RVA results as seen in Tables 4.8 – 4.10 and Fig. 4.10 show that SPS has a higher peak viscosity, trough, breakdown and final viscosity as compared to pregelatinized and acid modified starch in the order SPS > PPS > APS. This is as a result of depolymerization of starch chains by acid and heat. This trend was also seen with the various dispersions in mucilage with a decrease in peak viscosity, trough, breakdown and final viscosity as the mucilage concentration increased. An increase in peak viscosity of starch paste in the presence of a hydrocolloid has been previously reported (Liu *et al*., 2003, Sasaki *et al*., 2000). The reason for an increase in peak viscosity could be accounted for by a thickening gum that enhances the

forces being exerted on the starch granules in the shear field. Yoshimura *et al*., (1996) indicates that an addition of hydrocolloid increase the effective starch concentration by immobilizing water molecules. The mucilage could also form a strong entanglement with the amylose released from starch granules (Liu *et al*., 2003). The effect of mucilage on gelatinization and pasting properties are dependent upon the source of starch and the concentration of mucilage (Huang *et al*., 2010). The set back and peak time were in the order: pregelatinized starch > native starch > acid modified starch, and also with their dispersions, which decreased with increase in mucilage concentration and increased with increased mucilage concentration respectively in the same order. The secondary increase in viscosity (set back) during the cooling phase is associated with the retrogradation phenomenon and relates to the amylose content (Mishra and Rai, 2006). The pasting temperature was higher with acid modification as compared with native and pregelatinized starches in the order: acid modified > pregelatinized starch > native starch. Similar trends were seen with their various dispersions, which increased with increase in mucilage concentration. This increase could be due to the interaction of mucilage with a small amount of amylose released by the limited swelling of starch granules (Liu *et al*., 2006).

5.3 Thermal Properties of Native and Modified Starch Dispersions

The thermal properties as seen in Table 4.11 show that the addition of mucilage caused marked increase in the onset temperature for the tested starches. This may be as a result of either interaction between mucilage and starch or competition of starch with water in the early stages of heat gelatinization. Several studies indicate that sugars or polyhydroxy compounds increase the

gelatinization temperature of starch (Kim and Walker, 1992; Liu *et al*., 2006). The onset of temperature, peak temperature, conclusion temperature and temperature range were in the order APS > PPS > SPS. For both native and pregelatinized starches, there was an initial increase in the onset temperature, peak temperature and conclusion temperature at lower concentrations of mucilage, followed by a reduction at higher concentrations as compared to acid modification which showed a decrease in the onset temperature with increase mucilage concentrations. Increase in gelatinization temperature can also be due to the presence of other components such as protein and lipids that would obstruct the swelling of granules and thus increase the amount of heat required to reach the final swelling. The enthalpy change for native and modified starches was in the order: SPS > PPS > APS. This trend also was seen with their dispersion in mucilage as seen in Table 4.11 with an increase in ΔH as the mucilage concentration increased. Enthalpy change is an indicator of a loss of molecular order within the granules, which increases with a decline of the degree of starch crystallinity (Tester and Morrison, 1990). Fasihuddin and Williams (1999) studied the effect of sugars on the thermal and rheological properties of sago starch. They found that sugars increased the gelatinization temperature and the gelatinization enthalpy. They discussed the effects in terms of the anti-plasticizing effect of sugars compared with water, the influence of sugar–starch interactions, and also the effect of sugars on water structure. Ahmad and Williams (1999) explained the influence of the sugars on the structure of the dispersions in terms of inhibition of chain organization.

5.4: Retrogradation Properties of Native and Modified Starch Dispersions

The syneresis of gels prepared from starches was measured as amount of water released from gels during storage (up to 7 days) at 4 ^{o}C. The result (Figs 4.11 – 4.13) shows that syneresis for native and modified starches were in the order: APS > PPS > SPS. Singh *et al* (2004) reported that the low amylose content might have caused less syneresis of the starch during the gel formation and resulted in weaker gel structure. In all the starch samples, there was an increase in syneresis with increase in mucilage concentration. Miles *et al* (1985) attributed the initial gel firmness during gelation to the formation of amylose matrix gel and the subsequent slow increase in gel firmness to amylopectin recrystallization. However, studies on the effect of sugars on starch recrystallization have been conflicting and inconclusive.

Various studies reported that certain sugars could retard (I'Anson *et al*., 1990; Katsuta *et al*., 1992, Slade & Levine, 1987) or accelerate starch recrystallization (Chang & Liu, 1991; Germani *et al*., 1983; Hoover & Senanayake, 1996; Prokopowich & Biliaderis, 1995; Ward *et al*., 1994). This could imply that sugars can behave differently, possibly depending on the host system and storage conditions. In fact, many of the above studies emphasized that sugars may be used either as plasticizers, like water, affecting the thermal transitions of starch, or as water immobilizers that reduce the mobility of water in the host system. Generally, native starch showed an increase in syneresis with time, while both modified starches and all dispersions showed a decrease in syneresis.

5.5 Tableting Properties of Compacts

Several factors such as the properties of the powder and specification of tableting press could affect the capacity of a powder system to decrease in volume under pressure resulting from the displacement of the gaseous phase. Closely related with the compression process is the consolidation process which can be described as the resultant increase in mechanical strength of a material due to particle re-arrangement and slippage, plastic deformation or fragmentation and particle-particle bonding. All tablets compacted from the starches and their dispersions were round and without any defects. Their colour ranged from white to brown depending on the colour of the starch and dispersions which ranged from white to brown as the percentage of the mucilage increased. There was increase in crushing and tensile strengths with starch modification (Tables 4.12 – 4.15) in the order: PPS > APS > SPS. This is in agreement with results of other workers like Ocheja (2000) and Odeku *et al* (2008), who reported that acid hydrolysis and pregelatinization of starches impart better physical properties (flow, compressibility and compactibility) to native starch and makes them amenable to direct compression. There was a decrease in disintegration time with modification of starch in the order: PPS > APS > SPS. This could be attributed to the results of crushing strength and porosity as seen in Tables 4.12 – 4.15 and Fig. 4.9 respectively. Disintegration depends not only on the strength of the bond existing between the particles but also on the porosity and swelling of the starch grains. Iwuagwu *et al* (1986) attributed poor disintegration of tablets to the formation of very strong inter-particulate bonds, while Keith (1976) attributed disintegration to porosity of the tablets. Generally, dispersions of native and modified starches showed an increase in disintegration time, crushing and tensile strength with a decrease in friability as the mucilage concentration increased. This is as a result of the mucilage which modifies the cohesive

properties of the starches by promoting the formation of strong cohesive bonds between the particles. So increased mucilage concentration leads to harder compacts with increased disintegration time, crushing and tensile strengths and as a result, improved friability.

All batches of native, modified starches and their dispersions passed the disintegration test as stipulated by BP (2010) except 40-MPPS. All modified starches dispersions showed good crushing strength (above 4 kgF) and friability (below 1 %), while native starch dispersions showed good crushing strength and friability for batches 30-MSPS and 40-MSPS. In comparison to mannitol and MCC PH 101, all the starches and their dispersions showed better crushing and tensile strength than mannitol but higher disintegration time. MCC PH 101 showed a much higher disintegration time as compared to all other compacts as seen in Table 4.15. . Generally, optimized tablet compact were exhibited by dispersion of 23.08 % w/w mucilage in starches (i.e. 30-MSPS, 30-MPPS and 30-MAPS) for all formulations and were used for further studies.

5.6: Compaction Studies of Native and Modified Starch Dispersions

Using the Heckel equation (Heckel, 1961a), a compression parameter can be derived that is generally considered to reflect the deformability of the particles in terms of a yield strength or yield pressure (Heckel, 1961b). From Fig. 4.14, a linear relationship was obtained with the correlation coefficient of ≥ 0.950 indicating deformation mainly by plastic flow. The values of the mean yield pressure, Do, D_A, and D_B for native and modified starches with their dispersions are presented in Table 4.16. The mean yield pressure (p_y) is inversely related to the ability of the starches to deform plastically under pressure. The order of P_y for native and modified starches was: APS > PPS > SPS. This indicates that SPS exhibited the fastest onset of plastic deformation

during compression, while APS exhibited the slowest. Low yield value reflects low resistance to pressure, good densification and easy compression (Jivraj *et al*., 2000). For native and modified starch dispersions, the order was: 30-MSPS > 30-MPPS > 30-MAPS indicating that 30-MSPS had the fastest onset while 30-MAPS had the slowest onset of plastic deformation. In other words, dispersion of modified starch (pregelatinized and acid modified) in mucilage led to a faster onset of plastic deformation as compared to their parent form.

As seen in Table 4.16, the values of D_o, D_A, and D_B for native and modified starch which represent the degree of initial packing in the die as a result of die filling, the total degree of packing at zero and low pressures and the phase of rearrangement of the particles in the early stages of compression respectively were in the order: SPS > PPS > APS. The reduction in D_o for modified starch was due to its particles, which were smaller than the native starch as seen in Tables 4.4 – 4.6. Thus, there were more mechanical and electrostatic forces to prevent packing (Paronem and Justin, 1983), but as the particle size increased, the electrostatic forces that could prevent closer packing of the particles decreased making native starch to have a higher D_o value. Conversely, the dispersions had higher D_o and lesser D_A as compared to their parent forms. This could also be related to their particle size as explained by Robert and Row (1987) that materials possess a critical particle diameter at which the densification mechanism turns from brittle to ductile when the particle size decreases. The stress necessary to cause particle fracture increases when the particle size decreases, whereas the stress causing plastic deformation of a material is independent of the particle size. The D_B value of native starch was slightly higher than that of modified starches translating to a greater degree of fragmentation of native starch as compared to its modified forms (Nystrom *et al*., 1993).

Fig 4.15 shows the Kawakita plots for native, pregelatinized and acid modified starches with their dispersions. A linear relationship was obtained at all compression pressures used with a correlation coefficient of ≥ 0.99 for all materials used. The D_i value which is a measure of packed initial relative density with application of small pressure or tapping was in the order: APS > PPS > SPS. These values were also seen to be higher than the value of loose initial relative density D_o which is in agreement with previous work carried out by Odeku and Itiola (1998). For native and modified starch dispersions, D_i value were in the order: 30-MSPS > 30-MPPS > 30-MAPS, which shows a significant reduction in minimum porosity (a) from its parent starches.

The value of P_k which is an inverse measure of the amount of plastic deformation occurring during the compression process was in the order: SPS > PPS > APS for native and modified starch. It has been established that the lower the P_k value, the more the total plastic deformation occurring during compression (Odeku and Itiola, 1998). In other words, modification of starch increases the plastic deformation of the native starch but reduces the plastic deformation of their dispersions in the order: 30-MAPS > 30-MPPS > 30-MSPS. This could be attributed to a reduction in fracture due to protection of the more fragile material (starch being ductile) from the more rigid network of the mucilage (being moderately hard and brittle). Mattsson and Nystrom, (2001) researched the positive effect of a "soft binder" on the tablet strength of a ductile material. They found that the ability of a soft binder to fill voids between the compound particles plays a decisive role in the increase of the tablet strength. Increase in tensile strength as seen with the dispersions could be as a result of higher bonding strength between starch and mucilage (Adolfsson *et al*., 1998, Jetzer, 1986), an increase of the number of antiparticle bonding sites in the compact (Mattsson and Nystrom, 2001), a higher densification of the mixture (Vromans and

Lerk, 1988) or a combination of these phenomenon. Generally, total plastic deformation creates more contact points for interparticulate bonding (Alebiowu and Itiola, 2002, Itiola and Pilpel, 1986).

5.7: Elastic Recovery and Brittle Fracture Index

During and after the removal of the applied load, a compressed powder bed generally shows an elastic recovery of its volume as an effect of stress relaxation. In case of a permanent deformation, the volume expansion will be small, whereas large tablet relaxations are caused by an important elastic component (Duberg and Nyström, 1986). The driving force for tablet relaxation has been suggested to be the elastic energy stored in the particles during densification (Maarschalk *et al*., 1997). On the other hand, the bonding between particles is regarded as the counteracting force against tablet relaxation. From Fig. 4.16, it can be seen that the elastic recovery were in the order: SPS > APS > PPS. This shows that modification of starch reduces the elastic recovery of the native starch. Dispersion of native and modified starches in mucilage showed a significant reduction in the elastic recovery of the parent starches in the order: 30-MAPS > 30-MPPS > 30-MSPS. The removal of compaction pressure causes the tablet to return to their former shape depending on the material elastic properties. When tablet elastic recovery takes place, this would result in decrease in the inter-particulate contacts and therefore the tensile strength of the tablet is negatively affected (Murad, 2009). This further suggests the decrease in mechanical strength seen with the native and modified starch as compared to their dispersions.

Fig 4.17 shows the gradient increase in tensile strength with increase in pressure for native, modified starches and their dispersions in the order: 30-MAPS = 30-MPPS > 30-MSPS > PPS > APS > SPS. This is characteristic of materials that are plastically deforming.

Brittle fracture refers to capping and lamination of tablets which occurs at the point of ejection of the tablet from the machine dies. It is as a result of stress concentration at the edge of the void or low density region. The results as seen in Table 4.18 show that modification of starch decreases the brittle fracture index (BFI) in the order SPS > APS > PPS, while for the dispersion, the BFI was in the order: 30-MAPS = 30-MPPS > 30-MSPS. These correlate with reports that thermal and acid treatments reduce the elasticity and BFI value of native starch (Eichie and Roland, 2002; Alebiowu and Itiola, 2002).

There was a correlation between the BFI and elastic recovery as seen in Table 4.18 and Fig 4.16 respectively which shows a lower BFI value when elastic recover was lower e.g. SPS with the higher elastic recovery had the highest BFI value, while 30-MSPS with a lower elastic recovery had the lowest BFI value. This means that predominantly elastic materials are more prone to brittle fracture than plastic materials. This correlates with the findings of Itiola and Pipel (1986), Okor *et al*. (1998) and Uhumwangho and Okor (2004) that sudden elastic recovery following tablet ejection from the die has been implicated as a possible cause of brittle fracture, supported by the evidence of direct correlation between the plasto-elasticity of the materials and the brittle fracture index of resulting tablets. Tablet samples with BFI value ≥ 0.5 display a high fracture incidence during actual tableting (Heistand, 1977). This means that native starch (SPS) would display a high fracture tendency if used in tablet production.

5.8: Dilution Capacity Index

Dilution capacity is a measurement of the proportion of poor compactable drug which can be incorporated into a vehicle to produce satisfactory tablets. The term "dilution potential" or "carrying capacity" is defined as the amount of active ingredient which the diluents can carry in the direct compression technique (Lachman *et al*., 1970). Most commonly, dilution potential is assessed by comparing the hardness (or tensile strength) versus compaction pressure curve for various binary mixtures of the filler and some poorly compactable substance, such as ascorbic acid. The tensile strength pressure profile of all powder mixture as presented in Figs 4.18 – 4.22 shows that increase in drug concentration reduces tensile strength of the powder compact. Subsequently, the measured area under the curve (AUC) obtained by the filled quadratic equation between the compaction limits is decreased. Since starch, microcrystalline cellulose and mannitol are plasto-elastic material, the curvature and gradual decrease of the tensile strength profile upon ascorbic acid loading was expected.

As seen in Table 4.19, the AUC and work potential decreased with the increase of ascorbic acid content. The decrease was simply due to the increase in the proportion of poorly compactable component. MA index, which is a theoretical measure of the maximum ability of the excipient to hold ascorbic acid in a tablet mass while its integrity upon release of pressure was maintained, is shown in Table 4.20. The order of decreasing MA index (dilution capacity) was MCC PH 101 > 30-MSPS > 30-MPPS > 30-MAPS > mannitol.

Habib *et al*. (1996) presented that the MA index reflected the decrease in AUC of excipient/ascorbic acid mixture relative to that of the ascorbic acid free blend as a function of the

percentage w/w of ascorbic acid. Thus, the higher value was the higher capacity of that excipient to compensate for poorly compactable ascorbic acid. In order to account for the higher AUC of the excipient, a new index was proposed. This index, the dilution capacity index (DCI) was determined from multiplying MA index by AUC percent of drug free blend. The DCI values from this study are shown in Table 4.20. The largest DCI was assigned to microcrystalline cellulose. The DCI is a multiplicative index combining the AUC of drug free excipient and the dilution capacity. Therefore, having high DCI value reflects a higher AUC of drug free excipient and/or less sensitivity of the excipient to loss of compactibility due to the presence of poorly compactable component. The result showed microcrystalline cellulose to be the highest compactable excipient and mannitol the lowest in the order: MCC > 30-MPPS > 30-MAPS > 30-MSPS > mannitol.

5.9: Lubricant Sensitivity Ratio

The effect of magnesium stearate concentration on the tensile strength of tablet at various compression pressures is illustrated in Fig. 4.23 – 4.27. As expected, the tensile strength increased with increasing compression pressure and decreased with increasing lubricant level. It was reported that the increase in alkali stearate lubricant markedly reduces the hardness of plastic and elastic materials (Bolhius and Holzer, 1996). The main reason behind the decrease in the mechanical strength is due to the formation of lubricant film around the powder particles. This film prevents the formation of excipient-excipient bonding and substitute with lubricant-lubricant bonding which are much weaker (Meyer and Zimmermann, 2004). This phenomenon of

lubricant sensitivity occur mainly in plastic deforming materials (Zuurman *et al*., 1999). In case of material that deform by fragmentation, it does break the lubricant film around its particles and can form excipient-excipient bonding (Vromans *et al*., 1988). The overall order of lubricant sensitivity ratios (LSR) at lower pressure was: MCC < mannitol < 30-MPPS < 30-MAPS < 30-MSPS and at higher pressure, the order was: 30-MAPS < 30-MPPS < 30-MSPS < MCC < mannitol. This means that at higher pressures, starch dispersions had lower LSR as compared to mannitol and MCC, which had a low LSR value at lower pressure. Both MCC and mannitol showed a higher LSR at high pressure because at higher pressure, the compaction phase has entered from the plastic deforming into the strain hardening (Murad, 2009). This can be explained based on the assertion that the sensitivity of excipient to magnesium stearate depend not only on the deformation behavior but also on the bonding mechanism of the materials (Lerk *et al*., 1977).

5.10: Ascorbic Acid Chewable Tablet

Ascorbic acid was used in the production of chewable tablets using 30-MSPS, 30-MPPS, 30-MAPS, mannitol and Avicel HFE as diluents using the direct compression method. Binary mixtures of 30-MSPS, 30-MPPS and 30-MAPS sugar alcohols such as mannitol and maltitol as diluents/sweeteners were formulated to determine the physical characteristics they would impact on the tablet formulation. In comparison, sodium saccharine was used as sweetener to compare the sensory perception in relation to other formulation.

FT-IR spectra matching approach was used for detection of any possible chemical interaction between ascorbic acid with 30-MSPS, 30-MPPS and 30-MAPS. There was no appearance or disappearance of peaks which indicate no interaction between ascorbic acid with 30-MSPS, 30-MPPS and 30-MAPS. The characteristic peaks and bands for ascorbic acid are presented in Figs. 4.28-4.30. Ascorbic acid showed the following absorption bands: The peak at 3317 - 3410 cm^{-1} represents O-H stretch; 1670 cm^{-1} represents C=0 stretch; 1328 cm^{-1} represents O-H plane bending; 1139 cm^{-1} represents CH_2 twisting; 1113 cm^{-1} represents C-H in plane bending; 988 cm^{-1} represents C-C symmetric stretch; 817 cm^{-1} represents C-H out of plane bending; 568 cm^{-1} represent C-C-C out-of-plane bending/C-C in-plane bending and 445 cm^{-1} is typical of the C-C-C out-of-plane deformation (See Fig. 1.1).

As seen in Figs. 4.31 – 4.33, the crushing strength, friability and disintegration of all the batches were reported. All the tablets made from starch dispersions were brown in colour, round without any tablet defects and had a characteristic sweet potato flavor but tablets made from mannitol and Avicel HFE were white, odorless and without any physical tablet defects.

As seen in Fig. 4.31, formulations F1-F3 contained 30-MSPS, 30-MPPS, and 30-MAPS alone as filer binder/sweetener respectively, while formulations F4-F6 which in addition to the starch dispersions contained sodium saccharine and Crosspovidone. Formulation F1-F6 had excellent friability (less than 1 %), crushing strength within 3.5 – 5.5 kgf and disintegration time of less than 7 min. There were no significant differences between the friability in batches F1 – F6 but batches with Crosspovidone showed a significantly ($p < 0.05$) higher crushing strength and lower disintegration time as compared to F1 – F3. This increase in crushing strength could be as a result of the highly compressible nature of Crosspovidone due to their unique particle

morphology and the lower disintegrant time might be due to the super disintegration properties of Crosspovidone that combines swelling and wicking as the mechanism of disintegration.

Fig. 4.32 shows the result of binary mixture of starch dispersion and mannitol in a ratio of 5:1 and 2:1. Increased mannitol ratios led to a reduction in crushing strength and disintegration time with an increase in friability. Formulations F7 – F12 all had friability less than 1 %, and disintegration time less than 6 min. There was a decrease in disintegration time with increased mannitol concentration which was due to the very soluble nature of mannitol and decreased crushing strength due to the poorly compactable nature of mannitol. Similar findings were exhibited with binary mixture of maltitol, which decrease in crushing strength, disintegration and an increase in friability as the concentration increased as can be seen in Fig. 4.33. The reason also is due to the very soluble nature of sugar alcohols and also their poor compaction profile. Ascorbic acid tablets made with Avicel HFE had friability less than 1 %, better disintegration time as compared to other formulation except F19, which contain mannitol alone as excipient and also, the crushing strength was above 4 kgf but not as high as formulations with starch dispersions alone as excipient. Formulation F19 which contained mannitol alone produced tablets with very poor friability and crushing strength.

Generally, formulation F1 – F6 which contained starch dispersions alone had acceptable friability (less than 1 %), crushing strength (above 3 kgf) and disintegration time (less than 7 min.). Increase in mannitol and maltitol in binary mixtures gave tablets with unacceptable properties with crushing strength less than 3 kgf. In total, there was no significant difference at $p< 0.05$ between formulations using modified starch dispersion (i.e. 30-MPPS and 30-MAPS)

but there was a significant difference between dispersion of native starch and modified starches for all parameters (i.e. friability, crushing strength and disintegration).

For the cummulative drug release (Table 4.22), formulations with acceptable friability (< 1 %), crushing strength (> 3 kgf) and disintegration (< 15 min) were used for the study. From the study, formulation F20 which contains Avicel HFE had the fastest onset of drug release (69.75 %) as compared to formulation F1 –F3 (contains starch dispersions alone) which has the slowest onset of drug release (4.35 – 7.8 %). This is as a result of the highly soluble and dispersible mannitol and microcrystalline cellulose which are the components of Avicel HFE as compared to the starch dispersions. Generally, formulation F13 – F15 and F20 had the highest cumulative drug release (≥ 100 %) within 15 min.

Tablets with acceptable friability, crushing strength and disintegration that were subjected to dissolution studies were used to determine the degree of acceptance, percentage response to taste and hardness of the formulated ascorbic acid chewable tablets. As seen in Fig 4.34, percentage response to sweetness between 45 – 70 % was recorded for formulation F4 – F6 as compared to all other formulations which had between 70 – 100 %. Formulation F1 – F3 which contained native and modified starch dispersions alone could not mask the taste of ascorbic acid as responded by the panel. This was expected due to the fact that most excipients which are appropriate bases for chewable tablets as their major property, has a level of sweetness that contributes positively to the overall taste of the product. Often, the sweetness imparted by these excipients is insufficient to overcome the bad taste of the drug. In these cases, the formulator most often uses artificial enhancers to increase the overall sweetness impact (Leon *et al*., 1989). Also, all other formulations with binary mixtures of sugar alcohols could not mask the taste of

sourness imparted by ascorbic acid. Formulation F4 – F6 which had a positive response to taste was as a result of sodium saccharine (0.53 %) present in the formulation.

Percentage response to hardness (Fig. 4.35) shows that there was a 100 % response to formulation F7 as being suitable, formulation F1, F3, F4, F5, F8, F13, F14 and F15 as either suitable or too soft and all other formulation as either too had, suitable or too soft by various respondents. There was no direct correlation between the crushing strength of the formulation to the panel response. Tablets were rated from 0 – 5 points for their appearance, aroma, hardness, taste, mouth feel sensation and after taste. The overall tablet quality was calculated as the sum of all recorded sensory properties. All tablet formulations had acceptable appearance, aroma, hardness, taste, mouth feel and after taste which were basically imparted by the starch dispersions without the addition of external colorant and flavoring agents. This is in line with Maruf *et al*. (2010) that sweet potato flour can be used to enhance food products through colour, flavor, natural sweetness and supplemented nutrients. Fig. 4.36 shows the degree of acceptance for the formulated chewable tablets. Formulation F6 (30-MAPS) had the highest acceptance while formulation F20 had the lowest. There was a significant difference ($p < 0.05$) between formulations F4 – F6 and other formulations. This could be as a result of the higher percentage response to taste (Fig. 4.34). Formulations F1 – F3, which contained native and modified starch dispersions alone, had a better degree of acceptance as compared to other formulations with sugar alcohols and Avicel HFE.

Formulations F4, F5 and F6, which had the highest degree of acceptance from the panel test, were subjected to accelerated stability studies at 40 ^{O}C / 75 % relative humidity for 3 months. The weight variation (Table 4.23) shows that there was only a significant change in weight by

the third month. This might be due to moisture adsorption from the atmosphere. Moisture adsorption plays an important role in physical and chemical stability, in the properties of solid dosage forms and excipients. The amount of moisture adsorbed by drugs and excipients affects the flow, compression characteristics, and hardness of granules and tablets (Ali, 2005). The amount of water associated with a solid at a particular RH and temperature depends on its chemical affinity for the solid and the number of available sites of interaction, surface area, and nature of the material (Dawoodbahai and Rhodes, 1989). As seen in Fig. 4.37, the result shows that there was a slight increase in crushing strength within one month and subsequently, a reduction for the remaining two months for all formulations. According to literature, as the moisture content of pharmaceutical substances increases the tablets' tensile strength increases (specifically at low moisture contents), reaches a maximum, and then decreases, specifically at higher moisture content (Ali, 2005). An increase in tensile strength with increasing moisture content or RH has been explained by two possible mechanisms. First, adsorbed water could function as a surface-restructuring medium, thus increasing the amount of solid bridges (Malamataris and Karidas, 1994). Another possible explanation for increasing tensile strength is that immobile water layers sorbed at particle surfaces can enhance particle–particle interaction (Coelho and Harnby, 1978). Fig. 4.38 shows that there was a gradual decrease in disintegration time within the duration of study for all formulation. This could be as a result of the decreased crushing strength obtained from Fig. 4.37. There was no significant difference ($p < 0.05$) between the cumulative drug release of optimized formulation for the 3 month period of stability testing.

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMENDATION

6.1 Summary

Native starch (SPS) and mucilage was extracted from *Ipomoea* batatas. Subsequently, SPS was pregelatinized (PPS) and acid modified (APS), and dispersions of mucilage with SPS, PPS and APS in a ratio of 1:20, 1:10, 2:10, 3:10 and 4:10 respectively were produced. All starch samples except SPS, PPS and APS possessed slight characteristic sweet taste and aroma with brown colouration which increased as the ratio of the mucilage increased. No chemical interactions between the native and modified starch with their dispersion were observed using FT-IR spectra matching approach. There was an increment in water solubility index, particle size, moisture sorption capacity, true density and flow properties with a decrease in moisture content, pH, hydration capacity, swelling capacity and porosity as the mucilage concentration increased. SPS had a higher peak viscosity, trough, breakdown, setback, pasting temperature and final viscosity as compared to PPS and APS. This trend was also seen with various dispersions in mucilage which decreased with increase in mucilage concentration. Addition of mucilage caused marked increase in the onset of temperature, peak temperature, conclusion temperature, temperature range and enthalpy. Generally, SPS showed an increase in syneresis with time, while both modified starches and all dispersions showed a decrease in syneresis with increase in mucilage concentration. All tablets compacted (placebo) showed an improvement in crushing and tensile strength and a decrease in disintegration time with starch modification. Native and modified starch dispersions showed an increase in disintegration time, crushing and tensile strength with a decrease in friability as the mucilage concentration increases. Generally, optimized tablet compact were exhibited by dispersion of 23.08 % w/w mucilage in starches (i.e. 30-MSPS, 30-MPPS and 30-MAPS) for all formulations and were used for further studies. A linear relationship was obtained with the correlation coefficient of $\geq$ 0.95 indicating deformation

mainly by plastic flow for starch, its modified product and their dispersions. The order of P_y and D_i for native and modified starches was: APS > PPS > SPS and for native and modified starch dispersions, the order was: 30-MSPS > 30-MPPS > 30-MAPS. The value of P_k, D_o, D_A, and D_B for native and modified starch were in the order SPS > PPS > APS and for native and modified starch dispersions, the order was: 30-MAPS > 30-MPPS > 30-MSPS. Modification and dispersions of starches in mucilage reduced the elastic recovery and brittle fracture index of the native starch. The order of decreasing MA index (dilution capacity) was MCC PH 101 > 30-MSPS > 30-MPPS > 30-MAPS > mannitol. The overall order of lubricant sensitivity ratio at lower pressure was MCC < mannitol < 30-MPPS < 30-MAPS < 30-MSPS, and at higher pressure, the order was 30-MAPS < 30-MPPS < 30-MSPS < MCC < mannitol. All ascorbic acid chewable tablets made from starch dispersions were brown in colour, round without any tablet defects and has a characteristic sweet potato flavor. Generally, formulation F1 – F6 which contained starch dispersions alone had acceptable friability (< 1 %), crushing strength (above 3 Kgf) and disintegration time (< 7 min). Increase in binary mixtures of mannitol and maltitol gave tablets with unacceptable properties with crushing strength < 3 Kgf and friability > 1 %. Formulation F20, which contained Avicel HFE had the fastest onset of drug release (69.75 %) in one min as compared to formulation F1 – F3 (contained starch dispersion alone), which had the slowest onset of drug release (4.35 – 7.8 %). Generally, formulation F13 – F15 and F20 had the highest cummulative drug release (≥ 100 %) within 15 min. Tablets with acceptable friability, crushing strength and disintegration that were subjected to dissolution studies were used to determine the degree of acceptance, percentage response to taste and hardness of the formulated ascorbic acid chewable tablets. Percentage response to sweetness between 45 – 70 % was

recorded for formulation F4 – F6 as compared to all other formulations which had between 70 – 100 % responses to sourness. All the tablet formulations had acceptable appearance, aroma, hardness, taste, mouth feel and after taste which were basically imparted by the starch dispersions without the addition of external colourant and flavouring agents. Formulation F6 (contain 30-MAPS) had the highest acceptance, while formulation F20 had the lowest. Formulations F4, F5 and F6 which had the highest degree of acceptance from the panel test were subjected to accelerated stability studies at 40 ^{0}C/75 % relative humidity for 3 months. The weight variation shows that there was only a significant change ($p < 0.05$) in weight by the third month. There was a gradual decrease in disintegration time and crushing strength within the duration of study for all the formulations. There was no significant difference ($p< 0.05$) within the cummulative drug release of optimized formulation for the 3 month period of stability testing.

6.2 Conclusion

Incorporation of mucilage into native and modified (pregelatinized and acid modified) starches imparted a brownish, sweetened and characteristic sweet potato flavor to the respected starches obtained from *Ipomoea batatas*, which increased as the ratio of the mucilage increased. There was a decrease in hydration, swelling and porosity with an increase in flow properties of the excipient. These properties would be evidently important if an excipient is to be considered for chewable tablets. The influence of mucilage and modification on the thermal, pasting and retrogradative properties may be useful for modifying *Ipomoea batatas* starch based pharmaceutical and food products in terms of product texture and process development. Dispersion of native, pregelatinized and acid modified starches showed an increase in tensile

strength, disintegration time and a reduction in friability as compared to their parent forms. Generally, in comparison to their parent forms, compaction parameters of the dispersions revealed an acceptable BFI value with a reduction in total plastic deformation and elastic recovery. Pregelatinized and acid modified starch dispersions in mucilage showed good MA index (dilution capacity) as compared to microcrystalline cellulose (MCC PH 101) although a lower dilution capacity index. Generally, the modified starch dispersion would have an optimum tablet tensile strength in the presence of lubricant (magnesium stearate) if compressed at a higher compressional pressure. Modified starch and mucilage dispersion possessed excellent properties as excipient for ascorbic acid chewable tablet formulations using the direct compression method in view of its physicochemical and material properties as well as its positive panel assessment and stability over time.

6.3 Recommendations

1. Further studies could be carried out in relation to the method of manufacturing of chewable tablets using modified starch and mucilage dispersions such as aqueous and non-aqueous granulation method, coating by wet granulation, microencapsulation, adsorbate formation techniques (solvent method and melting method), spray congealing and spray coating.
2. Also, drugs with various taste characteristics such as bitter and acidic could be used to assess the masking properties of the excipient.

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APPENDICES

A1: Specific Surface Area of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Specific Surface Area (m^2/g)		
	SPS	PPS	APS
0	0.233 (0.12)	0.239 (0.13)	0.201 (0.06)
4.76	0.201 (0.22)	0.214 (0.10)	0.157 (0.10)
9.09	0.219 (0.32)	0.206 (0.11)	0.168 (0.08)
16.67	0.231 (0.06)	0.225 (0.15)	0.205 (0.11)
23.08	0.199 (0.11)	0.222 (0.03)	0.170 (0.02)
28.57	0.183 (0.02)	0.186 (0.04)	0.195 (0.03)

A2: Angle of Repose of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Angle of Repose (^{0})		
	SPS	PPS	APS
0	25.14 (0.07)	20.94 (0.33)	21.04 (0.07)
4.76	24.68 (0.11)	23.76 (0.18)	21.16 (0.33)
9.09	21.24 (0.21)	22.32 (0.12)	21.48 (0.09)
16.67	14.75 (0.09)	18.16 (0.09)	22.03 (0.14)
23.08	21.33 (0.33)	25.46 (0.34)	23.08 (0.06)
28.57	22.09 (0.22)	24.88 (0.17)	25.96 (0.11)

A3: Hydration Capacity of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Hydration Capacity (%)		
	SPS	PPS	APS
0	1.15 (0.13)	1.4 (0.11)	1.33 (0.08)
4.76	1.36 (0.81)	1.38 (0.14)	1.29 (0.11)
9.09	1.05 (0.41)	1.21 (0.20)	1.2 (0.04)
16.67	0.91 (0.17)	1.08 (0.05)	1.05 (0.08)
23.08	0.91 (0.09)	1.01 (0.07)	0.94 (0.01)
28.57	0.87 (0.06)	0.93 (0.11)	0.87 (0.02)

A4: Swelling Capacity of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Swelling Capacity (%)		
	SPS	PPS	APS
0	29.8 (0.07)	76.95 (0.09)	49.67 (0.06)
4.76	68.75 (0.11)	69.29 (0.06)	58.47 (0.04)
9.09	40.23 (0.04)	56.37 (0.11)	47.83 (0.09)
16.67	32.84 (0.01)	50.00 (0.05)	42.22 (0.01)
23.08	31.85 (0.02)	47.64 (0.05)	34.78 (0.01)
28.57	23.75 (0.12)	40.91 (0.02)	26.09 (0.03)

A5: Porosity of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Porosity		
	SPS	PPS	APS
0	3.52 (0.08)	2.78 (0.11)	2.64 (0.01)
4.76	2.92 (0.11)	2.44 (0.08)	2.27 (0.01)
9.09	2.78 (0.09)	2.44 (0.03)	2.27 (0.04)
16.67	2.44 (0.12)	2.44 (0.01)	2.18 (0.01)
23.08	2.14 (0.22)	2.09 (0.23)	2.10 (0.24)

28.57	2.14 (0.02)	2.09 (0.06)	2.10 (0.16)

A6: Peak Viscosity of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Mucilage (% w/w)	Peak Viscosity (RVU)		
	SPS	PPS	APS
0	307.8 (0.07)	228.5 (0.11)	19.5 (0.04)
4.76	176.8 (0.01)	150.5 (0.14)	18.58 (0.08)
9.09	153.1 (0.33)	124.3 (011)	16.83 (0.17)
16.67	117.5 (0.11)	96.0 (0.34)	13.83 (0.04)
23.08	94.0 (0.16)	66.8 (0.21)	10.92 (0.01)
28.57	75.0 (0.22)	51.5 (0.11)	8.67 (0.21)

A7: Heckel Indices of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Pressure (KN)	ln [1/(1-D)]					
	SPS	PPS	APS	30-MSPS	30-MPPS	30-MAPS
2.49	2.35	1.28	1.09	1.35	1.32	1.02
4.98	2.60	1.56	1.31	1.45	1.40	1.12
9.96	2.94	1.73	1.43	1.51	1.51	1.31
14.94	2.94	1.80	1.48	1.60	1.77	1.35
19.93	2.85	1.85	1.44	1.57	1.73	1.30
24.91	2.66	1.8	1.37	1.57	1.73	1.32
29.26	2.64	1.69	1.47	1.55	1.76	1.28
34.24	2.64	1.66	1.44	1.60	1.69	1.25

A8: Kawakita Indices of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Pressure (KN)	P/C					
	SPS	PPS	APS	30MSPS	30MPPS	30MAPS
2.49	4.45	5.55	5.78	5.89	5.82	5.49
4.98	8.86	10.04	10.31	11.27	13.35	10.32
9.96	17.41	19.27	19.76	22.04	21.51	19.12
14.94	26.17	28.53	29.18	32.19	30.24	28.25
19.93	34.97	37.75	39.39	43.33	40.59	38.42
24.91	43.47	47.54	50.32	54.15	50.84	47.56
29.26	50.89	57.04	57.26	63.98	59.35	56.67
34.24	61.47	67.27	67.67	73.79	70.45	67.14

A9: Tensile Strength of Binary Mixtures of Ascorbic Acid in Modified Starches Dispersions obtained from *Ipomoea batatas,* Mannitol and Microcrystalline Cellulose

Pressure (KN)	Tensile Strength (KN/M^2)				
	0 % As. A	20 % As. A	40 % As. A	60 % As. A	80 % As. A
30-MSPS					
2.49	3.50	2.60	2.04	1.04	0.97
4.98	9.20	6.74	5.13	4.11	2.45
9.96	11.85	8.63	7.59	5.59	2.98
14.94	10.51	9.71	7.85	6.74	4.13
19.93	11.38	8.01	8.27	7.09	4.19
30-MPPS					
2.49	8.73	3.02	2.47	2.01	0.78
4.98	16.95	8.64	5.39	2.74	1.94
9.96	18.77	14.19	7.47	4.46	3.07
14.94	20.47	16.07	8.85	7.01	4.04
19.93	19.05	16.49	10.81	8.07	3.85
30-MAPS					
2.49	4.26	2.54	1.98	1.33	0.85
4.98	14.52	8.06	5.72	2.90	1.87
9.96	20.55	11.04	8.04	4.64	2.91
14.94	21.70	13.07	9.88	5.81	4.25
19.93	22.29	14.89	10.38	7.08	4.29
MANNITOL					
2.49	5.04	4.1	2.94	2.26	1.96
4.98	9.87	7.89	5.16	3.70	2.32
9.96	11.04	5.48	6.22	2.58	2.12
14.94	10.19	4.62	3.3	2.26	2.12
19.93	5.79	4.11	3.12	2.13	2.09
MCC					
2.49	57.00	32.87	22.48	9.81	5.10
4.98	77.29	57.6	42.21	21.08	8.05

9.96	83.6	71.49	47.18	31.26	11.18
14.94	84.04	75.8	52.24	35.51	11.45
19.93	84.79	73.14	51.90	40.36	14.90

A10: Tensile Strength of Binary Mixtures of Magnesium Stearate in Modified Starches Dispersions obtained from *Ipomoea batatas,* Mannitol and Microcrystalline Cellulose

	Pressure (KN)	Tensile Strength (KN/M^2)		
		0 % mag.st.	0.25 % mag.st	0.5 % mag.st.
30-MSPS				
	2.49	3.60	1.70	1.54
	4.98	7.56	5.11	3.99
	9.96	7.86	5.39	3.99
	14.94	8.20	5.15	4.77
	19.93	7.92	5.07	3.86
30-MSPS				
	2.49	7.86	5.47	4.40
	4.98	17.34	11.41	9.89
	9.96	17.59	11.65	10.76
	14.94	18.82	14.39	12.15
	19.93	18.55	13.35	11.73
30-MAPS				
	2.49	7.20	4.49	3.40
	4.98	15.6	12.54	7.10
	9.96	17.28	15.42	9.85
	14.94	17.79	14.78	10.29
	19.93	18.10	14.28	10.17
MANNITOL				
	2.49	4.94	3.30	2.78
	4.98	9.68	5.45	3.54
	9.96	10.82	3.83	2.76
	14.94	9.99	4.68	3.21
	19.93	5.68	2.49	2.44
MCC				
	2.49	57.00	40.95	36.97
	4.98	77.29	53.35	38.38
	9.96	83.6	60.09	47.51

	14.94	84.04	60.92	44.53
	19.93	84.79	50.53	41.08

A11: Indices of Retrogradation by Syneresis of Native Starches and their Dispersions in Mucilage obtained from *Ipomoea Batatas*

Parameters	Syneresis (%)			
	1st day	2nd day	4th day	7th day
SPS	63.01	67.34	67.45	69.31
5-MSPS	79.59	80.85	78.93	65.89
10-MSPS	80.55	82.73	79.73	69.30
20-MSPS	79.21	79.28	80.16	69.71
30-MSPS	81.03	83.21	82.10	71.16
40-MSPS	77.63	81.59	81.19	72.49
PPS	74.98	77.95	79.91	63.80
5-MPPS	76.30	79.96	78.93	64.95
10-MPPS	77.38	79.10	79.31	65.93
20-MPPS	81.11	81.06	80.65	69.26
30-MPPS	79.50	81.38	81.36	71.01
40-MPPS	81.46	81.56	80.94	74.41
APS	87.79	87.93	86.26	82.70
5-MAPS	87.43	87.83	87.09	82.36
10-MAPS	87.55	88.26	86.20	79.24
20-MAPS	88.71	89.30	87.08	80.55
30-MAPS	90.20	89.53	88.50	80.60
40-MAPS	90.75	89.89	87.71	83.39

A12: Elastic Recovery Indices of Native and Modified Starches Dispersions in Mucilage obtained from *Ipomoea batatas*

Pressure (KN)	Elastic Recovery (%)					
	SPS	PPS	APS	30MSPS	30MPPS	30MAPS
2.49	6.17	6.12	8.19	2.64	4.74	5.44
4.98	7.50	6.49	8.83	3.13	5.81	6.01
9.96	8.70	6.74	9.42	2.90	5.73	6.00
14.94	8.85	6.18	8.17	3.40	5.84	6.68
19.93	9.07	6.68	8.49	3.02	5.86	6.56
24.91	10.27	6.10	8.32	3.01	5.84	6.62
29.26	10.07	6.68	8.39	3.38	5.56	7.01

34.24	9.32	6.61	7.78	3.42	5.92	6.74

A13: Friability Value, Crushing Strength and Disintegration Time for Ascorbic Acid Chewable Tablet Formulations

Formulations	Friability (%)	Crushing Strength (KgF)	Disintegration Time (min.)
F1	0.157	3.73 (0.60)	6.30 (0.11)
F2	0.390	4.12 (0.47)	6.62 (0.65)
F3	0.313	3.97 (0.47)	6.74 (0.36)
F4	0.233	4.37 (0.69)	5.37 (0.16)
F5	0.276	4.72 (0.34)	6.04 (0.23)
F6	0.197	4.93 (1.34)	6.21 (0.08)
F7	0.044	3.38 (0.25)	3.66 (0.27)
F8	0.133	4.50 (0.61)	4.21 (0.02)
F9	0.092	4.65 (0.30)	4.22 (0.02)
F10	0.506	2.48 (0.15)	2.24 (0.08)
F11	0.359	3.11 (0.34)	2.96 (0.19)
F12	0.463	2.65 (0.43)	3.18 (0.05)
F13	0.130	3.35 (0.03)	3.91 (0.32)

F14	0.170	4.01 (0.56)	4.33 (0.11)
F15	0.220	3.80 (0.40)	4.41 (0.06)
F16	0.570	2.04 (0.03)	3.17 (0.06)
F17	0.260	2.94 (0.33)	3.41 (0.08)
F18	0.430	2.71 (0.24)	3.71 (0.25)
F19	11.530	0.57 (0.32)	0.26 (0.06)
F20	0.420	4.50 (0.22)	0.57 (0.07)

A14: Values for Percentage Response to Taste of Ascorbic Acid Chewable Tablet Formulations

Formulations	Sweet	Sour	Others
F1	0	100	0
F2	0	100	0
F3	0	100	0
F4	68	16	16
F5	50	50	0
F6	45	55	0
F7	0	100	0
F8	0	100	0
F9	0	100	0
F13	0	100	0

F14	0	100	0
F15	0	85	15
F20	0	65	35

A15: Values for Percentage Response to Hardness of Ascorbic Acid Chewable Tablet Formulations

Formulations	Too hard	Suitable	Too soft
F1	0	68	32
F2	14	72	14
F3	0	40	60
F4	0	85	15
F5	0	50	50
F6	28	56	16
F7	0	100	0

F8	0	85	15
F9	28	44	28
F13	0	72	28
F14	0	65	35
F15	0	60	40
F20	70	15	15

A16: Values for Degree of Acceptance of Ascorbic Acid Chewable Tablet Formulations

Formulations	Appearance	Aroma	Hardness	Taste	Mouth feel	After effect
F1	3.50	3.40	3.50	3.17	3.67	4.00
F2	3.86	3.83	3.43	3.00	3.43	3.43
F3	4.00	3.50	2.80	3.00	3.20	4.20
F4	3.67	3.20	3.83	3.50	3.83	4.33
F5	3.83	3.40	3.00	3.67	4.00	3.67

F6	4.00	4.00	3.86	3.71	4.00	4.00
F7	3.86	4.00	3.57	3.00	3.14	3.57
F8	3.83	3.80	3.50	2.83	3.33	3.33
F9	3.71	3.50	3.29	2.86	2.86	3.29
F13	3.71	3.14	3.86	2.71	3.71	3.14
F14	3.67	3.67	3.50	2.67	2.67	3.67
F15	3.71	4.00	3.43	3.14	2.86	3.29
F20	3.67	3.33	2.50	3.17	2.50	3.17

List of Papers Accepted for Publication

I. Achor, M., Saringat, H.B., Allagh, T.S., Hassan, M and Isah, A.B (2014). Effects of Mucilage on the Material and Physic-Chemical Properties of Native and Modified Starches obtained from *Ipomoea batatas*. Accepted for publication in *America Journal of Pharmtech Research*.

II. Achor, M., Saringat, H.B., Allagh, T.S., Hassan, M and Isah, A.B (2014). Effects of Mucilage on the Pasting, Thermal and Retrogradative Properties of Native and Modified

Starches obtained from *Ipomoea Batatas*. Accepted for publication in *Journal of Food Science and Quality Management*.

III. Achor, M., Saringat, H.B., Allagh, T.S., Hassan, M and Isah, A.B (2014). Consolidative Properties of Native and Modified Starch Dispersions in Mucilage obtained from *Ipomoea Batatas.* Accepted for publication in *International Journal of pharmaceutical research.*

IV. Achor, M., Saringat, H.B., Allagh, T.S., Hassan, M and Isah, A.B (2014). Modified Starch and Mucilage Dispersions obtained from *Ipomoea Batatas:* Assessment of Dilution Capacity and Lubricant Sensitivity Ratios. Accepted for publication in *International Journal of pharmaceutical research.*