TABLETING BEHAVIOUR OF SOME DEPOLYMERIZED LOCAL STARCHES

BY

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DECLARATION

I hereby declare that this thesis has been written by me and that it is a record of my research work, done under the supervision of Professor A.B. Bangudu. It has not been presented in any previous application for higher degree. All sources of information are specifically acknowledged by means of references.

.....

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Date: 14th Febraury, 1995

CERTIFICATION

This thesis entitled: "**Tableting Behaviour Of Some Depolymerized Local Starches**" by Linus Agbo **JOSEPH**, meets the regulations governing the award of the degree of Master of Science (Pharmaceutics) of Ahmadu Bello University, Zaria, Nigeria and is approved for its contribution to Knowledge and literary presentation.

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DEDICATION

To all the people who have and always will wish me well

ACKNOWLEDGEMENT

During my studies, I have grown to hold critical comment on work I do (and those who offer it) in high esteem. A constructive critic is a true friend. In this regard, I must offer my sincere thanks to my supervisor, **Prof. A.B. Bangudu**. His unfailing ability to criticize the work that I do has been as valuable as his persistent friendship and willing assistance whenever needed.

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ABSTRACT

Starches extracted from millet, sorghum and yam were subjected to various degrees of hydrolysis. Investigations showed that the starch particles remained superficially unchanged but microscopic examination revealed a tendency of the particles to be more regularly shaped and there was a gradual reduction of average particle size with increasing depolymerization. It was also shown that hydrolysis generally improved the flow of all starch specimens, except for modified millet starch (MMS) which exhibited an initial increase in flow followed by a reduction with increase degree of depolymerization.

In an evaluation of the compressibility of the starches in relation to degree of hydrolysis, it was observed that acid modification improved compressibility of all starch samples, and that with increased hydrolysis, there was improved compressibility. Compressibility as determined by tablets' hardness and density shows MMS to be the most compressible followed by modified sorghum starch (MSS) and modified yam starch (MYS) respectively. Microcrystalline cellulose (MCC) compressed better than all the modified starches but tablets made from products of the highest degree of starch hydrolysis had very good physical properties comparable to those made from MCC. All the parent starches were unable to form coherent tablets even at very high compression pressure settings. Using the modified starches as direct compression filler-binder-disintegrant in a Trimethoprim tablet formula, tablets with greater hardness and

density values were obtained and were less friable compared to tablets of the modified starches alone.

A study of the compactional behaviour of physical mixtures of the modified starches with MCC and with Starch 1500 respectively indicated better flowability for all the modified starches irrespective of starch type or mixture composition compared to the modified starches alone. The binary mixtures with MCC flowed better than those with Starch 1500. Increasing the proportion of modified starch in the mixtures resulted in reduced flow. MYS mixtures compacted best at all proportions of mixing.

In a comparative study of the properties of tablets from the unmodified starches and their hydrolysed forms as fillers respectively in wet granulation tableting, it was found that flow of the granules made from starch in their unmodified forms was lower than those from the modified starches. Compared to the direct compression tableting, very low compression forces were required to compact the granules to produce tablets with good physical properties. In addition, tablets made from modified starches as fillers possessed better tablet properties than those from their parent forms.

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CHAPTER ONE

GENERAL INTRODUCTION

1.0 STARCH

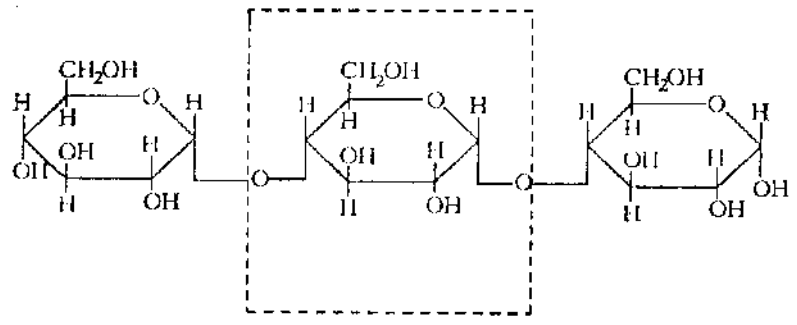
1.1 Introduction

The unqualified noun, starch, is used only to designate naturally occurring granules or cells, ranging from one to one hundred microns (1-100 μm) or more in diameter, isolated from vegetable raw material with little or no attending modification. Starch is the reserve carbohydrate of the plant kingdom. It can be found in nearly all of the organs of most higher plants including pollen, leaves, stems, woody tissues, rhizomes, bulbs and fruits. However, the main storage areas of starch granules are seeds, roots and tubers. Starch is found in Mosses and Ferns and in some protozoa, algae and bacteria. The availability and relatively low cost are the major factors governing the use of starch and its modified forms. Most commercial starch is derived from corn, but potato and wheat are also important sources (Visavarungroj and Remon, 1992).

Chemically, starch is not a single compound. It is a heterogeneous material consisting of two types of polymers, amylose (β-amylose) and amylopectin (α-amylose). Starch is crystalline in nature and shows birefringence so that in polarised light a cross is observed branching from the centre of the grain. Amylose is a linear molecule composed of 250 to 300 D-glucopyranose units uniformly linked by α-1,4

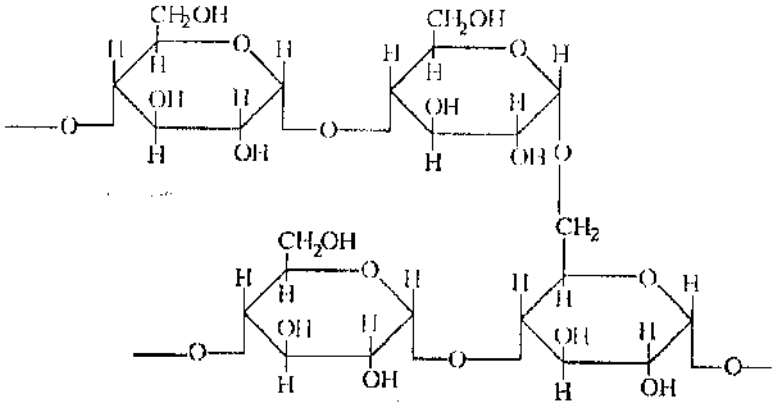
glucosidic bonds, which tend to cause the molecule to assume a helix-like shape. Amylose, although water soluble, gives an unstable solution which irreversibly precipitates. It is mainly responsible for the deep blue colouration given by starch and iodine. Amylopectin constitutes over 80% of most starches. It consists of 1000 or more glucose units that are also connected with α-1,4 linkages. However, a number of α-1,6 links also occur at branch points. These links amount to about 4% of the total linkages or 1 for approximately 25 glucose units. Amylopectin gives a blue-violet or purple colour with iodine. The structures of amylose and amylopectin are given below:

Amylose:



Glucose Unit

Amylopectin:



The amounts of amylose and amylopectin found in starch vary depending upon the source. Most starches such as corn starch, wheat and potato contain 18-28% amylose. Corn and wheat are at the high end of the range, and potato is at the lower end. Certain starches including genetic modification of corn such as waxy corn, contain little more than trace levels of amylose.

1.2 Gelatinization of Starch

The starch granule is composed of linear and branched molecules associated by hydrogen bonding either directly or through water hydrate bridges to form radially oriented micelles or crystalline areas of various degrees of order. An interconnected three-dimensional micellar lattice is formed by the participation of segments of individual molecules in several micellar areas. The overall strength of the micellar network (which is itself dependent on the degree of association and the molecular arrangement) controls the behaviour of starch in water (Leach, 1965).

The inter-micellar network possess a limited degree of elasticity, since starch granules exhibit a limited capacity for absorbing cold water and swelling reversibly. The subjection of an aqueous suspension of starch to the influence of heat or appropriate chemicals weakens the micellar network within the granules by disrupting hydrogen bonds. This permits further hydration and irreversible granule swelling, a process termed gelatinization.

If an aqueous suspension of starch is heated, the granules do not change in appearance until a certain critical

temperature is reached. At this point, some of the granules swell tangentially and simultaneously lose their characteristic polarisation crosses. This point is the gelatinization temperature. The tangential swelling and loss of polarisation cross originate at the botanical centre or hilum and progress rapidly to the granule periphery. In any given species of starch, the individual granules do not all commence to swell at the same temperature, but rather over a range that is normally about 10°.

1.3 Acid Modified Starch

Acid modified starch is a starch material in the form of superficially unchanged granules obtained by the action of acid on starch in water suspension at sub-gelatinization temperature and characterised by the following differences from its parent starch:

a. less hot paste viscosity;
b. higher alkali number; and
c. higher ratio of cold to hot paste viscosity (Schildneck and Smith, 1965).

Acid modified starch differs characteristically from its parent starch as to behaviour 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 chains by the acid.

The alkali number of acid modified starch, which rises progressively with increasing degree of acid treatment, is the milliequivalent of alkali consumed per 10 g of dry substance of starch material during a standard 1 hour digestion in 0.1N aqueous sodium hydroxide at the temperature of a boiling water bath. The alkali is consumed by acids produced from the reducing ends of the polymer chains and is a measure of chain lengths (direct index of hydrolysis) rather than a quantitative determination of aldehyde content (Gallay, 1936).

.4 History of Acid Modified Starch

Lintner (1886) was the first to describe the preparation and properties of a material meeting the foregoing definition of acid modified starch. Potato starch was allowed to stand for several days at room temperature in contact with 7.5% aqueous hydrochloric acid or 15% sulphor ic acid; then it was washed free of acid with water and dried. Naegeli (1874), had previously formed the defined product during the early stages of acid treatment, but the final undissolved material (amylodextrin) consisted of highly fragmented granules. In 1897, Bellmas obtained a German patent for a method differing from that of Lintner by the use of a more dilute acid at higher temperature for a shorter time. Duryea (1902) independently discovered much the same variation of Lintner's method.

The modern method of producing acid modified starch on a large scale for industrial uses is essentially the same as that described by Bellmas (1897) and by Duryea (1902).

1.5 Theory of Acid Modification

Hydrolysis of starch by mineral acids ultimately produces D-glucose (referred to as dextrose in American commerce) in nearly quantitative yields. The course of hydrolysis may be conveniently followed by the 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 measurements of osmotic pressures 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 20 fluidity. In Industry, acid-modified starches are generally designated or classified according to fluidity number, an inverse measure of viscosity (Bechtel, 1949). Fluidity number is the number of millilitre of a standard alkaline starch paste delivered by a funnel with a special tip in the time, generally 40-70 Sec., required by the funnel to deliver 100 ml of water. The standard starch paste is made by wetting 5 g of starch, dry weight basis, with 10 ml of distiled water, adding 90 ml of 1% aqueous sodium hydroxide solution, stirring the mixture for 3 min., then allowing it to stand for 27 min., all at 25°C.

Meyer and Bernfeld (1940) advanced the theory that the points of early attack lie in the amorphous inter-micellar regions of the granule through which the gigantic branched amylopectin molecules pass as they extend from one crystalline micellar region to another. 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.

1.6 Uses of Acid Modified Starches

Large tonnages of acid modified corn starch are consumed annually by U.S.A textile manufacturers in warp sizing and fabric finishing. The acid modified starch imparts superior strength and smoothness to the sized yarn and pointed thus to higher efficiency. In the manufacture of starch gum candy, acid modified starch has produced better results than the parent starch. In the paper industry, acid modified starch is used for calender sizing of special grades of paper to improve scuff resistance and printability. Acid modification improves the penetration and distribution qualities of the starch, thus providing the laundered fabric with better hand and appearance. Acid modified starch is also the basis for substantial manufacture of liquid laundry starch for home use.

1.7 Other Products of Starch Modification

1.7.1 Hypochlorite Oxidised Starches

Hypochlorite oxidation of starch is one of the most useful reactions developed for the modification of starch.

Schmerber (1896) was the first person to treat starch with a hypochlorite for the purpose of obtaining a starch having new properties. Hypochlorite-oxidised starches are made by treating a suspension of starch granules with a solution of an alkaline hypochlorite such as sodium hypochlorite. After the reaction is finished, the suspension is neutralized with acid, and the starch is washed to remove salts and then dried.

The most noticeable characteristic of this starch is its whiteness; within limits, the bleaching effect increases with the degree of oxidation. In general, the oxidised starches are very sensitive to heat, and if they are dried at too high a temperature, browning will occur.

1.7.2 Starch Phosphates

Starch phosphates may be divided into two general classes:

1. monoester of phosphoric acid in which a starch hydroxyl group is esterified with only one of the three acidic functions of phosphoric acid, and

2 mixtures of mono-, di- and triesters of phosphoric acid in which more than one of the acidic functions of phosphoric acid are esterified. Starch phosphate monoesters {starch disodium (or dipotassium, etc) phosphate} are prepared by heating a dry mixture of starch and a water soluble phosphate salt, such as the acid salts of ortho-, pyro-, or tripolyphosphorous acid. Starch phosphate diesters contain an ester bridge or bridges connecting adjacent starch molecules. They are prepared by the use of various

derivatives of phosphoric acid to obtain cross-bonded starches.

1.7.3 Pregelatinized Starches

These are cold water pasting starches, hence so called soluble starches. Puffing is a means of preparing pregelatinized starch products (Kerr, 1950). A recent improvement in the technique of puffing that shows promise of practicality is continuous cooking - extrusion - puffing. One example uses the equipment developed by the Wagner Mixer Manufacturing Company.

Each pregelatinized starch, upon reconstitution with cold water, shows less thickening power and less tendency to set to a gel than pastes of the parent starch.

1.7.4 Cross-Linked Starches

Cross-linking is the mechanism by which a wide variety of poly-functional agents insolubilize starch. The cross-linking may be through primary linkages, or through weak temporary bonds as those formed between starch and borax. The linkages not only tie adjacent starch molecules together but, in many cases, cross-link to a substrate that is often a cellulose matrix.

In general, any molecule capable of reacting with two or more hydroxyl groups can cross-link. Cross-linked starches have been prepared by treatment with formaldehyde. These cross-linked starches have reduced swelling power. Also the treatment of intact starch granules with very low levels of

phosphorus oxychloride gave products with controlled swelling power and viscosity stability.

1.8 Local Starches and Modified Starches in Tablet Formulations

In recent years, Nigerian scientists especially in the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria have been giving increasing attention to the extraction, development and use of starches in the formulation of solid dosage forms. Investigations have shown that local starches could be incorporated in tablet formulations using the wet granulation technique, though the tablets were rather soft when starch proportions were high (Akande and Omojuwa, 1990; Akande *et al*, 1991; Deshpande and Panya, 1987; Garr and Bangudu, 1991; Kunle and Bangudu, 1990).

One of 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 by incorporating them in tablet formulations using lactose, sodium hydrogen carbonate and calcium carbonate as organic and soluble and insoluble inorganic substances, and found the starches to compare favourably with potato starch. Nasipuri (1975), reported that cassava starch has good binder and disintegrant properties as does potato starch in tablet formulations. Billi (1975) evaluated the efficiency of cassava starch as disintegrant and binder in chloroquine phosphate tablet formulations and observed that the efficiency of the starch as a tablet disintegrant and its paste as a binder

compared favourably with maize starch and gelatin solution respectively.

Nasipuri (1979) studied the use of cocoyam starch obtained from tubers of *Coloceasia escudenta* as a tablet binder and disintegrant using sulphadimidine and chlorpheniramine maleate. He found cocoyam to be as good a binder as potato starch or acacia at the concentrations used. It was also a good disintegrant. Nasipuri (1979b) worked on the suitability of yam starch as a tablet binder and disintegrant. Yam starch was found to be an efficient binder and disintegrant in the formulation of tablets containing soluble and insoluble organic medicinal substances. Using plantain starch obtained from *Musa paradisiaca*, Esezobo and Ambujam (1982) found that plantain starch can be used both as binder and disintegrant in tablets, and that it has about twice the binding efficiency and half the disintegrant power of maize starch.

The use of sorghum starch as a disintegrant was studied in tablet formulations containing sulphadimidine and chloroquine phosphate by Deshpande and Panya (1987). They concluded that the disintegrating properties of sorghum starch are comparable to those of corn starch. Garr and Bangudu (1991) employed sorghum starch as a disintegrant in sodium bicarbonate tablets, and found sorghum starch to exhibit twice the disintegrating power of corn starch. An evaluation of the disintegrant and binding characteristics of millet starch was carried out by Akande, Deshpande and Bangudu (1991). Tablets produced compared favourably with maize starch with respect to the tablets' physical properties. Kunle and Bangudu (1990) have been able to establish that yam starch could be

incorporated as an excipient in the manufacture of promethazine tablets. Akande and Omojuwa (1990) have used millet starch as a glidant in tablet production.

Several types of modified starches have been studied as tablet excipients. A modified starch is a starch in the form of superficially unchanged particles obtained by treating the parent starch with chemicals or heat. In 1975, Schwartz *et al*, evaluated the incorporation of starch USP and a modified corn starch (starch 1500) within the granules of several drug formulations. They found that the modified starch generally exhibited improved processing characteristics and tablet properties compared with starch USP. Starch 1500 is a partially hydrolysed starch. This modified starch gives results comparable to those of starch USP in terms of dissolution rate and disintegration time when used at equivalent levels (Manudhane *et al*, 1969). Modified starches with three different degrees of oxidation were studied as new auxiliary substances in the production of tablets in comparison with commonly used auxiliary materials (Rak *et al.*, 1983). The oxidised starches proved to be even more useful diluents and binders than commonly used tablet excipients such as carboxymethyl starch, potato starch, lactose, polyvinyl-pyrrolidne and methylcellulose.

One of the modified products from starch has been developed and used successfully as a disintegrant. This chemically modified starch, sodium starch glycolate or sodium carboxymethyl starch, is a low-substituted derivative of potato starch. Khan and Rhodes (1971 and 1973) found that sodium starch glycolate is a more effective disintegrant

compared with native corn starch in dicalcium phosphate tablets prepared by direct compression. The disintegration time of tablets containing sodium carboxymethyl starch was unaffected by an increase in the compression force or by a decrease in tablet porosity (Shangraw *et al*, 1980). Sarisuta and Parrott (1988) prepared acetaminophen tablets by wet granulation using povidone or pregelatinized starch as binder. The investigators found that the tablets granulated with pregelatinized starch were less susceptible to changes caused by humidity than were tablets granulated with povidone. In addition, the dissolution rate of acetaminophen tablets prepared with pregelatinized starch was less affected by high humidity.

Visavarungroj *et al* (1990) investigated the use of different types of thermally modified and cross-linked (phosphate and adipate) waxy-corn starches as hydrophillic matrices in sustained-release formulations. The study showed that the cross-linked waxy-corn starches had poor swelling characteristics and dispersion viscosity compared with pregelatinized, starch and pregelatinized, cross-linked waxy-corn starches. The pregelatinized cross-linked starches showed a lower degree of swelling than the pregelatinized starch but showed a higher dispersion viscosity than the pregelatinized starch.

Okafor and Udeala (1991) incorporated acid modified starches obtained from cassava, cocoyam and rice in a folic acid tablet formular and established that the starches could be used as fillers in direct compression, having produced tablets with very good physical properties.

1.9 Research Objectives and Scope

Most of today's tablets are manufactured by direct compression using high speed rotary tableting machines. This increases efficiency, saves space, machinery, personnel and time hence cost effective. Nigerian pharmaceutical manufacturers depend heavily on imported excipients (Avicel®, Encompress®, Starch 1500, etc) for their direct compression requirements. With the devaluation of the Nigerian naira (currency) due to the deregulation of the foreign exchange market and the structural adjustment programme (SAP), firms which depend on imported raw materials are encountering problems in bringing these materials regularly and reliably into the country. Nigeria's economic recovery policy is centred on local sourcing of raw materials.

Tablets containing a high concentration of unmodified starch as filler are often soft and may be difficult to dry, especially in a fluidized-bed drier. The compressiblity of the native starches is too poor to make a tablet of sufficient hardness. Its poor flowability makes it unsuitable for use in direct compression formulations.

This research aims at modifying local starches, obtained from yam, millet and sorghum by acid hydrolysis and incorporating them in tablet formulations as fillers. The quality of the tablets would be evaluated, to ascertain if acid modification has improved their flow and compression characterisitics, and compared with those of tablets produced from a standard direct compression excipient: Avicel®. Binary mixtures of the modified starches with Avicel® and starch

1500 respectively will be made to determine any advantages the mixture would have over the individual components alone. Also the modified starches and their unmodified forms would be used respectively as fillers in tablets prepared by wet granulation and characterized.

CHAPTER TWO

2.0 TABLET AND TABLETING PROPERTIES

2.1 Tablet Adjuvants

In addition to the therapeutic ingredient(s), tablets may contain a number of inert materials known as additives or excipients. Additives may be classified according to the role they play in the finished tablet. The first group contains those which help to impart satisfactory compression characteristics to the formulation. These are diluents or fillers, binders and lubricants.

The second group of added substances give additional desirable physical characteristics to the finished tablet. In this group are disintegrants, colours and in the case of chewable tablets, flavours and sweetening agents.

2.1.1 Fillers

These are bulking agents. Frequently, the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression.

Commonly used fillers include sucrose, dextrose, conventional and spray-dried lactose, mannitol, sorbitol, calcium phosphate, sodium chloride and powdered starch. Great care must be exercised in the choice of diluents to avoid physicochemical incompatibilities and instability. For example, the combination of amine salts with lactose in the

presence of alkali lubricants resulted in tablets which discoloured on ageing (Browley and Lachman, 1963).

2.1.2 Binders

These "glue" powders together and cause them to form granules. They impart a cohesiveness to the tablet formulation which ensures the tablet remaining intact after compression as well as improving the free flowing quality by formulation of granules of desired hardness and size.

The quantity of binder used must be optimized since the tablet must hold together until swallowed and then must disintegrate and dissolve to release the medicaments.

The common binders in current use include starch, gelatin, sugars, natural and synthetic gums. In certain circumstances, polyethylene glycol, ethyl cellulose, microcrystalline cellulose, waxes, water and alcohol are also used as binders.

Alcohol and water are not binders in the true sense of the word but because of their solvent action on some ingredients such as lactose and starch, they convert the powdered material to granules and the residual moisture retained enables the materials to adhere together when compressed.

Binders are mostly used in solutions, although some are used in the dry form. In some formulations, the binders are added dry and blended with the diluents and drug(s). They are then activated by the addition of water or other solvents. In other methods, adhesives are dissolved or slurried in a liquid and in this form, added to the mixed powders. Binders added in

solution have more adhesivesness than the identical one added dry and then moistened.

The liquid binders are used in different concentrations depending on the nature of the binder and the powdered material to be granulated. The nature, concentration and mode of incorporating the binder will influence the compression characteristics of tablets. Therefore, these factors must be evaluated empirically for each formulation to prevent adverse effects. Jacob and Plein (1968) have shown that increasing the binder concentration caused an increase in mechanical strength of phenobarbitone tablets, but simultaneously resulted in a decrease in the dissolution rate of the tablets.

High concentration of binder results in premature wear out of the sets of punches and dies due to regular compression of such formulations. High concentrations of binder can also result in tablet capping. Too much binder may also make granules which require heavy pressure to compact into tablets. Inadequate incorporation of binders will cause inadequate binding and formation of extremely soft tablets.

Dry binders are often used as vehicles for direct compression of tablets. The most popular dry binders are microcrystalline cellulose, amylopectin and polyethylene glycol.

2.1.3 Disintegrants

A disintegrant is a substance or a mixture of substances, added to a tablet to facilitate its break up after administration (Gumsel, 1976). The disintegrant opposes the physical forces that act under compression to form the

mechanical body of the tablet (Gumsel *et al*, 1976). Disintegrants have been classified by Feinstein and Bartillucci (1966) into starches, cellulose, algins, gums and clays based on their natural sources. Fakhoulin *et al* (1963) based their classification on the mechanism of action of the disintegrants as:

- agents that react with moisture to constitute foam;
- effervescent substances that react with moisture to form a gas;
- substances that react with moisture to swell. This group absorbs moisture and swell and are by far the most commonly employed in research and industries today.

The starches derived from wheat, corn, rice and potato when included as part of granules aid in the disintegration of a tablet. Many researches consider starch as the best tablet disintegrating agent, and in fact corn starch frequently serves as standard in the evaluation of other disintegrating agents (Burchison and Pickering, 1950; Mital and Ocran, 1968; Khan and Rhodes, 1971).

Other disintegrating agents of less importance are the gums, veegum, methylcellulose, agar, bentonite, cellulose, wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp, carboxymethylcellulose, cross-linked polyvinyl pyrrolidone, magnesium and aluminium silicate.

2.1.3.1 Methods of Addition of Disintegrants

A concentration range of 5-20% of the granule weight is usually added. There are three basic methods of adding disintegrants:

i. The addition of the total amount of disintegrants to granules before compression

ii. The addition of the total amount of disintegrant to the total mass of powdered material before the wet granulation process. It is believed that the drying cycle of the process will dry the agent sufficiently to permit it to function maximally. This method of addition places the disintegrant in the granules where it can readily oppose the effects of binder.

iii. This involves the division of the total amount of disintegrant into two. A part is added to the powdered material before wet granulation, while the second part is added to the finishing stage of granulation prior to compression. It is assumed that this method of addition allows disintegrant to be within and between granules so that disintegration action will force tablet apart into original granules and also break down the granules into fine particles.

2.1.3.2 Mechanisms of Action of Disintegrants

The mechanisms of action of disintegrants in current use have generated a lot of controversy among researchers. The

following are some of the theories that have been postulated to explain how disintegrants act.

a. **Evolution of Gas:**

The basis of effervescent tablets is the evolution of carbon dioxide gas- the product of the reaction of sodium bicarbonate with citric and tartaric acids in the presence of water. As carbon dioxide is released within the tablet, an internal pressure develops until the tablet breaks apart and carbon dioxide dissolves or disappears from the reaction vessel.

b. **Water Absorption Capillary Theory:**

This theory maintains that a disintegrant especially starch, by virtue of its relative incompressibility forms chains around granules. These chains form a capillary network within the tablet and the higher the concentration of the starch, the greater the number of capillaries formed. The capillaries are thought to promote the rapid absorption of water into the tablets and the subsequent disintegration of tablets.

Crisafi and Becker (1958) have shown that starch will absorb about 20% of its weight of water in 24 hours when exposed to an atmosphere of 95% relative humidity at 27°C.

Kerr (1950) in his book on starch, states that "in the natural states, starch is insoluble in cold water but appears to absorbs 20-30% and does not swell appreciably. Curlin (1955) has suggested that the disintegrating effect of starch is due to capillary action

rather than swelling. Kornblum *et al* (1973) have also shown that the disintegration properties of PVP is also based on the same principle as mentioned above.

Capillary *per se* may not have a disintegrating effect although under certain conditions related to pore size, it may play a part in increasing the rate at which water is introduced into the tablet matrix. Many fluids e.g. alcohol and glycerin have been found to penetrate tablet without causing disintegration.

c. **Swelling Rupture Theory**:

Most disintegrants have the ability to absorb water and swell to several times their own size (Patel and Hopponen, 1966; Manudhane *et al* (1969); Lowenthal, 1972). If for example, starch is added to the dry granules before compression, the tablet will absorb gastric fluids causing starch to swell and mechanically disrupt the tablet. This is called the rupture theory. Lowenthal and Wood (1973) postulated that water hydrates the hydroxyl group of the starch molecules causing them to move apart. They indicated that the slight swelling that occur is due to the rapid hydration step and a slower sorption or addition of water step. The swelling which takes a few seconds would result in significant increase in volume. The combined effect of the attachment of water molecules and the increase in volume of the grain cause sufficient force to break up the tablet.

The antagonists of the rupture theory have expressed the observation that there are many substances which

swell to a greater degree than the starches but are poor disintegrants, while other materials do not swell but have good disintegrating properties e.g. Amylose (Manudhane *et al*, 1969).

In tablets containing disintegrants which are adhesive in the hydrated state (e.g. sodium carboxymethyl cellulose), the positive forces of penetration of water and swelling of particles must overcome the opposing forces of adhesion within the particles to produce tablet disintegration. When opposing forces are equal to or greater than the positive forces, the result is a longer disintegration time (Khan and Rhodes, 1975). Because the extent of hydration increases with the number of polar groups, one would expect higher grades (of viscosity) to produce greater swelling of particles, thus causing disintegration at low concentration. At higher concentrations however, the higher grades, because of their higher viscosities may become more adhesive in the hydrated state. Thus the opposing forces of adhesion within the particles would become dominant, resulting in a longer disintegration time of tablets.

The mechanisms of action of disintegrating agents are complex and mediated through several unrelated phenomena. In most cases, however, the principal mechanism of disintegrants especially starch is pressure exerted by increased volume in the presence of water, although capillary may facilitate rate of penetration of water.

2.1.4 Lubricants

The flow of granulation, adhesion of granules or powders to punches and dies and the release of tablet from its mold after compression are the three main problems associated with tablet compression which are ameliorated by the group of chemically diverse substances collectively referred to as "Lubricants". Cooper *et al* (1958) defined "lubricants" in tablet technology as substances which facilitate the passage of a granulation through the various orifices of a tableting machine.

Based on their ability to carry out certain functions, lubricants may be classified into three groups (Gumsel *et al*, 1976).

i. **Glidants**: These reduce inter-particulate friction and eliminate the problems associated with flow of materials from larger through smaller apertures in the tablet presses. They are also termed "flow regulators". Examples are talc and starch.

ii. **Anti-adhesives**: Also referred to as anti-sticking agents. These are easily deformed and prevent adhesion of the tablet surface to punches and dies during compression e.g. stearic acid and soaps.

iii. **Lubricants**: These are the proper lubricants and reduce inter-particulate friction during ejection cycle, thereby facilitating tablet ejection. Examples are magnesium stearate and talc.

The absence of a lubricant during tablet ejection results in severe straining of the press and this is frequently audible as a characteristic grunting sound. Another manifestation of poor lubrication at this critical stage is the presence of vertical irregular striations or "scratch" marks on the edges of the ejected tablets.

Lubricants reduce the tendency of tablets to cap. Gumsel and Kanig (1976), defined capping as an expression *which describes the partial or complete separation of the top* of a tablet from the main body. "Picking" of tablets which results from micro expansion of the tablet immediately after compression is also reduced. Tablets tend to increase by about 1/1000 of their original sizes immediately after compression due to the elastic nature of the granules.

Lubricants must be added to a granulation properly to achieve satisfactory results. They must therefore, be finely divided by passing through a 60-80 mesh sieve. This is called "bolting" of the lubricants.

2.1.4.1 Methods of Incorporating Lubricants:

There are two principal ways of incorporating a lubricant into the tablet formulation:

1. The lubricant is added to the dried granules prior to compression. These "external lubricants" are thought to function by coating the surface of the granules with a film which reduces interfacial friction between the granules and the compressing surfaces. Magnesium stearate and calcium stearate are good examples.

2. Internal Lubricants- Cooper *et al* (1958) found that it was possible to add the lubricant to the initial powdered mixture of therapeutic agent and excipients and subject such to wet granulation without the loss of lubricating properties. The impression that the lubricant would be enclosed within the granule and covered by the binder, thereby losing its function, proved to be unfounded since tablets prepared by this method had good physical properties and additionally exhibited a reduced disintegration time.

The most commonly used lubricants are hydrophobic substances, therefore, the primary problem in the preparation of a water soluble tablet formulation represent a number of compromises between compression efficiency and water solubility (King, 1980), and so the optimum proportion of lubricant must be empirically selected.

2.2 Manufacture of Compressed Tablets

Compressed tablets are made by compressing fine crystals, free flowing powders and granules in a die between punches. For a material to be formed into tablets in the tablet press, it must posses certain physical properties. These include:

* ability to flow freely (fluidity);
* "cohesiveness", that is, tendency of its individual particles to stick together (compressibility); and
* lubrication.

Very few pharmaceutical powders possess the above qualities. Examples of such materials are: sodium chloride, sodium bromide and potassium chloride. Methods of tablet formulation and preparation have been developed to impart these properties to materials to be compressed. There are basically three main methods for manufacturing compressed tablets namely:

* Wet granulation
* Slugging
* Direct compression

2.2.1 Wet Granulation Method

This used to be the traditional and is the oldest method of granulation. The mixed powders are moistened with granulating fluid, which is usually a solution of binding agent. The moist mass is broken up into coarse granular aggregates by passing it through a hammer mill or oscillating granulator equiped with screens of large perforations. This process is called wet screening.

The granules produced are then dried in an oven on trays or in a fluidized-bed dryer. After drying, the granules are screened again to break down aggregates and to remove excess fines. The remaining excipients - lubricants, external disintegrants, etc are then added to the granules before compression. The strength and quality of the binding solution may determine the performance of the granules and the quality of their tablets.

friable and a considerable amount of fines tend to be produced during the break down stage.

2.2.3 Direct Compression Method

Most of today's tablets are manufactured by direct compression. The technique offers the simplest possible approach to tablet production. The term "direct compression" was long used to identify the compression of a single crystalline compound into a compact without the addition of any other substances. However, the term now includes the process by which tablets are compressed directly from powder blends of the active medicament and suitable excipients (e.g. fillers, disintegrants and lubricants) which will flow uniformly into the die cavity and form a firm compact. It does not require pre-treatment of the powder blends by wet or dry granulation procedures.

There are only a few crystalline substances such as inorganic salts (sodium chloride, sodium bromide and potassium chloride) which may be compressed directly. Since the vast majority of medicinal agents are not directly compressible, directly compressible vehicles may be used. These are inert substances which may be compacted with no difficulty and even when quantities of drugs with poor compressibility are mixed with it. Excipients of significance in direct compression technique include: anhydrous lactose, spray-dried lactose, microcrystalline cellulose, amylose, dicalcium phosphate dihydrate, granular mannitol and crystalline sorbitol (Gumsel and Kanig, 1976).

Direct compression excipients should be:

1. Free flowing;
2. Highly compressible so as to produce tablets with a good hardness - pressure profile;
3. Physiologically inert and not impair the drug bioavailability;
4. Chemically compatible with the drug;
5. Colourless;
6. Tasteless and have a good mouth feel;
7. Relatively inexpensive;
8. Capable of reworking with no loss of flow or compressibility;
9. Materials with high dilution potential.

These properties though are not embodied in a single material and in practise it is desirable to blend two or more compression aids together (Wells and Langridge, 1981).

2.3 Tableting Equipment

The basic mechanical unit in all tablet compression *equipment includes the following:*

a) Hopper for storing the materials for compression;
b) Feed frame for distributing the material into the die;
c) Dies for controlling the size and shape of the tablet;
d) Punches (upper and lower) for:
    i. compacting the materials within the dies, and
    ii. shaping the tablet.
e) cams for guiding the punches.

All other parts of a tablet press are designed to control the functioning of those listed above. Features such as capacity, speed, maximum weight and pressure vary with the equipment design, but the basic elements remain essentially the same.

Generally, tablet compression machines are classified into two:

a) Single punch press,
b) Multi-station rotary press.

Although these machines may vary considerably in the rate of production (output), mode of compression and the mechanical features designed to control the compression process, the principles of construction and operation are very much the same, accomplishing the same task.

Most of today's tablets are manufactured by direct compression using high-speed rotary tableting machines. These machines compress a constant volume of powder or granules between two rollers using an upper and lower punch. Once the amount of powders or granules in the die has been determined, the force used to compact the tablet is adjusted by varying the distance between the two rollers. When the compression force has been set, the position of the rollers remain fixed and the tablets are considered compressed to a constant thickness.

With the rollers fixed, the force applied during compression varies with the weight of powder or granules in the die. Therefore, a slight variation in granule flow can alter tablet weight, tablet weight variation (even beyond the

pharmacopoeia limits), and the maximum compression force. Variables that can influence the die-filling process include granule size and size distribution; poor flow; variation in punch lengths; and irregular movement of the lower punch, which creates a die space of varying capacity.

Recently developed machines compress to constant force using a hydraulic system that supports the compression roller. Tablets compressed on these systems are expected to have constant density and, in theory, little variation in strength and disintegration characteristics (Rubinstein *et al*, 1991).

2.4 Tableting Defects

Tableting defects are problems that occur in the process of tableting. They may be immediately visible after compression or occur on storage.

2.4.1 Capping

Gumsel and Kanig (1976) defined capping as an expression which describes the partial or complete separation of the top of a tablet from the main body. The type and state of both punch and die sets can be responsible for capping. The concave or bevelled edge faces of punches gradually curve inward with use and form a claw which can pull the top of the tablet loose.

Dies develop wear in the area of compression. A "ring" develops and enlarges to a point which the tablet diameter is to great to pass easily through the narrower orifice above the ring.

Carelessness in setting the press can also cause capping. High elastic recovery, polymorphic forms of drug, particle size where there are excess fines leading to air entrapments in the compacts, inadequate binding and moisture content variations are other factors that may cause capping in tableting. Scored tablets are more prone to capping.

2.4.2 Lamination

This is the separation of tablet into two or more distinct layers. The most important cause is usually ascribed to the entrapment of air among the granules which does not escape during compression but afterwards when the pressure is released. Granules that contain large amount of powder due to insufficient binders are prone to this difficulty. Inadequate die wall lubrication can also lead to lamination of tablets on ejection.

2.4.3 Chipping

In less severe cases of carelessness in setting up the press, the tablet may merely chip. Another possible cause of chipping is the setting of the sweep-off blade. If it is set too high, the tablet can dip partially under it and break off. Chips then enter the feed frame and may affect the other tablets.

Tablets with flat faces or bevelled edges are more apt to chip when they strike each other than those with convex faces which tend to "shingle" (inter leave) more readily and reduce the amount of edge contact.

2.4.4 Picking

This describes the removal of material from the surface of the tablet and its adherence to the face of the punch. Picking of tablet may also result from micro-expansion of the tablet immediately after compression. Tablets increase by about 1/1000 of their original sizes immediately after compression due to the elastic nature of the granules.

2.4.5 Sticking

This is the adhesion of granules to the die wall. When it occurs, the lower punch fails to move freely with consequent strain on cam tracks and punch heads. The term may also refer to build up of material on punch faces. Binding and sticking lead to "grunting" of the machine and pitting of the tablet.

Insufficient lubrication of granules may cause sticking and picking. Low melting point substances, either active ingredients or additives such as stearic acid and polyethylene glycol may soften sufficiently from heat of compression to cause sticking. Dilution of the active ingredient with additional high melting material and a consequent increase in weight may help to solve this problem. The level of low melting point lubricants may be reduced or higher melting point material substituted.

Excessive moisture may be responsible for sticking and further drying of the granules is then required.

2.4.6 Spontaneous Cracking

Irregular cracking within the tablet may occur immediately on ejection. This is due to formation of very hard parts in the tablets which expand differentially during decompression. This is usually caused by the use of recycled material - regranulation process.

2.4.7 Weak Equator

Some tablets may be weak at the centre due mainly to inadequate compaction as a result of pressure drop along the depth of the die. This happens when the length to diameter ratio of the tablet is very high.

2.4.8 Weight Variation

When a granulation is unsatisfactory, each tablet made from it may vary in weight beyond acceptable limits. The causes of weight variations in tablets include:

The size and distribution of granules being compressed where excess large granules interfere with the filling of the void spaces leading to weight variation. Poor flow of granules may lead to incomplete filling of the die in some cases.

Poor mixing - when the lubricants and glidants have not been thoroughly mixed with the granules leading to inefficient filling of the dies. Poor mixing is sometimes revealed by the sound of strain during tablet ejection. When the lower punches are of unequal lengths, leading to change in volumetric fill of the die can also lead to varying weight.

2.4.9 Hardness Variation

Some of the causes of weight variation can also lead to variations in hardness. In addition, hardness depends on the weight of the material and the space between the upper and lower punches at the moment of compression. If the volume of material varies or the distance between the punches vary, hardness likewise becomes inconsistent. Such other properties as density and porosity of granules could also affect hardness and magnitude of compression force.

2.4.10 Double Impression

This involves the lower punches which have a monogram or other device on them. At the moment of compression, the tablet receives the imprint of the punch. On some machines, the punch is free to drop and then travel uncontrolled for a short distance before it rises up for the ejection cam to push the tablet out of the die. During the free travel, it rotates, at this point, the punch may make a new although higher impression on the bottom of the tablet resulting in a double imprint (Gumsel and Kanig, 1976).

2.5 Quality Standards of Tablets

Programmes in tableting technology include appropriate test methods and specifications which are developed to guarantee quality on a batch to batch basis. Haphazard operations can not be permitted in the manufacture of tablets which are used to save life or to restore or preserve health.

The recommended parameters for evaluation of tablets are:

2.5.1 Uniformity of Diameter

This is a standard for uncoated tablets and is an attempt to rationalize the diameter of tablets containing a certain dose of drug. It is usually measured with the aid of a micrometer screw guage. The diameter of a tablet is determined by those of punch and die. The constant compression of a given amount of material in a given die for a long time may lead to increase in diameter due to wearing of the die.

2.5.2 Thickness

Wide variations in tablet thickness can lead to packaging problems. Variations in tablet thickness can also affect patient acceptance. Thickness variation should not be more than 5%. The possible causes of variation in thickness include:

a. Inadequate flow rate - this can result in powder/granule segregation and erratic flow;

b. constant compression pressure setting for different weight of granules.

The thickness of tablets can be measured by the use of callipers and individual measurement is more desirable than group measurement.

2.5.3 Weight Variation Test

This is an attempt to minimize dose variation in tablets. For a uniformly dispersed drug in a tablet mix, variation in tablet weight results in variation in dosage. This is particularly true in formulations containing a high proportion of active ingredients. There may be no significance between tablet weight and drug content in tablets containing very small amount of potent active ingredient, therefore, this quality parameter may not be of vital importance.

2.5.4 Mechanical Strength

A tablet should be sufficiently hard to withstand normal handling during packaging, transportation, storage, dispensing, etc. The mechanical strength describes the resistance of tablets to these stresses. Measurement of crushing strength is the most widely used technique and may be defined as "that compressional force which when applied diametrically to a tablet, just fractures it" (Brook and Marshall, 1968).

Numerous instruments have been devised to measure tablet hardness. These include the Monsanto hardness tester, Pfizer hardness tester, Stron Cobb hardness tester and Erweka hardness tester.

2.5.5 Friability Test

Tablets must be sufficiently robust to withstand chipping, etc. during handling. Friability testing measures resistance to abrasion due to falling or rolling when in contact

with similar tablets and therefore is a measure of inter-particulate cohesiveness in a tablet. Resistance to chipping may be tested by means of a friabilator and usually a weight loss of about 0.8% is acceptable (Gumsel and Kanig, 1976).

2.5.6 Content Uniformity

This tests the dose variation in tablets that are of the same weight. Such variation arises from a non-homogeneous distribution of drug in the tablet mix. Content uniformity can be determined by single assay in which active content of individual tablet is investigated by a composite test.

2.5.7 Colour test

This is an attempt to determine possible tablet mottling, which could be an indication of inadequate mixing.

2.5.8 Disintegration Test

This test tries to evaluate the availability of the drug from the tablet. The disintegration test for tablets determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under prescribed experimental conditions. The British Pharmacopoeia (1980) defines disintegration as "..... that state in which no residue of the tablet, except fragments of undissolved coating, remains on the screen of the test apparatus or if any residue remains, it consists of a soft mass having no palpably firm, unmoistened core." This often makes tablet disintegration a necessary step to achieve rapid availability of the active ingredient.

2.5.9 Dissolution Studies

The disintegration test as a means of predicting drug availability fails because of its inability to distinguish between fast and slow dissolving particles. In an effort to overcome this problem, the USP has introduced a dissolution test. In-vitro dissolution test is carried out mainly for two reasons:

a. to ensure that the active medicament in the tablet is totally released on time;
b. to ensure batch to batch uniformity in the release of active ingredient.

The dissolution assembly consists of four main parts:

a. a water bath
b a covered vessel - one litre in volume
c. a variable speed motor
d. a cylindrical stainless steel basket

The temperature is maintained at 37°C ± 0.5°C and the dissolution medium is specified in the individual tablet monograph.

The crucial test in any in-vitro model is the correlation to the in-vivo situation. In the design and use of a reliable in-vitro dissolution test model, it is essential that the model is capable of simulating in-vivo dissolution process. One such condition is the maintenance of nearly perfect "sink conditions", during in-vitro dissolution rate determinations, i.e. the drug concentration in the dissolution medium does not exceed 10-20% of drug solubility- this condition is required

because in dissolution rate limited drug absorption process, there is no appreciable build up of drug concentration in the gastro-intestinal fluid which act as infinite sink. It is therefore conceivable that unless similar sink conditions are embodied in the in-vitro dissolution test model, in-vitro results will bear little or no relation to the in-vivo observations.

The various dissolution apparatus in current use, both official and unofficial have been reviewed by Swarbrick (1970) and Wagner (1971). They range from the beaker method of Levy and Hayes (1960), rotating disk method of National Formulary, to the oscillating tube method. These methods differ in intensities of agitations of the dissolution medium, geometry of apparatus, surface area generation, sink or non-sink condition, etc. It must be noted that no single dissolution apparatus has been designed that completely simulates the in-vivo conditions.

CHAPTER THREE

3.0 EXPERIMENTAL MATERIALS AND METHODS

3.1 Extraction of Starches

3.1.1 Sorghum Starch

The sorghum grains (white seeded, sorghum bicolour variety L-187 obtained from National Seed Service, Zaria, Nigeria) were cleaned by seiving to remove impurities, broken grains and foreign seeds.

The cleaned grains were weighed into steep acid for 24 hours. The steep acid is a weak solution of sulphorous acid prepared by absorbing sulphur dioxide in process water, maintained at room temperature (Knight, 1969). The purpose of steeping is to soften the corn kernel and break down the protein structure within the endosperm so as to loosen the starch granules and facilitate the separation. The steeping process is a very important step in the complete extraction process, because if the grains are not correctly conditioned at this stage, the subsequent separation and the quality of the finished products can be affected.

The steep liqour was then removed and the sorghum grains were soaked in purified water and subjected to grinding, to partially macerate the grains, remove the pericap and free the germ from the endosperm. Germ separation was achieved by floatation method.

The underflow consisted of fibres, starch and protein. This mixture was finely ground, the fibres which were not reduced were removed by sieving.

The starch was allowed to settle and washed several times with 0.1N sodium hydroxide to neutralize the acidity and dissolve the gluten. Excess alkali was removed by washing the starch several times with purified water.

The starch was collected in a buchner funnel using a vacuum pump, dried at 70°C for 6 hours, reduced to fine powder and passed through sieve 180 μm size.

3.1.2 Millet Starch

The millet grains (pearl millet; *Pennisetum typhoides*, Family Graminae, ex-Borno variety obtained from the National Seed Service, Zaria, Nigeria) were washed thoroughly and soaked for 24 hours in distilled water. The seeds were then wet-milled using the Erweka Grinding Mill (Erweka Apparatebau GmbH, West Germany) to break up the kernel. It was then ground in a blender/mixer (Moulinex, Type 242, France) for 3 minutes. The cell debris were removed using a calico. The blending and sieving were repeated several times until no more starch was left in the stover (i.e. when it became brown).

A small quantity of 0.1N sodium hydroxide solution was added to help separate the gluten from the starch (Denston, 1951). The extract was decanted and washed several times with distilled water.

The starch suspension was then centrifuged at 1000 rpm for 20 minutes (Beleia *et al*, 1980). The upper protein

layer was scrapped off with spatula and discarded while the lower starch layer was again suspended in distilled water. The centrifugation and tailings were repeated until white prime starch free of brown layer was obtained.

The prime white starch was suspended in water and recollected using the buchner funnel in vacuum pump. The starch was dried at 70°C for 6 hours and milled to fine powder (less than 180 μm).

3.1.3 Yam Starch

The fresh tubers of yam (*Diascorea rotunda*, obtained from Samaru market, Zaria, Nigeria) were washed and peeled. They were cut into small pieces, washed and then grated. The grated mass was reduced to a fine pulp using a blender mixer (Moulinex, Type 242, France) after adding sufficient quantity of distilled water. The pulp was passed through a 180 μm sieve with the addition of sufficient water to ensure good recovery of starch.

The starch was allowed to settle and then washed several times with 0.1N sodium hydroxide to neutralize the acidity. Excess alkali was removed by washing several times with distilled water. A suspension of the starch in distilled water was then centrifuged. The supernatant fluid was discarded and the non-starch layer scrapped off. The tightly packed starch was then collected and dried in an oven at 70°C for 6 hours. The dried starch was ground to fine powder and passed through 180 μm size sieve.

3.2 Determination of Gelatinization Temperature

The temperatures of gelatinization of the starch samples were determined by making 0.29% w/v suspension of each starch sample in water in a 25 ml beaker and heating in a thermostated water bath at 40°C. The temperature was then gradually raised by about 2°C and withdrawn samples observed under a polarised microscope after each rise to ascertain the temperature at which the granules lost their polarisation crosses totally.

3.3 Modification of the Starches

40% w/w slurry of each starch sample in dilute hydrochloric acid solution was heated at 50°C with constatnt stirring for 2 hours, 4 hours and 6 hours. The reaction mixture was cooled and neutralized to a pH of 7.0 with dilute sodium hydroxide solution. The recovered starches were washed and dried at 50°C for 6 hours and then passed through 180 µm sieve.

3.4 Microscopic Examination

A small quantity of each of the unmodified and modified starches was mounted on a slide in glycerol. The size of the starch grains were measured using the calibrated eye piece micrometer and the shapes of the starch particles were also observed and drawn.

3.5 Identification of the Starches

The British Pharmacopoeia (1980) test for identification of starch was used: 1.0 g of each of the starches

was boiled with 15 ml water, cooled and iodine solution added and the colour change was observed.

3.6 Flow Tests and Carr's Index

The time required for 100 ml of the samples to pass through the orifice of an Erweka Granule flowability tester (Erweka Type GDT, Erweka Apparatebau GmbH, West Germany) was determined automatically. Three readings were taken for each batch of starch and the mean recorded.

Carr's index was calculated using the following equation (Schwartz *et al*, 1975):

$$CI = \frac{TD-BD}{TD} \times 100$$

where CI = Carr's Index

TD = Tapped density

BD = Bulk density

Bulk volume was determined by allowing 50 g of powder to flow freely into a 100 ml measuring cylinder and the volume taken. Tapped volume was measured by tapping the cylinder containing the powder 500 times with the aid of a stirring rod and taking the volume thereafter.

The densities were calculated using the formular:

$$\text{Density (g/ml)} = \frac{\text{Mass (g)}}{\text{Volume(ml)}}$$

3.7 Determination of Moisture Content

2 g of each of the starch samples was weighed into a tarred evaporating dish. It was then placed in an oven at 105°C and dried to constant weight. The weight was then

recorded. The moisture content was expressed as a percentage thus:

$$MC = \backslash F(IW - FW;IW) \times 100$$

where MC = Moisture content
IW = Initial weight
FW = Final weight

3.8 Tablet Formulations and Compressions

Compressions were carried out using an Erweka Sinlge station tablet press (Erweka Type EKO, Erweka Apparatebau GmbH, West Germany) fitted with 8 mm flat faced bevel-edged punches which were lubricated (in the case of starch tablets) by applying a 1% w/v solution of magnesium stearate in acetone with the aid of a very light brush.

200 mg tablets of microcrystalline cellulose and of the modified starches were made at different compression pressures. An attempt was also made to make 200 mg compacts of the native starches and Trimethoprim.

Tablets of Trimethoprim were then formulated and prepared by direct compression. The modified starches were employed as direct compression filler-binder-disintegrant. A Trimethoprim tablet formular using microcrystalline cellulose instead of the modified starches as filler-binder-disintegrant was used as a basis for the modified starches' evaluation.

The following formulae were used for producing the tablets:

1.	Trimethoprim	100 mg
	Modified starch	100 mg
2.	Trimethoprim	100 mg
	modified starch	50 mg
3.	Trimethoprim	100 mg
	Microcrystalline cellulose	50 mg

In all the formulations, the mixture of excipient(s) and Trimethoprim was blended for 5 minutes in a glass bottle by tumbling and compressed at three different compression pressures.

The ratio of Trimethoprim and modified starch was varied to determine the performance of the modified starches in the presence of increasing proportions of a poorly compressible drug, Trimethoprim.

3.9 Binary Mixtures

Sieve fractions less than 180 μm of each modified starch sample (millet, sorghum and yam), starch 1500 and microcrystalline cellulose were dried in an oven to constant weight at 105°C. Blends of the materials were prepared by weighing the appropriate quantities and tumbling in a glass bottle for 10 minutes to produce homogeneous mixtures of 0, 25, 50, 75 and 100% of modified starch/starch 1500 and modified starch/ microcrystalline cellulose.

Compressions were carried out on the Erweka Single station tablet press fitted with 8 mm flat faced bevel-edged punches. Houndred tablets were produced at each of three

different compression pressure settings. 200 mg constant weight was maintained for all the tablets.

The die wall and surfaces of the punches were prelubricated with 1% w/v magnesium stearate in acetone before each compression.

3.10 Wet Granulation

All the powders were passed through sieve 180 µm size. The tablets formulae were:

1.	Starch (modified/unmodified)	247.5 mg
	Magnesium stearate	2.5 mg
	Maize starch (USP)	25.0 mg
	Maize starch (USP) mucillage (5% w/v)	2.5 mg(dry starch)
2	Trimethoprim	150.0 mg
	Starch (modified/unmodified)	100.0 mg
	Magnesium stearate	2.5 mg
	Maize starch (USP)	25.0 mg
	Maize starch (USP) mucillage (5% w/v)	2.5 mg

The magnesium stearate was mixed with the starches (and with Trimethoprim in the second formular). The maize starch (USP) was then blended with the initial mixture. This final blend was granulated manually in a large porcelain dish with the weighed quantity of freshly prepared starch mucilage having a concentration of 5% w/v as binder. 50 ml of the starch mucilage was used.

The wet mass was then passed through an Erweka Oscillating granulator using 0.8 mm screen and dried in an

oven at 60°C for 4 hours. This was then dry-milled and screened again using 0.8 mm mesh.

The granulation was then compressed as earlier mentioned.

3.11 EVALUATION OF TABLETS

3.11.1 Uniformity of Weight

Ten tablets were weighed individually and collectively from each batch using the analytical balance (Gallenkamp, Mettler H35AR, Mettler Instruments AG., Switzerland) and the mean weights computed. The percent coefficient of tablet weight variation (% CV) was calculated according to the formular (Bolhuis, 1988):

% CV = \F(Standard deviation;Mean weight)

3.11.2 Hardness

The Monsanto hardness tester was used to determine the crushing strength of five tablets from each batch twenty four hours to allow enough time for elastic recovery to occur after the tablets had been made.

3.11.3 Friability Testing

Ten tablets were dusted, weighed together and subjected to abrasion test in the Roche Friabilator (Erweka Type TA3R, Erweka Apparatebau GmbH, West Germany) operated at 25 rpm for 4 minutes. The tablets were then dusted properly and weighed again collectively. The difference

in weight was then determined and expressed as percentage friability value.

3.11.4 Thickness and Diameter Measurements

The thickness and diameter of tablets were measured using the micrometer screw guage (Moore and Wright, Sheffields, England), 24 hours after the tablets had been compressed. 5 tablets were measured for each parameter and the mean calculated.

3.11.5 Density of Tablets

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

Tablet density (g/ml) = \F(Weight of tablet (g);Tablet volume (ml))

The volume of tablet was calculated from the relationship:

Volume of tablet = $\F(\Pi D^2 h;4)$

where D = diameter of tablet, and

h = tablet thickness

3.11.6 Disintegration Time Studies

The disintegration times of tablets were determined using the BP (1980) method. Water thermostatically maintained at 37° ± 0.5°C was the medium.

The time taken for each of the six tablets- one placed in each of the six tubes of the apparatus to disintegrate and pass through the mesh was recorded using a stop clock.

3.12 Tableting Schedule

1. Microcrystalline cellulose only
2. Unmodifiedd starches only
3. Modified starches only
4. Trimethoprim alone
5. Microcrystalline cellulose 100mg
   Trimethoprim 100mg
6. Modified starches 100mg
   Trimethoprim 100mg
7. Modified starches 50mg
   Trimethoprim 100mg
8. Binary mixtures of starch samples and Avicel/ Starch 1500
9. Wet granulation tablets
10. Trimethoprim tablets by wet granulation

3.13 **Summary of Modification Procedure**

Temperature of modification : 50°C
Strength of HCl used : 10% v/v Conc. HCl
Duration of heating : 2; 4; 6 hrs respectively
Samples of starch used : Millet (M)
Yam (Y)
Sorghum (S)

40% w/v suspension used for the heating.

KEY:

Each modified starch is coded with the alphabet denoting the starch source and the figure represents the duration of heating. For example, M_2 means slurry of millet starch heated for 2 hours at 50°C and M_2T means tablet of M_2 and Trimethoprim.

Batches

I	Avicel (A)	
II	M_0	
III	M_2	M_2T
IV	M_4	M_4T
V	M_6	M_6T
etc	S_0	S_2T
	S_2	S_4T
	S_4	S_6T
	S_6	Y_2T
	Y_0	Y_4T
	Y_2	Y_6T
	Y_4	
	Y_6	

CHAPTER FOUR

4.0 RESULTS AND DISCUSSIONS

4.1 Evaluation of the Physical Characteristics of Modified Starch Samples

The modified starch samples were white, very fine and possessed slight characteristic taste. None of the modified starches dissolved in water. A reddish-blue colour was observed after the iodine test for starches was performed and the moisture content for all the samples was within pharmacopoeia limits of 15% as shown on Table 1. The moisture contents of the modified starches were slightly higher than those of their corresponding unmodified starches. This can be ascribed to water absorption into starch granules during the hydrolysis process which was difficult to loose during the drying process. The duration of the hydrolysis had only very slight effect on the moisture content.

The heating of a suspension of starches in dilute hydrochloric acid is actually a controlled hydrolysis (depolymerization) of the samples. The physical properties of the products are mainly determined by the degree of starch hydrolysis which is represented by the dextrose equivalent of the product. The dextrose equivalent (D.E) value is defined as the amount of reducing sugars present and expressed as percentage of dextrose in the dry substance. A high D.E. value

indicates a low average degree of polymerization of the product which consists of a high percentage of low molecular weight saccharides (Li and Peck, 1990).

The highest degree of hydrolysis was achieved after 6 hours evident by the more reddish nature of the iodine reaction (reaction time of the starches and the dilute acid affects the degree of hydrolysis). Complete hydrolysis of the starches may occur just above 6 hours reaction time.

4.1.1 Particle Shape and Size

The size and shape of the starch samples are given in Table II and Figure 1 respectively. Modified millet starch (MMS) possessed particles with the smallest mean size of 7.5 μm while modified yam starch (MYS) had the highest mean particle size of 33.0 μm for the longest duration of acid hydrolysis. MYS had the highest particle size range of 15-50 μm and size ranges of both MMS and modified sorghum starch (MSS) were similar (5-12 μm and 10-17.5 μm).

Microscopic examination revealed a corresponding decrease in mean particle size with longer duration of acid hydrolysis. With millet starch (MS), mean particle size reduced from 10 μm after 2 hours to 7.5 μm after 6 hours of hydrolysis. For sorghum starch (SS), the corresponding mean particle sizes were 14.3 μm and 10.3 μm for 2 and 6 hours hydrolysis respectively. Yam starch (YS) particles reduced from mean of 35.3 μm after hydrolysing for 2 hours to 33.0 μm after 6 hours.

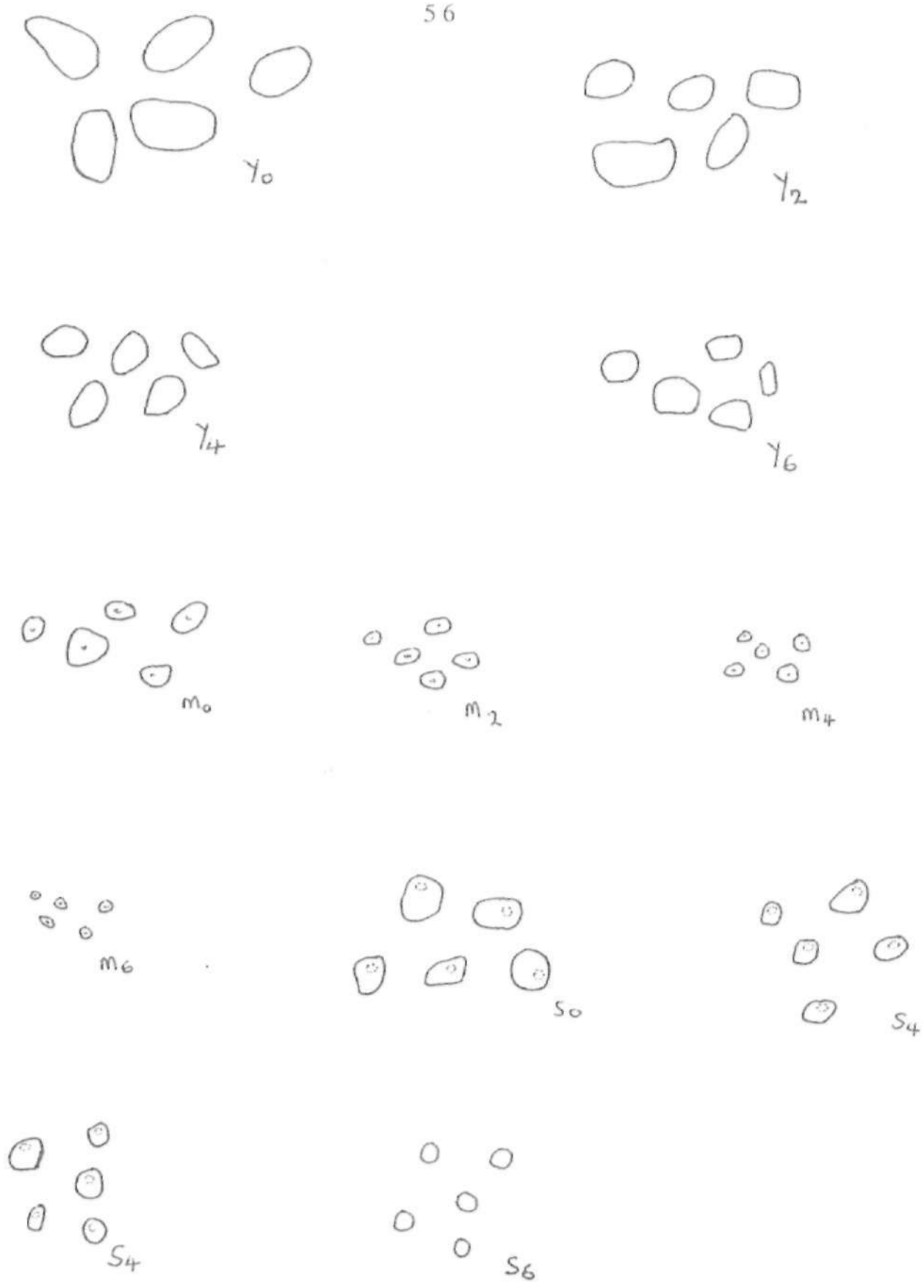


Fig. 1: Shape of Starches as seen under an Optical Micorscope (X 40)

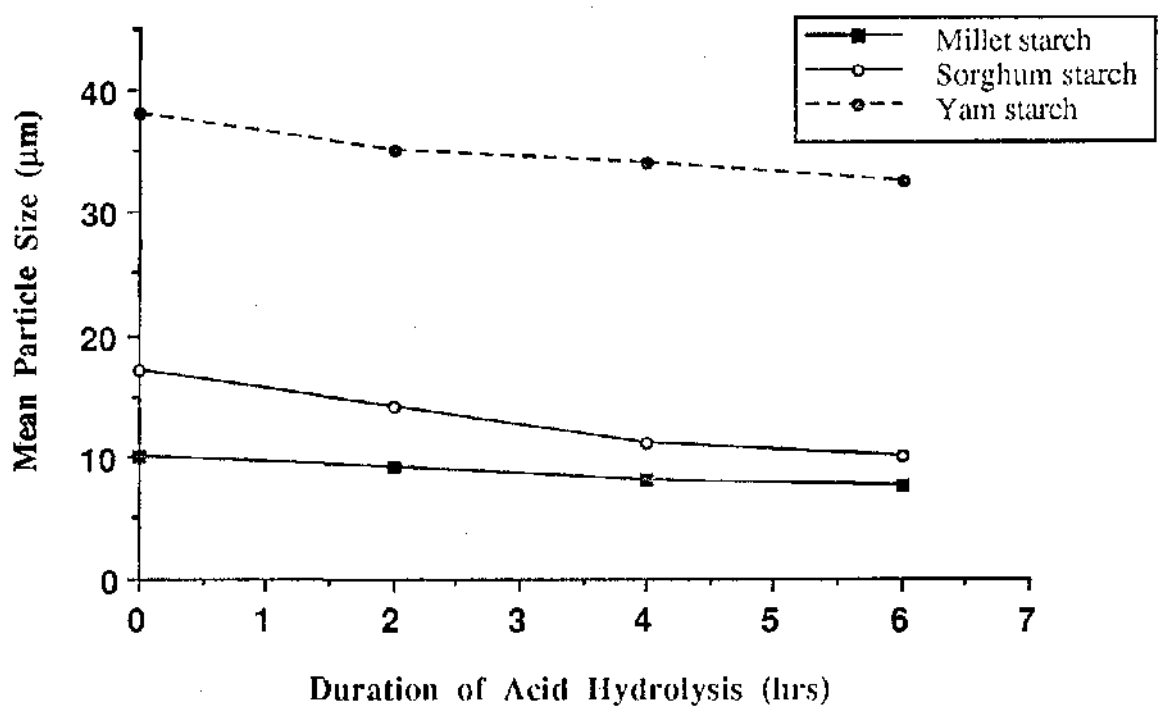


Fig. 2: Effect of Duration of Hydrolysis on the Mean Particle Sizes of Various Starch Samples Suspended in Dilute Hydrochloric Acid at 50°C

The reduction of mean particle sizes of starch particles on hydrolysis is attributed to the depolymerization of the starch granules, since hydrolysis involves the breaking of the amylopectin chains. Figure 2 shows the effect of degree of hydrolysis on the mean particle sizes of the starch particles. From the slopes of the curves, it is apparent that SS is more susceptible to hydrolysis, if reduction in particle size is used as the parameter for determining hydrolytic response as compared to YS.

4.1.2 Gelatinization Temperature

The gelatinization temperature of the starches have been recorded in Table 1. The gelatinization temperature of YS > SS > MS. YS may posses a higher degree of elasticity because of the nature of its source (Yam is a root tuber). The subjection of an aqueous suspension of starch to the influence of heat weakens the micellar network within the granules by disrupting hydrogen bonds. This suggested higher elasticity of YS granules would make hydrogen bond disruption more difficult and hence a higher gelatinization temperature. There could also exist very strong hydrogen bonds within YS granules compared to SS and MS. This thought is corroborated by the apparent lesser susceptibility of YS to hydrolysis as evident from its very high size range and large mean particle size for corresponding durations of acid-hydrolysis compared to the other starch samples.

Gelatinization is defined as the loss of the interference cross visible within the granule under polarised light and the gelatinization temperature is that point at

which this transition occurs. While each individual granule gelatinizes quite sharply, not all the granules in a starch sample gelatinize at the same temperature, but rather over a range of some 8°-10°C. This reflects differences in the internal bonding forces within individual granules. The temperature of gelatinization indicates the strength of hydrogen bond formation within the starch granule (Blanshard, 1987) or the amylose content of the starch (Sterling, 1978). The stronger the hydrogen bond or the higher the amylose content, the higher will be the gelatinization temperature.

4.1.3 Flow Properties

Table 2 shows the results of flow tests carried out on the starches. Modification of all the samples yielded products with better flow properties compared to their unmodified forms. The effect of increasing the degree of depolymerization on the flow characteristics is illustrated graphically in Figure 3. The flow rate for the unmodified starches was in the order: MS < YS < SS. The poor flow of millet starch may have been due to the high cohesive forces present in the powder brought about by its large quantity of fines. Unlike SS and YS, MS powder appears less susceptible to drying. The higher moisture content could also have increased the cohesiveness of MS. The better flow of SS as compared with YS may be attributed to the more spherically shaped particles of the former.

Table 1: Moisture Content and Gelatinization Temperature of the Unmodified Starches

Samples of Starches	Moisture Content (%)	Gelatinization Temperature (°C)
Millet	5.03	80
Sorghum	5.19	84
Yam	6.5	88

Table 2: Flow Properties and Particle Size Analysis of Various Starch Samples

Batches	Mean Particle Size (μm)	Particle Size Range (μm)	Angle of Repose (°C)	Efflux Time (s)
M_0	10.0	5-15	42.3	50.2
M_2	9.2	5-15	40.9	29.7
M_4	7.6	5-12.5	39.7	36.7
M_6	7.5	5-12.5	38.7	41.0
S_0	16.8	10-22.5	40.7	35.3
S_2	14.3	10-20.0	40.2	25.3
S_4	11.0	10-17.5	37.6	25.5
S_6	10.0	10-17.5	36.9	24.7
Y_0	39.0	22.5-50	39.2	42.0
Y_2	35.3	15.0-50	37.1	20.0
Y_4	34.1	15.0-50	35.3	20.3
Y_6	33.0	15.0-50	34.9	21.7

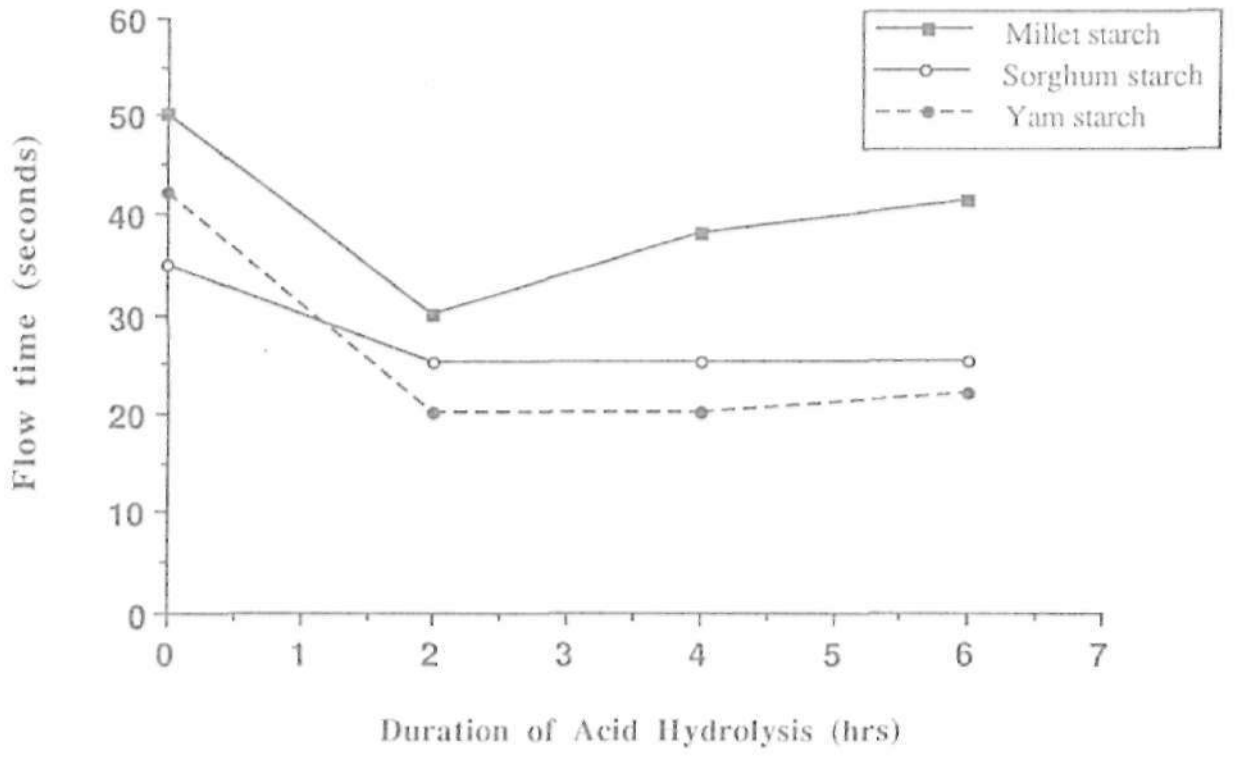


Fig. 3: Effect of Increasing Degree of Depolymerization on the Efflux Time of the Starches Suspended in Dilute Hydrochloric Acid at 50°C.

The ability of granules to flow properly is of immense importance during the tableting process. Neumann (1967) reported that the quality of a compressed tablet depends largely on a uniform flow of material from the hopper to the feed-shoe and then into the die cavity. Poor flowing powders could lead to variations in weight, hardness and content of tablets. The flow property is dependent on particle size, shape, porosity, density and surface texture. Poor flow could also result from presence of moisture in which case drying the particles will reduce the cohesiveness. Particle size, shape and moisture content of the unmodified and modified starches appear to have had interwoven effects on their flow. MS samples which seem to be less susceptible to drying had prolonged flow.

This work has shown that MYS has the best flow rate as determined by the automatic flow tester, followed by MSS and then MMS. The poor flow exhibited by MMS could be attributed to the fine state in which the particles exist as shown by microscopic examination and thus possessing the greatest inter-particulate cohesiveness due to very high inter-particulate forces of attraction.

Figure 3 shows an initial improvement in flow rate of starches after the early hours of hot acid treatment, then there was no further decrease in efflux time. For MMS, there was an increase in efflux time after 2 hours. Particle analysis had revealed an increased uniformity in shapes and sizes and thus reduced inter-particulate friction with hydrolysis. This may have been responsible for the initial increase in flow rate for all the starches, but with all the

starches there was no further increase in the flow rate with increased duration of hydrolysis, except for MMS where there was an increase in efflux time. The flow rate of MYS and MSS did not improve after 4 and 6 hours of hydrolysis because the resultant decrease in particle size could not have any influence on flow properties. The attendant decrease in particle size (Table 2) with longer duration of hydrolysis for MMS could have resulted in very small particles with very high cohesive forces, which decreased flow.

4.1.4 Carr's Index

Carr's index gives an insight into the packing characteristics of powders. The value of the index is determined primarily by the bulk and tapped densities of a powder. The greater the difference between the tapped and bulk densities of the powders, the greater the Carr's index and the poorer the flow of the material.

Carr's index is affected by the characteristics of the individual particles. Particle shape plays a major role, so also surface characteristics, particle size and size distribution and the packing configuration adopted by the powder during the bulk density determination. For instance, particles of a powder with poor flow characteristics may protect relatively large voids by bridging and thus would be expected to undergo considerable rearrangement when tapping is done. A low Carr's index could therefore equally imply a good initial packing arrangement, with less volume of voids.

Table 3: Density Properties of Starch Tablets

Batches	Bulk Density (gcm^{-3})	Tapped Density (gcm^{-3})	Carr's Index (%)
M_0	0.40	0.60	33.3
M_2	0.45	0.61	26.2
M_4	0.48	0.68	29.4
M_6	0.50	0.59	25.4
S_0	0.51	0.82	37.8
S_2	0.52	0.71	26.8
S_4	0.54	0.71	23.9
S_6	0.55	0.74	24.3
Y_0	0.72	1.00	28.3
Y_2	0.74	0.98	24.5
Y_4	0.75	0.96	21.9
Y_6	0.83	0.98	15.3

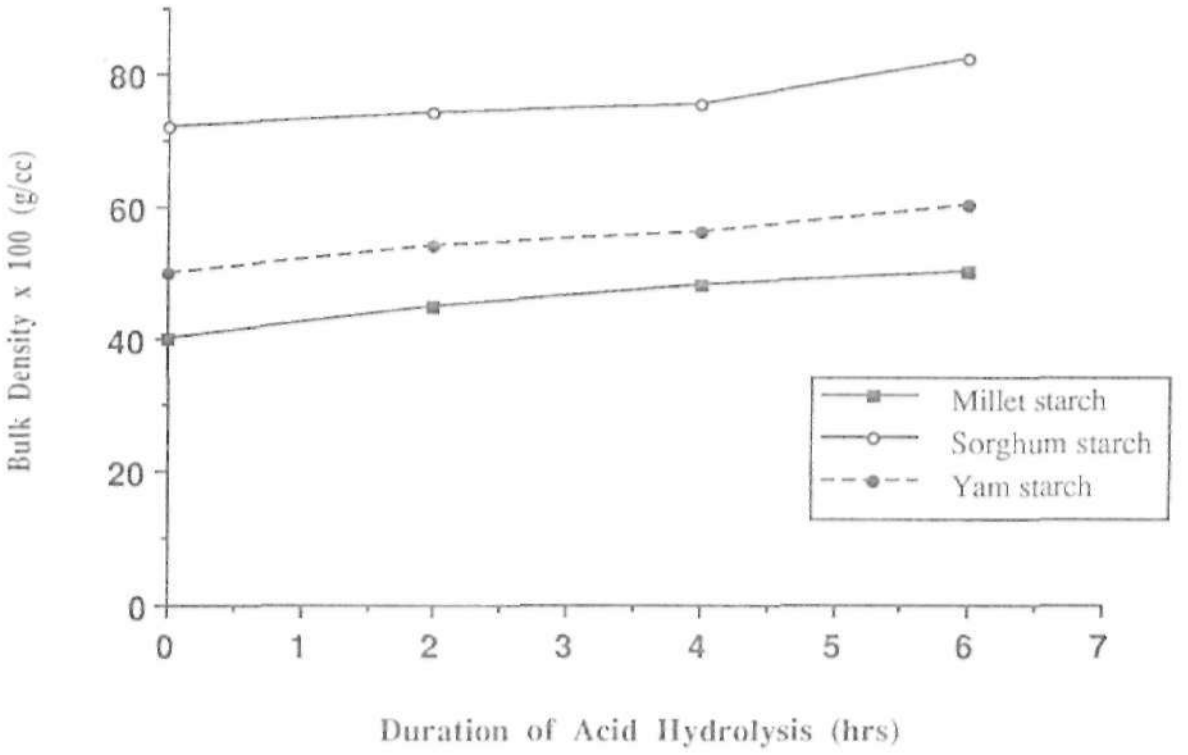


Fig. 4: Effect of Extent of Hydrolysis on the Bulk Density of Starch Samples Suspended in Dilute Hydrochloric Acid at 50°C

Table 3 shows the values of Carr's index for all the starch powder, the index increasing in the order: MYS > MSS > MMS. The results did not indicate any consistent pattern with different degrees of hydrolysis except in the case of MYS where Carr's index dropped with longer period of hot acid treatment, although this is contrary to the efflux time results. Due to the methodology involved in measuring Carr's index, it does not appear to be a very reliable parameter in determining flowability. However, in comparison with the unmodified starches, all corresponding modified starches exhibited lower Carr's index.

Table 3 and Figure 4 have illustrated that the bulk densities of all samples were increased with depolymerization. There was an increase in bulk densities as the duration of acid treatment increased. It is worthy to note that bulk density values would depend on the method adopted for its measurement and reproducibility of such methods is difficult. Therefore, bulk density values are not sensitive enough for the discrimination of powder properties. Figure 4 shows the bulk density values to be in the order: MSS > MYS > MMS. The graph indicates that bulk density values increased with hydrolysis and even more so with longer duration of hydrolysis. This can be ascribed to the more uniform sizes obtained with increasing hydrolysis and also due to more spherical nature of the granules with longer duration of hydrolysis, resulting in stronger or tighter packing of particles. The low bulk density of millet starch is due to the bridging of voids that occurred during the bulk volume determinations. This may have been caused by fines and/or by

the presence of moisture. MSS particles were more spherically shaped and had the least moisture content. It is suggested that this uniformity of shape and low moisture content contributed to making MSS powder the best flowing of the three types of powders.

The results correlate with the work of Ridgway and Rupp (1969) who investigated the effect of particle shape on powder properties. They found that the bulk density and flowability decreased with increasing departure from spherical shape, due to the greater resistance to shear of flow of an assembly of irregular particles compared to an assembly of spherical particles of same size and density.

4.2 Relationship Between the Degree of Depolymerization and the Compression/ Consolidation Properties of the Starches

The unmodified starches did not form firm tablets at the very high pressure setting of 10 on the machine, but the modified starches did even at much lower pressures. Tables 4 to 6 show some properties of tablets prepared at different pressure settings.

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 the material due to particle re-arrangement and slippage, plastic deformation or fragmentat-

ion and particle-particle bonding. Compaction of pharmaceutical powders encompasses compression and consolidation (Garr, 1992).

The powder properties which have played major roles in the compression/consolidation of the starches are the particle sizes and shapes. From most tablet parameters considered to evaluate compressibility, MMS showed the best compressibility (see Tables 4, 5 and 6), particle sizes of MMS were on the average smaller than those of other starch samples. The symmetrical shapes of the MMS also would allow for better packing of material under pressure and even the moisture present would act as binder. The better packing will increase the amount of contact there is between particles and therefore increase tablet coherence, from more particle bonding.

4.2.1 Structural Strength of Tablets

The hardness (structural strength) of the tablets at various compression pressures are shown on Tables 4 and 5. The results indicate increase in hardness in the order: Avicel > MMS > MSS > MYS. The hardness of a tablet provides a measure of the bonding potential of the materials concerned.

Figure 5 shows the effect of length of hydrolysis of the starches on the crushing strength of tablets made at different compression pressures. MMS produced the hardest tablets at all pressure settings. With increase in the duration of hydrolysis there was a corresponding increase in tablet's strength. The difference in the hardness of tablets produced after 4 and 6 hours of hydrolysis was not very pronunced. At

lower pressures, MSS and MYS manifested same degree of hardness and for all modified starch samples, hardness of their tablets remained the same for 4 and 6 hours of hydrolysis.

Compressiblity was also evaluated from the densities of tablets at corresponding compression pressures as shown on Table 6. The increasing order of compressibility is the same pattern as that of hardness, thus: Avicel > MMS > MSS > MYS). Density of tablets was found to increase with increase in duration of hydrolysis.

4.2.2 Friability of Tablets

The results of friability tests have been tabulated on Tables 4 - 5. The friability test determines tablets resistance to abrasion and it appears to be a more realistic test since, tablets are not subjected to a breaking load as determined by the crushing strength test. Friability values are usually considered satisfactory when the product exhibits a weight loss of less than 0.8% (Gumsel and Kanig, 1976).

For all starch samples, tablets made from products of 2 hours hydrolysis were either too soft or very crumbly. The tablets did not pass the friability tests because capping either occurred as in the case of modified millet starch tablets or crumbled totally as shown by MSS and MYS tablets. Increasing the duration of hydrolysis to 6 hours gave products with better, that is, reduced friability values. This suggests that compressibility/consolidation of the products may depend on the degree of hydrolysis and the higher the depolymerization the better the tablets attained.

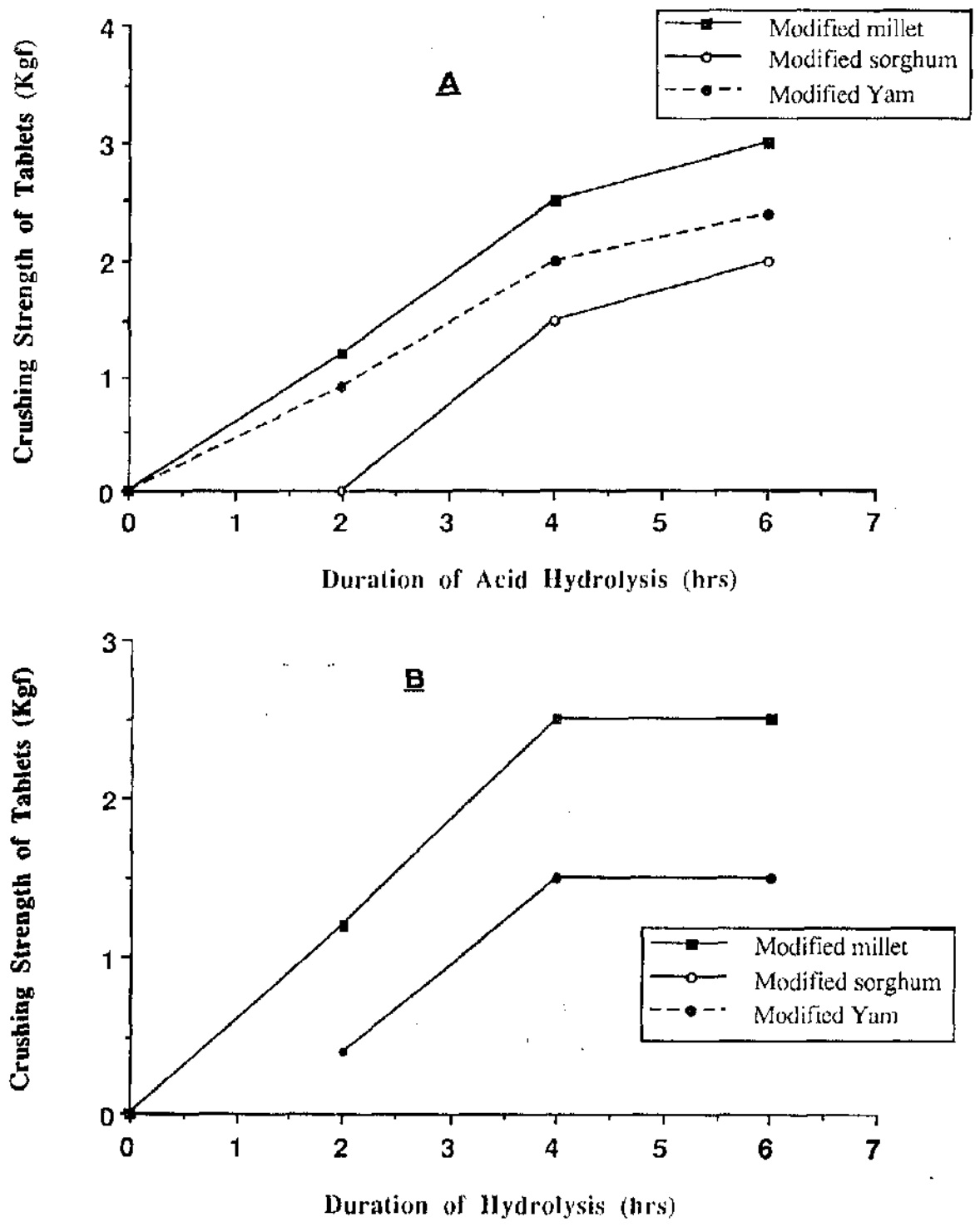


Fig. 5: The Effect of Duration of Hydrolysis of Starches on the Hardness of their Tablets at compression pressure setting of (A) 8 and (B) 6.

The present work has shown that there is a decrease in mean particle size with increasing degree of hydrolysis and that size of particles affect their compressibility. The mechanism of consolidation appears therefore be by plastic deformation. The reduced friability with decrease in particle size may be due to better and increased particle-particle bonding resulting in more tightly bond tablets. This also explains the result illustrated in Figure 6, where for all modified starch tablets there was an initial increase in friability followed by a reduction with longer periods of acid treatment.

At each compression pressure, friability values for the tablets is in the order: MMS < MSS < MYS. The hardness of tablets also followed the same pattern. All the modified starch samples exhibited lower hardness to compaction pressure ratio compared to microcrystalline cellulose (MCC) and also the starch tablets were more friable than that of MCC. The hardness to compression pressure ratio is the value of the ratio of hardness produced at any compression force to that compression pressure.

Particle size and shape affect hardness of tablets. The smaller the particle size, as obtained with longer duration of depolymerization, the higher the surface area and thus the higher the probability of more bond formation between the particles. This may suggest that the mechanism of compaction of the modified starches is mainly by plastic deformation. This correlates with the work of Iwuagwu *et al* (1986), who showed that the points of contact increase with

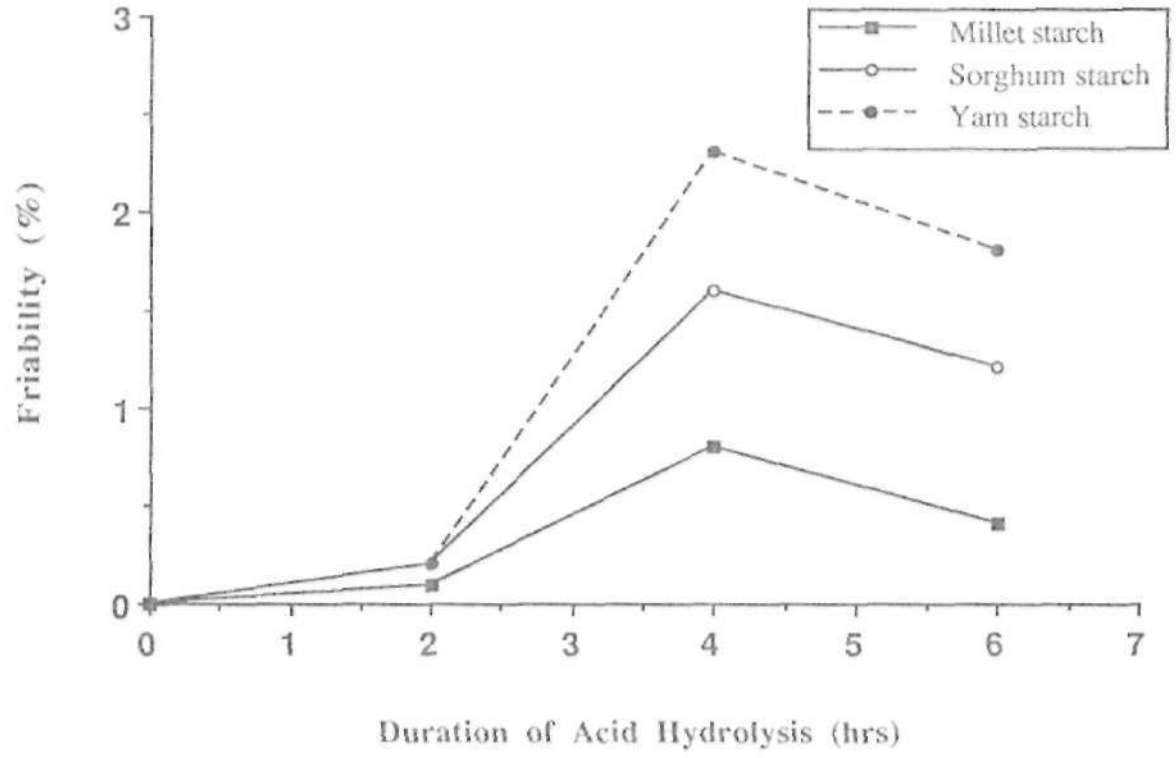


Fig. 6: Effect of Duration of Hydrolysis on the Friability of Tablets at Compressed at Pressure Setting of 8

increase in particles surface area and therefore more bonds are formed.

Materials undergo compaction by two types of ideal compaction mechanisms namely: brittle fracture and plastic flow (Train, 1956). The starch powders used for this work may have compacted by the plastic flow mechanism. In the case of brittle fracture mechanism, materials undergo fragmentation and tablet properties are not affected by initial particle size of the material. Powders that tablet by plastic deformation have the physical properties of the tablets been affected by the initial particle size of the powders. Since particles do not fragment under pressure, for such powders, but instead undergo flow to increase surface area available for bond formation, it therefore means that the smaller the initial particle size, the larger will be the surface area under pressure and so more bond formation occurs resulting in harder tablets with lesser friability.

4.2.3 Formulation and Production of Trimethoprim Tablets

Trimethoprim, an antimicrobial agent, has been formulated into tablets using unmodified, modified starches and MCC. Trimethoprim compressed into tablets with difficulty and possess a very high capping tendency after compaction. The tablets of trimethoprim and the unmodified starches were rather crumbly, and in most cases very difficult to form coherent units even with increasing magnitudes of compression force.

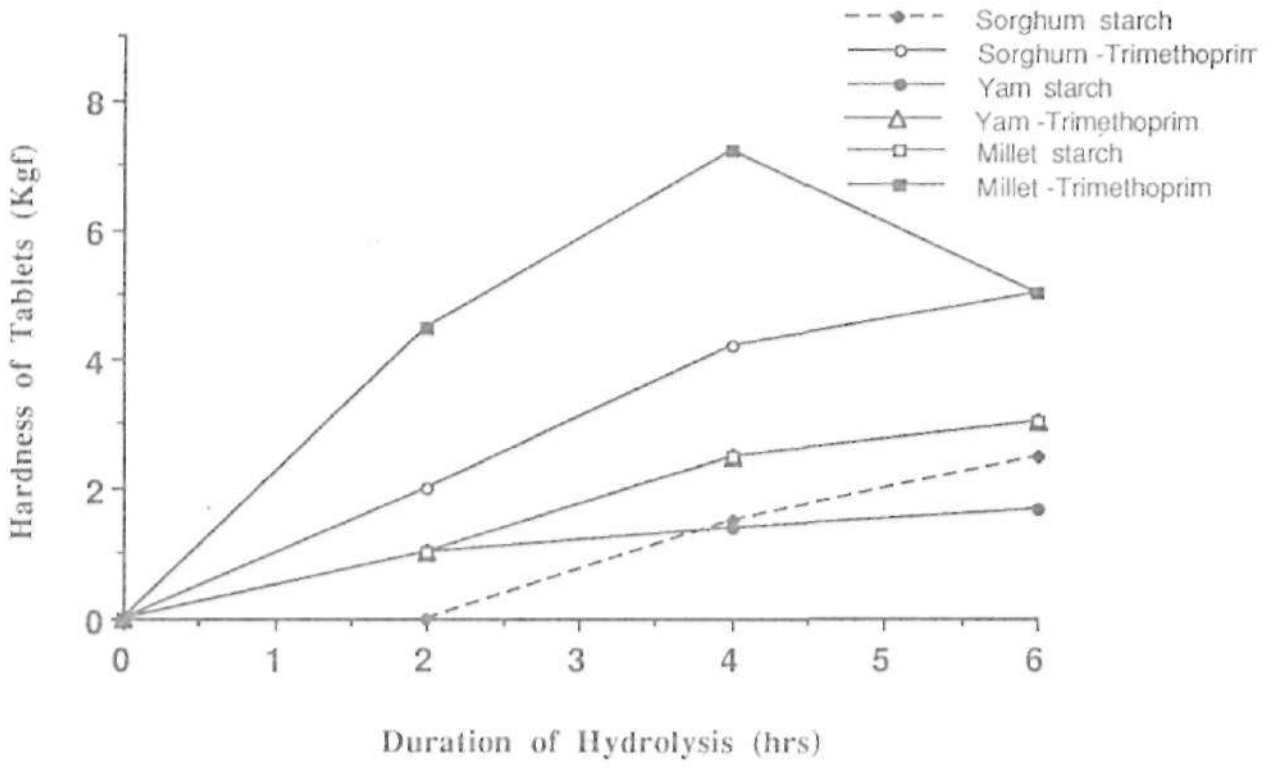


Fig. 7: Effect of Hydrolysis on Hardness of Starch and Trimethprim-Starch Tablets

The trimethoprim-modified starch tablets exhibited higher hardness values than the starch tablets alone. This is seen in Figure 7. This may be attributed to very high forces of attraction between the drug and the modified starches. MMS-trimethoprim tablets showed the greatest hardness while MYS-trimethoprim tablets had the least.

A reduction of the quantity of modified starches in the tablet formula to determine the performance of the modified starches as directly compressible vehicles, in the presence of increasing proportions of a poorly compressible drug substance yielded tablets that capped or laminated. Only a drug to starch ratio of 1:1 produced tablets that were acceptable.

4.2.4 Disintegration of Tablets

Disintegration is an important attribute of oral tablets, except those to be chewed before being swallowed. The BP (1980) recommends a maximum time of 15 minutes for uncoated tablets unless otherwise indicated in the monograph for a specific tablet. The process of disintegration is the breakdown of a tablet into the constituent granules/particles when in contact with gastric fluid. This helps in the release of a drug from the dosage form.

Disintegration depends on the strength of the bond existing between the particles. The disintegration of a tablet means that the binding force within the tablet has been overcome (Nicklasson and Nyguist, 1982). Iwuagwu *et al* (1986) attributed poor disintegration of tablets to the formation of very strong inter-particulate bonds between the

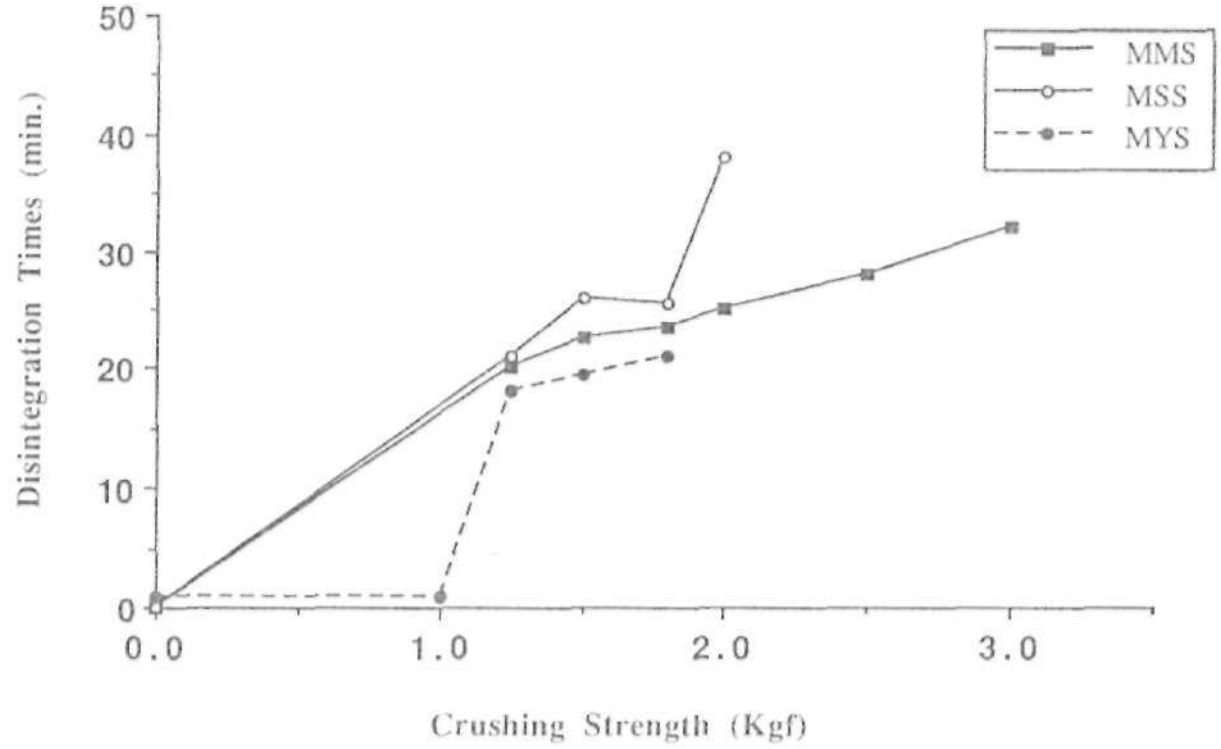


Fig. 8: Effect of Tablet Hardness on the Disintegrating Times of Tablets.

drug particles and/or between drug particles and the other excipients. The compact a tablet is, the less the porosity and the voids between the particles and thus less penetration of water into the tablet and hence longer disintegration time.

It is seen from the plot (Fig. 8) that the disintegration action of the tablets increase in the order: MYS > MSS > MMS. There is also an increase in disintegration time with longer periods of acid hydrolysis. It appears therefore, that the smaller the particle size, the slower the rate of disintegration of the tablet.

Smaller particles promote greater bonds in the starch tablets. Starch may act as a disintegrant by its capillaries promoting water absorption. The tighter bonds coupled with the impairment of capillary action and/or impairment of swelling ability by better compressibility could have led to the slower disintegrating action of the starches with increasing hydrolysis. The increased compressibility will reduce the porosity resulting in fewer capillaries, thus reducing the rate of ingress of water and thus a slower expansion of the disintegrating agent.

Increasing the hardness of tablets by increasing the force of compression resulted in tablets with longer disintegration times. It means therefore that unlike sodium starch glycolate, when incorporated into tablets as a disintegrant, which is unaffected by an increase in the compression force or by a decrease in tablet porosity (Shangraw *et al*, 1980), the modified starches as disintegrants are affected by both parameters: compression force and tablet porosity.

Modified starch-trimethoprim tablets exhibited even higher disintegration times than the starch tablets alone. This is so because the modified starch-trimethoprim tablets were harder than the starch tablets alone.

4.3 Tableting Behaviour of Binary Mixtures of Modified Starches and MCC/Starch 1500

Until very recently, studies on direct compression have principally focused on the tableting characteristics of single materials, and because of the many obvious advantages of tableting by direct compression, there is an abundance of publications on it (Riepma *et al*, 1990; Garr and Rubinstein, 1991; Garr and Rubinstein, 1992). Pharmaceutical tablets are usually tableted from multicomponent mixtures of excipients and drug(s). If the properties of the mixtures are linearly related to the composition of the mixtures, the strength of a tablet could be predicted from the strength properties of the individual components. Different and conflicting reports are cited in literature about the compression of binary powder mixtures (Riepma *et al*, 1990).

Panaggio *et al* (1984) demonstrated that mixtures of two or more matrices may have somewhat unexpected properties. They examined compaction and tablet properties of tablets containing varying proportions of dicalcium phosphate dihydrate (Emcompress) and pre-gelatinized starch (Sta-Rx 1500) in the presence of 0.5% magnesium stearate. The ejection force, disintegration time, tablet thickness and tablet hardness, did not vary linearly with the relative proportions of the two main components present. The different

observations may be attributed to partly non-documented differences in the experimental conditions, like moisture content and particle size fraction of the powder samples and the use of magnesium stearate (Riepma *et al*, 1990). For the present work, all powders have been dried to constant weight and same particle size fractions of less than 180 μm were used, while punches and dies were pre-lubricated with magnesium stearate before each compression.

4.3.1 Free Flow of Binary Mixtures.

The earlier experimental work had revealed an increase in the compressibility of modified starches which generally possessed poor flow characteristics. From the coefficient of weight variation results (Tables 7 and 8), it is apparent that the binary mixture of the starches possess better flow than the individual modified starch and no value was greater than 1.5%.

The binary mixtures of the modified starches with MCC produced better flow compared to those made with starch 1500. The order of increasing flow is thus: MYS-MCC > MSS-MCC > MMS-MCC. MCC alone flows better than any of the binary mixtures. The flow of the binary mixtures with starch 1500 followed the same pattern. These have been illustrated in Fig. 9. Increasing the proportion of modified starches in the binary mixtures resulted in reduced flow and best flow was observed when the mixture was in the combination 25% modified starch to 75% MCC or Starch 1500.

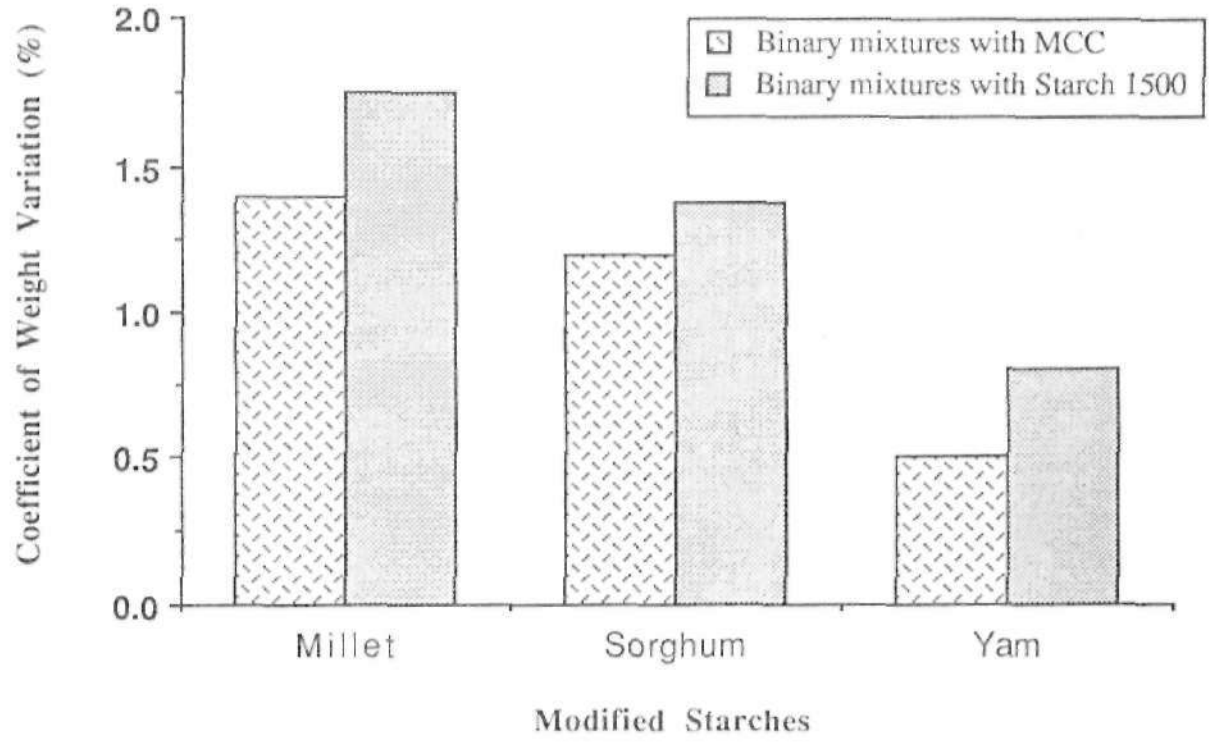


Fig. 9: Comparative Coefficient of Weight Variation of Tablets from the Binary Mixtures of the Modified Starches and MCC/Starch 1500.

These results indicate that the initial flow property of each modified starch sample contributed to the final flow of the binary mixture, that is, the flow of the binary mixtures was a function of the flow of the individual components. Those mixtures with individual components having good flow had their binary mixtures with corresponding good flow. The flow properties of the modified starches have earlier been given in Table 2.

Fig. 10 shows the effect of modified starch proportion on flow properties of mixtures. From the plot, it can be seen that with minimal starch proportion of 25% of mixture, there was an improvement of flow as indicated by the lower coefficient of weight variation values. The flow then gradually decreased with an increase in starch concentration to 100%, for all modified starch samples. The initial increase in flow with minimal starch content could be due to glidant effect of the starch powder. The fine state in which the modified starches exist filling up pores and cracks with the MCC/Starch 1500 particles and increasing their smooth texture resulting in less friction and good flow. Increasing the starch concentration could have caused aggregation of starch particles and

since the modified starches possess generally poor fluidity, there is a reduction of flow rate.

One of the properties of direct compression systems is excellent fluidity. Direct compression excipients should be free flowing, allowing continued and uniform flow of the formulation through the hopper, the feed frame and into the dies of the tableting press. Free flowing quality will permit the operation of modern high speed tableting machines at optimum speeds.

The flowability of the mixtures were determined by the method described by Bolhuis (1988) who expressed the flow properties of tablet excipients as the coefficient of variation of the weight of 40 tablets, compressed on a single punch machine. Poor flow properties with a tablet weight variation coefficient of over 1.5% were found for Avicel PH 101 and starch 1500.

The poor fluidity of Avicel PH 101 is ascribed to the presence of long drawn form of the particles and low density. The high coefficient of weight variation observed for starch 1500 is attributed to the large specific surface of the powder causing increase in particle cohesion.

4.3.2 Tablet Properties of Binary Mixtures

4.3.2.1 Structural Strength

Panaggio *et al* (1984) in a study of the properties of systems containing varying proportions of two direct compression tablet matrices, dicalcium phosphate dihydrate and pregelatinized starch, attributed some of the observation

such as inconsistent radial tensile strength and elastic recovery values, to the use of unidentical particle size distribution. In this present study, the same particle size fractions were used to enhance proper mixing and minimize the possible effect of particle size on consolidation.

The hardness of tablets are given in Tables 8 and 9 at various pressure settings and with different starch proportions. Only the unmodified starch samples and products of 6 hours hydrolysis were used for the binary mixtures. For all mixture combinations, the hydrolysed starches did better in terms of tablets' properties such as hardness as compared to the unmodified starches. Generally, increase in the magnitude of applied compression force produced tablets of increasing hardness. At each compression pressure, there was a decrease in tablet hardness with increasing concentration of modified starch sample. At any compression force, with the same proportion of unmodified starch and corresponding hydrolysed starch in respective mixtures, the mixture with the hydrolysed starch produced tablets with better physical properties such as tablet hardness, tablet density and friability values.

For binary mixtures with MCC and Starch 1500, all mixture combinations produced tablets with slightly lower hardness values than the individual substances tableted alone. Most binary mixtures with Starch 1500 tableted at lower compression forces compared to the MCC mixtures. This can be ascribed to similar forces of cohesion existing between the Starch 1500 and the modified starches.

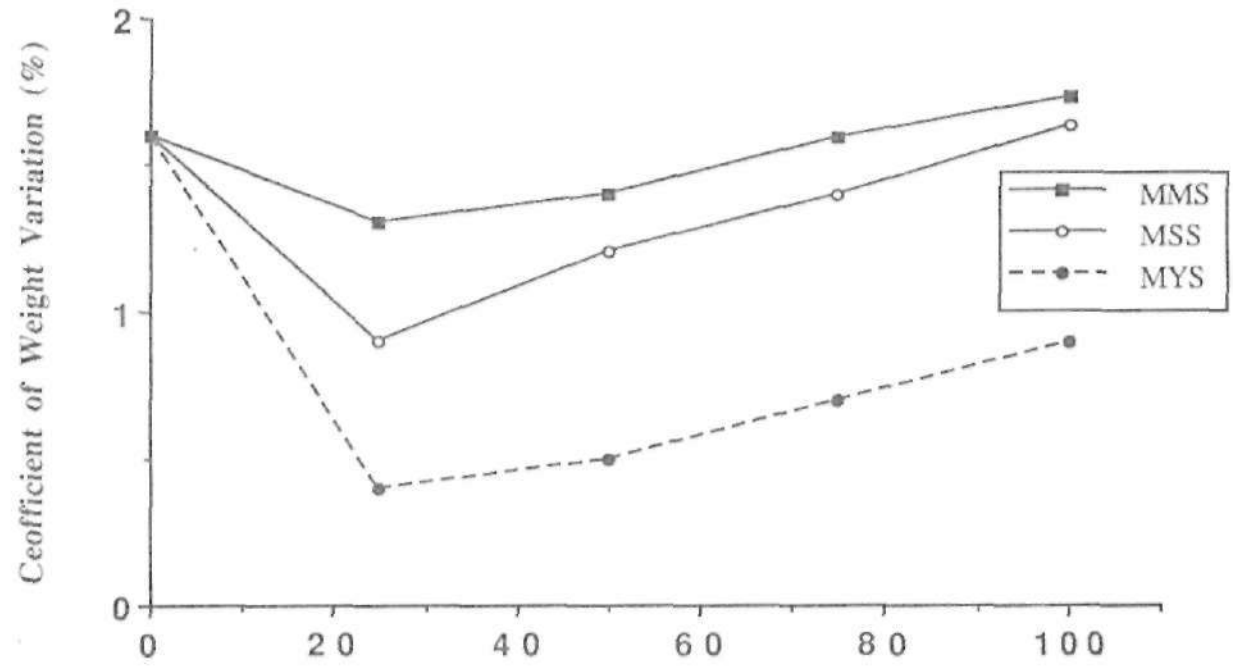


Fig. 10: Effect of Starch Proportion on the Coefficient of Weight Variation of Tablets from the Binary Mixtures

For all proportions, MYS mixtures resulted in tablets with better hardness and they compressed at lower pressures compared to other combinations. Of all the starches, MMS had better compressibility when tableted alone. Since MYS mixtures consolidated better, it means the strength properties of individual components cannot be used to predict tablet strength of the mixtures. The attractive forces between individual components appears to be a major determinant of mixture consolidation.

Tablet density was also used to evaluate binary mixture compressibility. The values are shown in Tables 7 and 8. There existed a direct relationship between hardness and tablet density and an increase in compression force resulted in a more tablet unit. Also, there was an inverse relationship between tablet density and proportion of modified starches in the mixtures. The tablet densities of binary mixtures of the mdified starches with Starch 1500 were higher than those with MCC. The compressibility of binary mixtures of Starch 1500 and the modified starches was better than those of mixtures of MCC. This is evident frm the tablet densities. This can be attributed to predominant cohesive attraction between Starch 1500 and the modified starches which are similar substances over the adhesive attraction between the modified starches and MCC which are dissimilar materials in nature.

Binary mixtures of the unmodified starches and the direct compression excipients (Starch 1500 and MCC) did not give tablets with good properties. As can be seen from Tables 7 and 8, excessive pressures were used to make tablets of very low tensile strength, low densities and low hardness

values. Capping was noticed with very high proportions (75%) of the unmodified starches.

Problems associated with directly tableting the modified starches alone such as sticking of materials to punches, forceful tablet ejection and use of excessive compaction load were either eliminated completely or reduced with the binary mixtures.

4.3.2.2 Friability of Tablets

Tables 7 and 8 show the friability of tablets. Friability of tablets should be a function of compression pressure, hardness and tensile strength of the tablets and also on the magnitude of bonding of the surface particles of the tablet. In compressing the MCC-modified starch mixtures, higher pressures were employed compared to the Starch 1500-modified starch samples, so the former tablets should be harder and be more firmly held. The hardness values indicated otherwise, but even then, the harder tablets of Starch 1500 mixtures are more friable. The Starch 1500 powder seems to be finer than the MCC powder. There may therefore, have been more particle-particle contact during the compression of the Starch 1500-starch mixtures resulting in more micro expansion on decompression and subsequent increase in friability.

The composition of mixtures had a slight effect on the friability of tablets and generally, the friability of binary mixture tablets appears to be lower than those of the individual components. Fig. 11 indicates the effect of mixture composition on friability. A reduction in the quantity of the

modified starches lowers the friability only very slightly. For the same starch proportion in the mixture, the unmodified starches produced more friable tablets. The friability values of the tablets were:

MCC-MYS < MCC-MSS < MCC-MMS < MCC and

St Rx 1500-MYS < St Rx 1500-MMS < St Rx 1500-MSS < St Rx 1500

4.3.2.3 Disintegration of Tablets

Disintegration for most of the tablets was by gradual erosion and usually very hard cores persisted for sometime during the testing process. The tablets from binary mixtures disintegrated faster than the individual components. This may be that the Starch 1500 and MCC used are good disintegrants.

The mixtures with MCC disintegrated faster than those with Starch 1500 even though higher compression forces were used for the former. MYS had the shortest disintegration times compared to MSS and MMS mixtures. For the Starch 1500 mixtures, increase in modified starch fractions led to increase in disintegration times of tablets, and this was also true for MCC mixtures. This can be ascribed to higher bonding forces between the mixture components, and the more the starch proportion, the higher the bonding and increased disintegration times. Also MCC and Starch 1500 are good disintegrants and their disintegrant action appear to be quantity dependent so a decrease in their quantity by increasing starch proportion led to increased disintegration times.

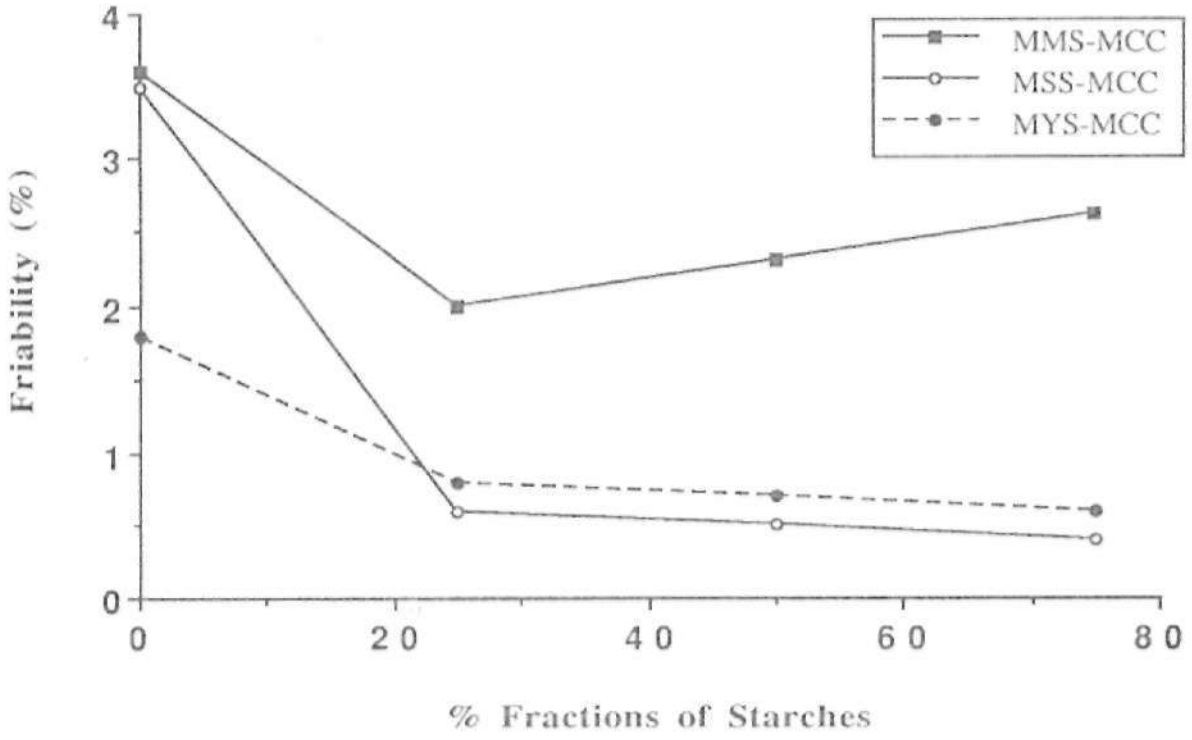


Fig. 10: Effect of Composition of Binary Mixtures of Modified Starches and MCC on the Friability of Tablets

4.4 A Comparative Study of the Physical Properties of Tablets from the Unmodified Starches and their Depolymerized Forms in Wet Granulation

Starch is one of the most widely used excipients in the manufacture of tablets. The ready availability and relatively low costs are major factors governing the widespread use of starch. Unmodified starch, however, has its limitations in pharmaceutical applications. Tablets[3] formulae containing a high concentration of starch as a filler are often soft and may be difficult to dry, especially in a fluidized bed drier. This causes a lot of problems especially in the presence of hygroscopic drugs. The compressibility of starch is too poor to make a tablet of sufficient hardness. Its poor flowability makes it unsuitable for use in direct compression formulations.

Granulation is the enlargement of the fine particles of drugs and excipients to form granules. The purposes of granulation are to impart flowability to a formulation and improve its compressibility. It also enhances uniform mixing and increases bulk density of formulations.

4.4.1 Tablet Properties

The flow properties of the granules were determined using the automatic flow tester (Erweka Granule Flowability Tester (Type GDT, Erweka Apparatebau GmbH, West Germany). Granules made from MYS had the fastest flow rate of 100 ml/15 sec, that is, 6.7 ml/s, and MMS granules had the least flow rate of 3.3 ml/s. Table IX shows the results which have

been illustrated in Fig. 12. The flow rates of granules made from the unmodified starches were lower than those made from the hydrolysed forms. Both forms of millet starch granules exhibited the least flow rates and MYS the highest flow rates. It seems therefore that initial material characteristics had an influence on flow rate of granules. The flow of the granules was by far greater than that of the corresponding ungranulated components and also followed the same trend as the ungranulated powders thus: (MYS > MSS > MMS) granules.

The flowability was also evaluated by the method developed by Bolhuis (1988). It was revealed that the weight variation coefficients were less than 1.5% in all cases, the tablets with the modified starches exhibiting the least values. These are given in Table IX.

A compression pressure setting of 3.5 was used for all batches. The hardness of tablets varied with MMS tablets exhibiting the highest values of 5.2 KgF while MYS tablets had the least values of 4.2 KgF. The compressibility of the initial materials also influenced the hardness of tablets from the granules. A direct relationship existed between tablet density and hardness. The densities of all tablets were higher than 1 gcm^{-3} and were much higher than those of tablets made from the direct compression of the starches at the corresponding compaction forces.

The friability of tablets was less than 1% indicating very good surface particulate bonding. The tablets from unmodified starches had friability values closer to 1% as is shown on Fig. 13. The friability increased in the order: MMS <

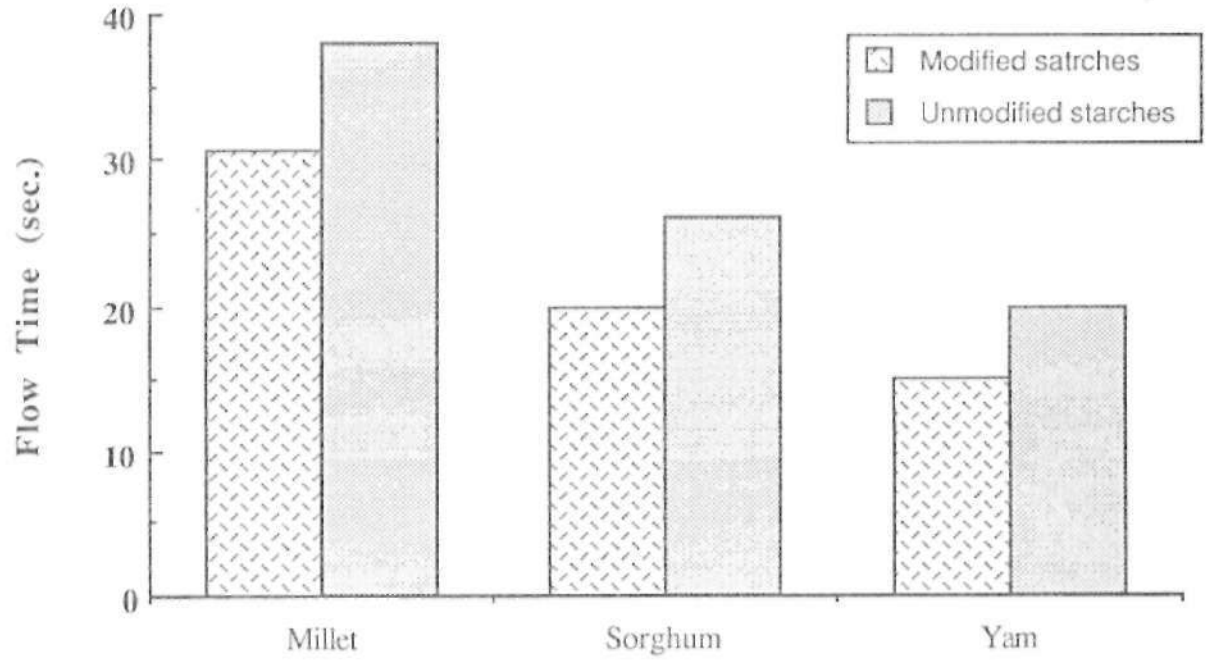


Fig. 12: Flow Time for 100 ml of Various Starch Granules Through an Orifice of 1 cm Diameter.

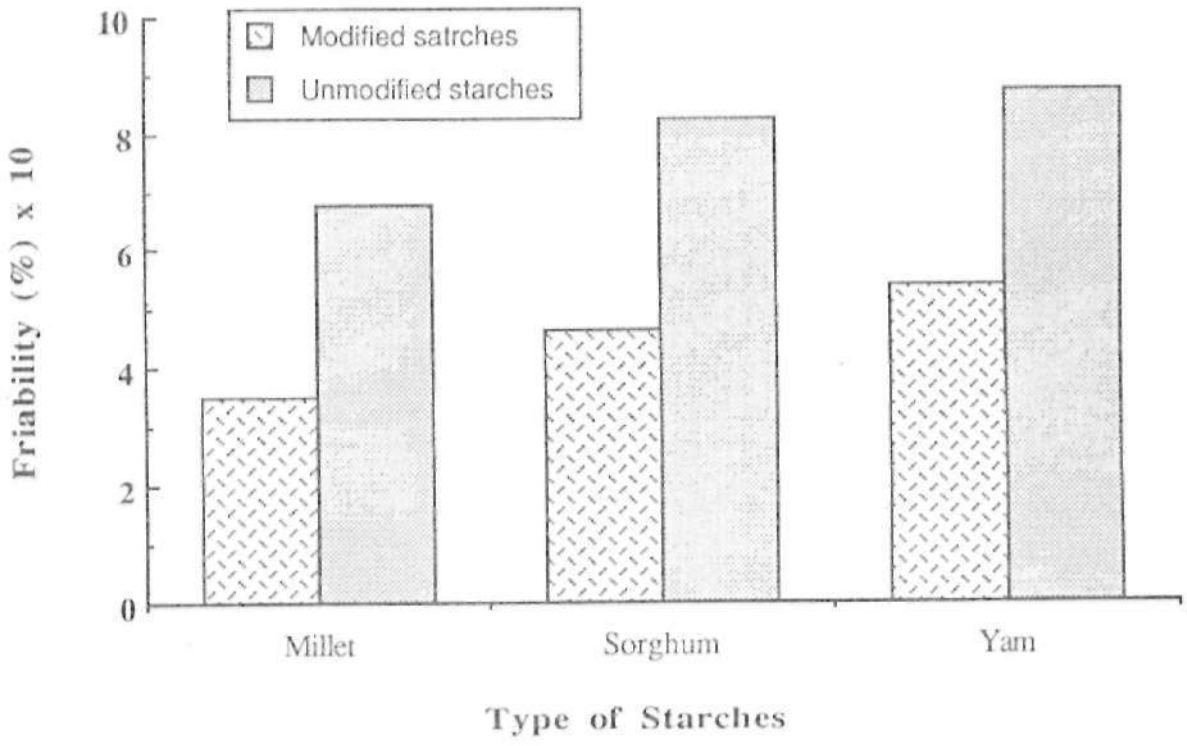


Fig. 13: Relationship between Friability of Tablets and Type of Starches used as Fillers

MSS < MYS and this was the same trend for the tablets from unmodified starches. Hardness of tablets had an influence on friability and an inverse relationship was noticed.

The disintegration of tablets was mainly determined by their hardness. There was a linear relationship between disintegration and hardness of the tablets. The influence of particle size on disintegration was minimized by the use of granules of similar size fraction (less than 180 μm) for the tableting process.

4.4.2 Formulation of Trimethoprim Tablets

277.5 mg tablets each containing 150 mg trimethoprim were formulated (See page 49). Unmodified and modified starches were used as fillers separately. Results indicated the need to use higher compression forces to form tablets.

The coefficient of weight variation revealed formulation with good flow characteristics. Trimethoprim tablets with MMS as diluents had a very high coefficient of 1.1% and those with MYS had the least with MSS being intermediate. Tablets with unmodified starches as diluents had higher coefficients than their modified derivatives and the order of increasing coefficients was MYS < MSS < MMS.

The higher compression pressure required to tablet the granules could have been due to the presence of the poorly compressible drug within the granules and therefore shows that the components of granules contribute to the compressibility of the formulation. The higher compression pressure did not result in higher tablet strengths (compared to tablets without trimethoprim) in terms of load required to

fracture the tablets diametrically. Tablets showed decreasing hardness in the order MMS > MSS > MYS and this was also the trend for tablets with unmodified starches as diluents. There was a proportional relationship between tablets' densities and hardness indicating good and uniform particulate bonding for the tablets.

All the tablets passed the abrasion test with those tablets containing unmodified sorghum starch as diluent exhibiting the highest friability of 0.94% and MMS tablets showing the least of 0.4%. This shows that friability of the tablets was determined by the compressibility of the granules since MMS granules were the most compressible.

All the tablets disintegrated within 15 minutes and have thus complied with the B.P (1980) requirement for disintegration of uncoated tablets. Disintegration was by fragmentation, the disintegrant breaking up the tablets into the starting granules. Trimethoprim tablets with MMS as disintegrant had the highest disintegration times of 10.7 minutes while the least time of 5.8 minutes was exhibited by tablets with unmodified yam starch.

MMS had proved to be the most compressible of all the starches so the increased bonding/consolidation may have retarded its swelling and water absorption, hence the high disintegration times. The lower disintegration times of the MYS and unmodified yam starch could have been as a result of higher water absorption leading to higher pressures being generated and thus faster disintegration of tablets.

CHAPTER FIVE

5.0 CONCLUSIONS

5.1 General Conclusions

Starches with very good pharmaceutical properties can be extracted from millet, sorghum and yam. Hot acid hydrolysis of these starches does not bring about any superficial change of the particles. The degree of hydrolysis, which is qualitative, is affected by the duration of hot acid treatment. More uniformly shaped and size reduced granules are produced upon hydrolysis. Acid hydrolysis of the starches generally improves the flow rate but for high fluidity and to prevent sticking of the modified starches to punches and dies, it is recommended that a glidant/anti-sticking agent be incorporated. The degree of starch hydrolysis should be such that average particle size does not get reduced to such a level to allow for excessive cohesive forces between particles which tend to retard flow.

The use of a high proportion of the starches in their unmodified forms for direct compression purposes pose a lot of problems, so also their binary mixtures with microcrystalline cellulose and Starch 1500 respectively. High compaction forces, which might strain the tablet press are required. Rather soft tablets are produced from the parent starches in wet granulation method of tablet manufacture.

Acid modification improves the compressibilty of the starches. This compressibility is directly proportional to the degree of hydrolysis. The mechanism of consolidation of the

modified starches may be by plastic deformation. The products of the 6 hours of hydrolysis possess compressibility properties comparable to those of standard directly compressible vehicles such as microcrystalline cellulose. The compressibility is in the order: MCC > MMS > MSS > MYS. The modified starches like MCC are self-binding and self-disintegrating. The flow of binary mixtures of the modified starches at all mixture compositions are comparable to those of MCC or Starch 1500 alone. The binary mixtures tablet at lower pressures than the modified starches alone. Binary mixtures consolidation is independent of that of individual mixture component.

The flow properties of the granules in wet granulation tableting is affected by the flow of granule components and lower forces are required to tablet the granules than the starch powders. Tablets produced from the unmodified starches as fillers are softer than those from the modified starches, this may be because the modified starches have better tableting properties.

5.2 Recommendations for Further Works

1. It is recommended that the effectiveness of the modified starches as disintegrants in formulations be studied especially in direct compression tableting.
2. The ability of the modified starches to act as binders should also be studied and compared to their parent forms.
3. A study should also be done to determine when complete hydrolysis of the starches will be achieved.

APPENDIX

Table 4: Some Properties of Starch and Trimethoprim Tablets Compressed at a Pressure Setting of 6 (Weight = 200 mg)

Batches	Hardness (KgF)	Friability (%)	Disintegrat-ion times (min.)
M_0	-	-	-
M_2	1.2	capped	14.0
M_4	2.5	capped	10.0
M_6	2.5	0.6	10.0
S_0	-	-	-
S_2	soft	soft	soft
S_4	1.5	-	6.0
S_6	1.5	1.2	9.3
Y_0	-	-	-
Y_2	soft	soft	soft
Y_4	1.5	-	7.0
Y_6	1.5	1.8	7.8
T	capped	capped	capped
AT	soft	soft	soft
M_0T	0	0	0
M_2T	3.5	1.2	42
M_4T	3.5	1.0	80
M_6T	3.6	1.6	81
S_0T	0	0	0
S_2T	2.0	3.3	24
S4T	2.5	4.4	25
S_6T	2.5	3.3	26
Y_0T	0	0	0
Y_2T	1.0	capped	9.8
Y_4T	2.0	2.0	29.8
Y_6T	2.5	2.0	65

Table 5: Some Properties of Starch and Trimethoprim Tablets Compressed at a Pressure Setting of 8 (Weight = 200 mg)

Batches	Hardness (KgF)	Friability (%)	Disintegrat -ion times (min.)
M_0	0	0	0
M_2	1.2	0	20.0
M_4	2.5	0.8	28
M_6	3.0	0.4	32
S_0	0	0	0
S_2	soft	soft	soft
S_4	1.5	1.6	26
S_6	2.0	1.2	29
Y_0	0	0	
Y_2	1.0	soft	soft
Y_4	1.3	2.4	18
Y_6	1.8	1.9	21
AT	soft	breaks	-
M_0T	0	0	0
M_2T	4.5	0.4	52
M_4T	7.2	0.4	over 90
M_6T	5.0	1.3	Over 90
S_0T	0	0	0
S_2T	2.0	1.6	49
S4T	4.2	1.1	59
S_6T	5.0	1.4	84
Y_0T	0	0	0
Y_2T	1.0	-	13.3
Y_4T	2.5	0.6	50.8
Y_6T	3.0	0.8	73.7

Table 6: Some Properties of Starch and Trimethoprim Tablets Compressed at a Pressure Setting of 6 (Weight = 200 mg)

Batches	Coefficient of Weight Variatin (%)	Tablet Density (gcm^{-3})
M_0	0	0
M_2	1.48	14.0
M_4	1.2	18.0
M_6	1.2	21.0
S_0	0	0
S_2	0	0
S_4	1.4	23.0
S_6	1.2	30.0
Y_0	0	0
Y_2	0	0
Y_4	1.5	27.0
Y_6	1.5	31.0
AT	1.2	28.0
M_0T	0	0
M_2T	1.3	30.0
M_4T	1.3	36.0
M_6T	1.5	36.0
S_0T	0	0
S_2T	1.1	26.0
S4T	1.01	34.0
S_6T	1.5	34.0
Y_0T	0	0
Y_2T	1.8	19.0
Y_4T	1.5	23.0
Y_6T	1.9	28.0

Table 7a: Some Properties of Tablets of Binary Mixtures of Millet Starches and Microcrystalline Cellulose.

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
Avicel	9.0	0.54	0.48	31.4	0.17	1.54
	10.0	1.0	0.54	9.1	0.17	
M_6 (75%) :A (25%)	8.0	0.5	0.91	2.3	2.5	
	8.5	3.5	1.06	0.7	7.5	
	9.0	5	1.13	0.6	15.7	
	5.0	-	-	-	-	1.6
M_6 (50%) :A (50%)	8.0	1.2	0.86	2.0	1.0	
	8.5	3.0	0.95	0.9	2.5	
	9.0	7	1.15	0.6	25	
	7.0	-	-	-	-	1.4
M_6 (25%) :A (75%)	8.0	1.2	0.67	2.8	0.42	
	8.5	2.5	0.80	0.5	0.78	
	9.0	6.5	1.23	0.3	10.0	
	6.5	-	-	-	-	1.3
M_0 (75%) :A (25%)	10.0	capped	capped	-	-	
M_0 (50%) :A (50%)	8.0	0.1	0.65	-	0.08	
	9.0	0.2	0.80	-	0.33	
	10.0	2.5	1.08	1.9	0.33	
M_0 (25%) :A (75%)	8.0	-	-	-	-	
	9.0	0.5	0.65	27.8	0.17	
	10.0	1.5	0.75	5.9	0.17	

Table 7b: Some Properties of Tablets of Binary Mixtures of Sorghum Starches and Microcrystalline Cellulose.

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
S_6 (75%)	8.0	4.5	1.16	0.5	20	
:A (25%)	9.0	5.0	1.17	1.1	25	1.4
S_6 (50%)	8.0	3.0	0.92	0.6	6	
:A (50%)	8.5	6.6	0.88	0.4	11	
	9.0	11	0.51	0.2	18	1.2
S_6 (25%)	8.0	1.0	0.67	4.5	0.2	
:A (75%)	8.5	1.8	0.71	1.4	0.2	
	9.0	3.5	0.83	0.6	1.0	0.9
S_0 (75%)	6.0	-	-	-	-	
:A (25%)	7.0	-	-	-	-	
S_0 (50%)	7.0	0.1	0.9	-	-	
:A (50%)	8.0	1.5	1.11	2.6	0.2	
	9.0	4.5	1.14	0.9	0.2	
S_0 (25%)	8.0	1.0	0.68	23.8	0.1	
:A (75%)	9.0	2.0	0.57	2.2	0.2	
	10.0	4.0	0.98	1.1	0.3	

Table 7c: Some Properties of Tablets of Binary Mixtures of Yam Starches and Microcrystalline Cellulose.

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
Y_6 (75%) :A (25%)	6.0	6.0	1.28	0.7	28	
Y_6 (50%) :A (50%)	8.0	6.0	1.07	0.4	40	
	8.5	6.2	1.24	0.8	32	
	9.0	10.0	1.36	0.3	40	0.5
Y_6 (25%) :A (75%)	9.0	1.2	0.76	0.4	0.5	0.4
	10.0	3.0	0.74	0.9	4.5	
Y_0 (75%) :A (25%)	5.0	1.0	1.18	-	0.2	
Y_0 (50%) :A (50%)	6.0	1.0	0.81	12.9	0.2	
	7.0	2.0	0.94	2.1	16	
	8.0	6.5	1.22	0.37	29	

Table 8a: Some Properties of Tablets of Binary Mixtures of Millet Starch and Starch 1500 (Tablet weight = 200 mg).

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
Starch 1500	3.0	0.5	0.92	14.7	18.0	1.6
	4.0	2.8	0.78	1.9	19.0	
	5.0	5.7	1.18	0.5	26.5	1.63
M_6 (75%) St (25%)	6.0	0.2	0.87	15.3	3.5	1.8
	7.0	3.3	1.08	0.7	12.5	
	7.5	4.6	1.13	0.25	10.5	
M_6 (50%) St (50%)	5.0	0.5	0.84	capped	2.0	
	6.0	3.3	1.11	0.5	7.5	1.74
	7.0	4.3	1.18	0.4	9.0	
M_6 (25%) St (75%)	3.0	0.2	0.79	capped	2.0	
	4.0	1.3	1.04	4.1	7.0	
	5.0	3.2	1.12	0.6	13.0	

Table 8b: Some Properties of Tablets of Binary Mixtures of Sorghum Starch and Starch 1500 (Tablet weight = 200 mg).

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
S_6 (75%) St (25%)	8.0	0.8	0.11	21.7	3.0	
	8.5	2.0	1.10	2.6	38.5	
	9.0	3.8	1.11	0.9	10.5	1.5
S_6 (50%) St (50%)	7.0	0.5	1.06	11.1	2.7	
	7.5	2.0	1.06	2.3	7.5	
	8.0	2.0	1.18	1.7	8.5	1.38
S_6 (25%) St (75%)	5.0	0.4	0.82	capped	1.0	
	5.5	1.0	1.07	6.5	3.0	
	6.0	2.3	1.08	3.8	7.5	1.1

Table 8c: Some Properties of Tablets of Binary Mixtures of Yam Starch and Starch 1500 (Tablet weight = 200 mg).

Batches	Compress-ion Pressure Setting	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegra-tion times (min.)	Coeff. of Weight Variation (%)
Y_6 (75%)	4.0	4.0	1.12	0.7	5.0	
:St (25%)	4.5	5.0	1.25	0.6	8.5	1.0
Y_6 (50%)	3.5	1.8	0.96	2.3	3.5	
:St (50%)	4.0	4.1	1.13	0.8	9.5	
	4.5	5.0	1.16	0.6	10.0	0.8
Y_6 (25%)	3.0	0.4	0.87	27.6	1.5	
:St (75%)	4.0	3.5	1.06	1.4	2.5	
	5.0	4.7	1.22	1.6	9.0	0.6

Table 9a: Some Properties of Tablets of unmodified and modified Starches Prepared by Wet Granulation (Pressure setting = 3.5; Tablet weight = 200 mg).

Batches	Hardness	Tablet density gcm^{-3}	Friability (%)	Disintegration times (min.	Coeff. of Weight Variation (%)	Efflux time (seconds)
*M_6 D	5.2	1.20	0.35	10.7	0.9	30.2
M_0 D	3.0	1.06	0.68	6.3	1.3	38.0
S_6 D	4.8	1.18	0.46	8.6	0.7	20.0
S_0 D	2.8	1.02	0.83	6.0	1.1	26.0
Y_6 D	4.2	1.16	0.54	6.3	0.4	15.0
Y_0 D	2.0	1.00	0.88	5.8	0.9	20.0

* M_6 D = means modified millet starch used as diluent in the formulation.

Table 9b: Some Physical Properties of Trimethoprim Tablets containing unmodified and modified Starches as Diluents Prepared by Wet Granulation (Pressure setting = 4.5; Tablet weight = 200 mg)..

Batches	Hardness	Tablet density gcm^{-3}	Friability (%)	Disinte-gration times (min.)	Coeff. of Weight Variation (%)
*M_6DT	5.0	1.30	0.4	11.3	1.1
M_0DT	3.2	1.12	0.7	6.2	1.5
S_6DT	4.3	1.21	0.5	9.1	0.9
S_0DT	2.6	1.11	0.94	6.0	1.3
Y_6DT	4.3	1.19	0.7	6.5	0.6
Y_0DT	2.0	1.09	0.8	6.0	1.2

* M_6 DT = means hydrolysed millet starch used as diluent in Trimethoprim tablets.

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