THE EFFECTS OF SOME LOCAL STARCHES ON THE PROPERTIES OF GRANULES AND TABLETS

BY

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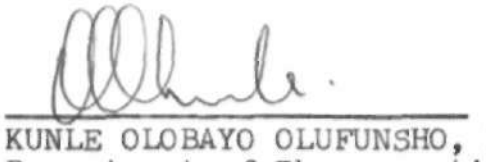
A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU BELLO UNIVERSITY, ZARIA IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICS.

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DECLARATION

I hereby declare that the work reported in this thesis was carried out by me under the supervision of Dr. A. B. Bangudu of the Department of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University Zaria. It has not been presented in any previous application for higher degree. The work of other investigators are acknowledged and referred to accordingly.



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CERTIFICATION

This thesis entitled "THE EFFECTS OF SOME LOCAL STARCHES ON THE PROPERTIES OF GRANULES AND TABLETS" by KUNLE OLOBAYO OLUFUNSHO meets the regulations governing the award of the degree of MASTER OF SCIENCE of Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

This work is dedicated to MUM and DAD for everything. You've been simply great.

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O. O. K.

ABSTRACT

Starches have been extracted from the fresh tubers of yam (Diascorea rotundata) and cassava (Mannihot utilissima) and cocoyam (Colocasia esculenta) rhizome. The starches extracted were subjected to the B.P. (1980) identification tests for starches which they all passed. The starch particle size, swelling power, moisture sorption capacity, moisture content, mucilage viscosity and the effect of temperature on the viscosity of the mucilages were determined. These were also determined for the official maize starch.

The local starches and the official maize starch were used as binders and disintegrants in the preparation of granulations and tablets of sulphadimidine and promethazine. The comparative effects of all the starches on the properties and quality of granulations and tablets were determined. The properties of granulations studied were size distribution, moisture content flowability, bulk/tapped densities of tablets were investigated included hardness, friability, packing fraction, disintegration time and dissolution rates.

Differences were observed in the properties of granules and tablets made with the different starches. These have been explained based on the fundamental properties of the starches used.

6. Flow curves of starch mucilages

   A 5%w/w starch mucilage

   B 7.5%w/w starch mucilage

   C 10%w/w starch mucilage

7. Effect of temperature on viscosity of Starch mucilages

   A 5%w/w starch mucilage

   B 7.5%w/w starch mucilage

   C 10%w/w starch mucilage

8.A Effect of binder type and concentration on the disintegration time of Promethazine tablets

  B Effect of disintegrant type and concentration on the disintegration time of Promethazine tablets

9.A Effect of binder type and concentration on the disintegration time of Sulphadimidine

  B Effect of disintegrant type and concentration on the disintegration time of Sulphadimidine tablets.

LIST OF APPENDICES

1. Amylose-Amylopectin content of Starches
2. Granule size distribution of Promethazine using starch as binder
   - A 5%w/w starch mucilage as binder
   - B 7.5%w/w starch mucilage as binder
   - C 10%w/w " " " "
3. Granule size distribution of Promethazine using starch as disintegrant
   - A 2.5%w/w starch as disintegrant
   - B 5%w/w starch as disintegrant
   - C 10%w/w starch as disintegrant
4. Granule size distribution of Sulphadimidine using starch as binder
   - A 5%w/w starch mucilage as binder
   - B 7.5%w/w starch mucilage as binder
   - C 10%w/w " " " "
5. Granule size distribution of Sulphadimidine using starch as disintegrant
   - A 5%w/w starch as disintegrant
   - B 10%w/w starch as disintegrant
   - C 15%w/w starch as disintegrant

23. Dissolution rate profiles for Promethazine tablets using 10%w/w starch as disintegrant

24. Dissolution rate profiles for Sulphadimidine tablets using 15%w/w starch as disintegrant.

12. Effect of disintegrant concentration on tablet disintegration time (Sulphadimidine and Promethazine)
13. Dissolution rate profiles for Promethazine tablet using 5%w/w starch as binder.
14. Dissolution rate profiles for Sulphadimidine tablet using 5%w/w starch as binder
15. Dissolution rate profiles for Promethazine tablet using 7.5%w/w starch as binder
16. Dissolution rate profiles for Sulphadimidine tablet using 7.5%w/w starch as binder
17. Dissolution rate profiles for Promethazine tablet using 10%w/w starch as binder
18. Dissolution rate profiles for Sulphadimidine tablet using 10%w/w starch as binder
19. Dissolution rate profiles for Promethazine tablet using 2.5%w/w starch as disintegrant
20. Dissolution rate profiles for Sulphadimidine tablet using 5%w/w starch as disintegrant
21. Dissolution rate profiles for Promethazine tablets using 5%w/w starch as disintegrant
22. Dissolution rate profiles for Sulphadimidine tablets using 10%w/w starch as disintegrant

LIST OF FIGURES

1. Beer-Lambert's Curve of Absorbance Vs Concentration for sulphadimidine at max 244nm using UV spectrophotometer
2. Beer-Lambert's Curve of Absorbance Vs Concentration for promethazine at max 249nm using UV spectrophotometer
3. Starch Particle Size Distribution
4. Effect of Concentration On The Viscosity of starch mucilage
5. Granule size distribution of Promethazine using 5%w/w starch mucilage as binder
6. Granule size distribution of Sulphadimidine using 5%w/w starch mucilage as binder
7. Granule size distribution of Promethazine using 2.5%w/w starch as disintegrant
8. Granule size distribution of Sulphadimidine using 5%w/w starch as disintegrant
9. Effect of binder concentration on Promethazine tablet hardness and friability
10. Effect of binder concentration on Sulphadimidine tablet hardness and friability.
11. Effect of binder concentration on tablet disintegration time (Sulphadimidine and Promethazine)

b) Effect of disintegrant type and concentration on the dissolution of Promethazine tablets

14a) Effect of binder type and concentration on the dissolution of Sulphadimidine tablets.

b) Effect of disintegrant type and concentration on the dissolution of Sulphadimidine tablets.

a) 5%w/w disintegrant concentration

b) 5%w/w " "

c) 10%w/w " "

9. Properties of Sulphadimidine tablets using starch mucilage as binder

a) 5%w/w binder concentration

b) 7.5%w/w binder concentration

c) 10%w/w binder concentration

10. Properties of Promethazine tablets using starch mucilage as binder.

a) 5%w/w binder concentration

b) 7.5%w/w binder concentration

c) 10%w/w binder concentration

11. Properties of Sulphadimidine tablets using starch as disintegrant

a) 5%w/w disintegrant concentration

b) 10%w/w disintegrant concentration

c) 15%w/w disintegrant concentration

12. Properties of Promethazine tablets using starch as disintegrant

a) 2.5%w/w disintegrant concentration

b) 5%w/w " "

c) 10%w/w " "

13a) Effect of binder type and concentration on the dissolution of Promethazine tablets

LIST OF TABLES

1. Calculation of specific gravity of starch
2. Calculation of packing fraction of tablets.
3. Results of Investigations of Starches Used in Tablet Formulation

4a) Sulphadimidine Tablet Composition
b) Promethazine HCl Tablet Composition

5. Properties of Sulphadimidine granules using starch mucilage as binder
a) 5%w/w binder concentration
b) 7.5%w/w binder concentration
c) 10%w/w binder concentration

6. Properties of Promethazine granules using starch mucilage as binder
a) 5%w/w binder concentration
b) 7.5%w/w binder concentration
c) 10%w/w binder concentration

7. Properties of Sulphadimidine granules using starch as disintegrant.
a) 5%w/w disintegrant concentration
b) 10%w/w " "
c) 15%w/w " "

8. Properties of Promethazine granules using starch as disintegrant.
a) 2.5%w/w disintegrant concentration

TITLES		PAGE
2.2.1	Investigation of the starches	
2.2.2	Preparation of granules	
2.2.3	Characterisation of granules	
2.2.4	Compression of granules	
2.2.5	Tests on tablet properties	
CHAPTER 3:	RESULTS AND DISCUSSION	
3.1	Tests On Starches	
3.2	Tests on Granules and Tablets	
CHAPTER 4:	SUMMARY AND CONCLUSION	
	REFERENCES	
	APPENDICES	

TABLE OF CONTENTS

TITLES		PAGES
Title Page		i
Declaration		ii
Certification		
Dedication		
Acknowledgement		
Abstract		
Table of Contents		
List of Tables		
List of Figures		
List of Appendices		
List of Symbols		
CHAPTER 1:	INTRODUCTION AND LITERATURE REVIEW	
1.1	General Introduction	
1.2	Tablets and Tabletting	
1.3	Disintegration and Disintegrants	
1.4	Binders	
1.5	Starch	
1.6	Research Into Local Sources of Starch for the Pharmaceutical Industry	
1.7	Statement of Objective	
CHAPTER 2:	MATERIALS AND METHODS	
2.1	Materials	
2.2	Method	

The effects of binder and disintegrant concentration on granules and tablets of sulphadimidine and promethazine were also determined. The results obtained using each of the starches (yam, cassava, cocoyam and maize) were compared. Changing the binder and disintegrant concentrations affected granule and tablet properties. The magnitude and nature of such effects depended on the type and the concentration of starch used. These results have also been explained based on the fundamental properties of the starches.

The relative properties of granules and tablets of promethazine and sulphadimidine made using the different starches varied. The variation depended on the nature of the drug used (soluble or insoluble), the function of the starch (binder or disintegrant) and the quantity of starch used (binder/disintegrant concentration).

SYMBOLS

X	CASSAVA STARCH
Δ	COCOYAM "
O	YAM "
●	MAIZE "
a	Cassava Starch
b	Cocoyam "
c	Yam "
d	Maize "

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 General Introduction

Drug substances are rarely administered in their natural or pure state, but rather as part of a dosage form, where they are present in combination with other non-medicinal agents. The tablet, an oral dosage form containing one or more medicinal substance with suitable tablet excipients is today the most popular dosage form. This is because it offers a means of repeatedly administering an accurate dose of drug, easy to use by the patient, readily amenable to dispensing and less expensive to manufacture than other dosage forms.

To be able to offer these advantages however, tablets must be carefully formulated and manufactured. When this is properly carried out, the following properties are conferred on the tablet - ability to withstand the rigours of the mechanical treatment involved in production, packaging, shipping and dispensing, freedom from defects and contamination and ability to release the medicament in a reproducible and predictable manner.

Various additives are used in the tabletting process to confer these attributes on tablets. These include binders, diluents, lubricants, disintegrants and colorants.

Starch, one of the most widely distributed substances in nature is the most versatile additive used in the manufacture of compressed tablets. It is used mainly as

binder and disintegrant although it can also be used as a diluent and lubricant. All additives have effects on tablets and starch is no exception to this. Such effects may be adverse and so may negatively affect the bioavailability and hence the in vivo activity of the drug.

A good knowledge of the effect of starches as additives in tablets on the properties of tablets is thus imperative especially for new starches that are just being developed for use in the pharmaceutical industry. This is because it not only gives an insight into how they will affect the ability of the tablet to withstand handling but also give an idea as to how they will affect the in vivo absorption characteristics and physiological availability of the drug contained in the tablet.

1.2 Tablets And Tabletting

1.2.1 Introduction:

Tablets are solid dosage forms prepared by compression or moulding and contain medicinal substances with or without suitable diluents, disintegrants, coatings, colorants and other pharmaceutical adjuncts. Compressed tablets are the most frequently employed dosage form throughout most areas of the world. (Gunsel and Kanig, 1976). This is because of several advantages that the compressed tablet has over other oral dosage forms, some of which are precision of dosage, durability of physical characteristics

for extended periods of storage, stability of chemical and physiologic activity of the drugs and convenience of administration. Other advantages are low cost of production since it can easily be mass produced, and the possibility of incorporating two or more incompatible drugs in one dosage form.

Different tablets may vary in shape, size, weight hardness, thickness, disintegration characteristics, and in other aspects, depending upon the intended use of the tablets and their method of manufacture.

1.2.2 Tablet manufacture:

Tablets are prepared primarily by compression. This is done by compressing fine crystals, free flowing powders and granules in a die between punches. Tablet machines used are capable of exerting great pressure in compacting the powdered or granulated tabletting material through the use of various shaped punches and dies. The machines consist essentially of:

(1) hopper for storing the materials for compressing
(2) feed frame for distributing the materials into the the dies
(3) dies for controlling the size and shape of the tablet
(4) punches for compacting the materials within the dies and
(5) cams for guiding the punches.

All other parts of the tablet press are designed to control the functioning of those listed above.

Generally, there are two types of tablet compression machines, the single punch and the multi-station rotary presses. These machines are similar in their principles of operation and only differ in such aspects as output, mode of compression and the mechanical features designed to control the compression process.

For a material to be formed into tablets in the tablet press it must possess certain physical properties. These include:

(a) the ability to flow freely (to give an even fill of the die)

(b) cohesiveness (for formation of strong tablets) and

(c) lubrication (to reduce frictional effects on the die wall).

Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material to be compressed. The process of granulation is usually used to achieve this.

There are two main reasons for granulation;

(1) To convert the powder into a free flowing form suitable for compression.

(2) To aid cohesion of the material, during compression thus forming firm tablets.

To achieve these aims, the granulation should:

(a) Contain particles which approach spherical shape.

This is because spheres minimize interparticulate friction.

(b) Present a range of particle sizes that resembles a normal distribution curve. This implies a small percentage of coarse and fine particles, with the rest in a narrow range in between.

(c) Have a uniform distribution of all the ingredients in the formulation, so that all the tablets produced will be alike.

(d) Possess compressible components that will confer physical strength and form to the tablets. When the dose of the drug is low, the diluents largely govern the physical properties of the granulation and tablet; when the dose is high, the drug will have the greatest influence.

There are basically two different methods of granulation:- wet granulation method and the dry granulation method

Wet granulation:

This is the most widely employed method for the production of compressed tablets. It can be represented as below.

Drug + Diluent $\xrightarrow{\text{Mix}}$ Drug Diluent mix $\xrightarrow{\text{Granulation with binder solution}}$ Wet Mass

$\xrightarrow{\text{Wet Sieving}}$ Wet granules $\xrightarrow{\text{Dry}}$ Dry Granules $\xrightarrow{\text{Dry Sieving}}$ Dry Granules

$\xrightarrow{\text{Mix}}$ Dry granules + Lubricant + Disintegrant $\xrightarrow{\text{Compress}}$ Tablets.

The active ingredients and any diluent and part of the disintegrating agent required in the tablet formulation are

mixed thoroughly. The effectiveness of this mixing stage determines the distribution of the active ingredient and therefore affects dose uniformity among the tablets produced.

The granules are now formed by adding a liquid binder. Mixing continues until uniform dispersion is attained and all the mucilage has been activated. The amount of binder solution added is dependent mainly upon the formulative ingredients and the nature and concentration of the binder material.

The wetted mass is then passed through a screen of the desired mesh size. This results in the breaking up of the wet mass into coarse, granular aggregates. It is usually done by an oscillating granulator which prepares the granulation by extrusion through screens with large perforations. The purpose of this step is to increase the surface area from which moisture can be lost and thus increase the rate of drying of the granulation.

The granulation is then dried in one of several equipments available. A hot air oven with circulating air whose temperature is thermostatically controlled may be used. Newer driers such as the fluidised bed drier may also be used. The drying process removes the solvent that was used in forming the aggregates and reduce the moisture content to an optimum level of concentration within the granules.

After drying, the granules are again sieved by passing them through a screen, the size of which depends on the size of the tablet to be made. This step helps breakdown aggregates that could have been formed during the drying process. The lubricants are now added to the granulation, after any lumps or aggregates in the lubricants have been broken down to increase their covering power. Any disintegrant that is left to be added is added at this stage. This is usually referred to as an exo-disintegrant.

Dry granulation:

In this method, large masses of the mixture are compacted and subsequently crushed and sized into smaller granules. For this method to be used, either the active ingredient or the diluent must have cohesive properties in order for the large masses to be formed.

First, the ingredients are mixed thoroughly, the powder is then compressed into large tablets or slugs. The slugs are then broken up by a mill and passed through a screen of desired size, lubricant is added and the material is ready for compression. Alternatively, compaction mills may be used (instead of a tablet press) to increase the density of a powder by pressing it between high-pressure rollers. The densified material is then broken up, sized and lubricated ready for compression.

1.2.3 Factors That Influence The Choice Of Granulation Method

a) Drug properties: The properties of the active ingredient in the powder mixture to be granulated is important. Its moisture sensitivity and water solubility may preclude the use of the wet method of granulation. Since the drying process requires the use of heat, thermolabile drug material can also not be granulated using this method. In such cases the dry method of granulation will have to be used.

b) Dose of the drug:- If the quantity of active ingredient in a powder mix is very high, then the mixing step is not very important since it would not be too difficult for the drug to be well distributed in the mix. Such a drug can thus be easily granulated using the dry granulation method of either slugging or compaction. Where the reverse is the case i.e. low quantity of drug, the wet granulation method which involve extensive mixing will be best to ensure dose unformity.

c) The type of equipment available also determines the method of granulation to be employed.

1.2.4 Factors That Affect Granulation:

These can be divided into process and product variables. Process variables are those factors which

crop up during the process of granulation and may vary depending on the method of granulation. They include, the speed of agitation, load of mixer, liquid binder addition method, liquid flow rate, binder type and concentration, massing time and amount of liquid.

The product variables are those which are inherent in the components of the powder mix used for granulation. They include particle size distribution of the drug, (the smaller the particle, the easier fluidisation is in a fluidised bed drier), wettability of the particles, solubility of the components, and the type of the powder.

1.2.5 Forces Responsible For Cohesiveness Of Powders

These forces are of various origins. Basically there are two groups - mechanical and natural. The mechanical forces are applied with either the paddle or the tumble mixer. They bring the particles close enough to themselves for the more important natural forces to act.

There are various natural forces in operation between particles. The most important ones are the van der Waals forces, valency and electrostatic forces and mechanical interlocking of the particles.

a) van der Waals forces: These forces result from molecular attraction due to dipole-dipole interaction. Bipolar molecules tend to align themselves with their neighbours, so that the negative pole of one molecule points toward the positive pole of the next, which results in molecular attraction. The distance separating the two particles is very important since these forces usually operate at a maximum range of 100 Å, beyond which their effects are not pronounced. The nature of the particle surface (that is its roughness) also affect the operation of these forces since it determines to a large extent how close the particles can be to each other.

b) Electrostatic forces: These develop as a result of the rubbing together of particles with the associated loss or gain of electrons. Charges, either positive or negative are thus developed on the particles depending on whether electrons have been gained or lost. Since opposite charges will be developed on different particles, there is an attraction between such particles.

c) Mechanical Interlocking: This is most important in the case of fibrous materials that are spongy

in nature with rough surfaces. These surfaces can interlock and give rise to frictional forces.

1.2.6 Forces Responsible For Formation Of Tablets

The binder solution contributes in two important ways in bond formation between particles. These are

i) by the crystallisation of soluble components. Some materials which are soluble in the binder solution crystallise out on drying or evaporation of the wet mix. This results in particles of those materials being cemented together.

ii) by the hardening of the binders on drying. The viscous binder thus forms a solid bridge between the particles.

The presence of a liquid, which in most cases is water can also exert forces that can hold solid particles together. This is due to the formation of liquid bridges. The nature and strength of the forces depend on the amount of water present in the formulation. There are three main states of water when it is added to solid particles, these are

(a) Pendular Stage: The solid particles are held together by lens shaped rings of liquid with air spaces between the particles. A force is thus developed, this (force) can be represented by the

Fischer (1926) equation,

$$F = \frac{2\pi r T}{(1+\tan\theta)} \quad - - - - - - - - - - \quad (1)$$

where F = Pendular force between the particles

r = Radius of the solid particles

T = Liquid surface tension

θ = Contact angle between solid and liquid.

(b) Funicular Stage: This is a transition stage resulting from the addition of more water. The air voids are displaced by the liquid with more bridges being formed.

(c) Capillary Stage: All the air voids have been completely eliminated but the particles are still held together by the liquid. The forces by which the particles are held together are capillary forces. It can be represented by the Rumpf's equation (1958, 1962)

$$c = 6\left(\frac{1-E}{E}\right)\frac{T}{d}\,\text{Cos}\,\theta \quad - - - - - - - - \quad (2)$$

where c = Capillary forces

E = Porosity (void fraction)

T = Surface tension

d = diameter of particles

θ = Solid/Liquid contact angle

The heat produced during compression can cause the melting of asperities and of the binding agents at temperatures below their conventional melting point if the pressure is high enough. On releasing the pressure and cooling, solid bridges are formed (Kurup and Pilpel, 1979).

Solid bridges can also be formed when crystalline substances are heated by friction during compression and then cooled (Murray, 1968). The water of crystallisation liberated during compression partially dissolves some of the solid and finally reforms a crystalline bridge (Kurup and Pilpel, 1979).

1.2.7 Evaluation Of Tablet Quality

Drug manufacturers are aware that tablets must meet some physical specifications in order to guarantee the quality of the tablets. These specifications would include hardness, disintegration time, dissolution rate, friability, weight, thickness and diameter (Gunsel and Kanig, 1976). These specifications must be controlled within the production of a batch of tablets as well as from batch-to-batch in orde to guarantee not only the outward appearance of the product

but also its therapeutic efficacy. While some of these quality tests are official, there are others which are not, and have only been added by various manufacturers to ensure that their tablets are of very high quality.

1) Tablet Hardness:

A tablet should be sufficiently hard to resist breaking during packaging, shipment, and normal handling and yet soft enough to dissolve or disintegrate properly after administered. Numerous instruments have been devised to test the hardness of tablets. These include; a) Monsanto Hardness Tester, which consists of a barrel containing a compressible spring held between two plungers. The lower plunger is brought into contact with the tablet, pressure is then applied to the spring by rotating a screw. This forces the upper plunger against the spring and the force is transmitted to the tablet. The instrument has a calibrated gauge on the barrel with a zero adjustment which expresses the crushing force in Kg. In the industry, a force of about 4kg is considered to be the minimum permitted for a satisfactory tablet (Ansel, 1981).

b) Pfizer Hardness Tester: The tablet is placed in the jaws of a plier-like instrument. The tablet is squeezed manually until it cracks. The force required to crush the tablet is indicated on a dial indicator.

c) Strong-Cobb Hardness Tester: It measures the applied force required to break a tablet across its diameter, The tablet is held between 2 jaws and pressure is applied by means of a hydraulic pump. A dial indicator records the final breaking force.

These instruments are very popular because of their ease of operation and maintenance. But they suffer from some important defects which must be considered when they are being used. These are inconsistencies in the zeroing of the instrument which might vary depending on the operator, the rate and nature of application of force are important determinants of the values given by the instruments. Since this can vary from one operator to another and even when used by the same operator at different times, the results obtained become highly subjective and difficult to correlate . Finally it should be noted that all of these instruments actually measure resistance to crushing and not the tablet hardness per se.

A number of more exact instruments which do not suffer from most of the defects of the instruments discussed above are available. They include the Instron tester and the Transverse tester which measure the tensile strength of tablets. They also take into consideration the dimensions of tablets.

ii) Friability:

A tablet must be sufficiently robust to withstand chipping, capping or breaking. These problems are most frequently as a result of friction and shock, which is why equipments such as the Roche friabilator are used to measure the resistance of tablets to these problems. Usually, 20 tablets are weighed and placed in the drum in which a curved baffle is mounted. The drum is rotated at 25 r.p.m for 4 minutes making the tablets roll and drop. The tablets are then removed, dedusted and weighed. There should not be more than 1% decrease in weight. If the free fall within the drum results in the breakage or excessive abrasion of the tablets, they are considered unsuitable to withstand shipment without being damaged.

The hardness and friability of tablets are measures of their mechanical strength. They thus give an indication of the extent of cohesiveness among the particles in the tablet.

iii) Uniformity of weight:

Testing for the uniformity of weight is an attempt to minimise dose variation in tablets. Since the tablet weight is adjusted to give the quantity of granulation that will contain a unit dose of the medication, any variation in weight will result in dose variation assuming uniform dispersion of the active ingredient in the tablet mix. The standard requires that 20 tablets (10 tablets can be used if

there are not enough tablets) be taken and their average weight determined. The tablets are then weighed individually and deviation in tablet weight must be within official (USP, BP) limits. There are various factors that could affect the die fill and as such result in weight variation among tablets. These are poor flow properties of the material; bridging of the material in the die or particle segregation during flow through the hopper. Since the tablet mix may consist of particles of widely differing sizes, segregation could occur during flow through the hopper. Thus there may be excessive fine material at the start of the run resulting in closer packing and higher tablet weight. At the end of the run, there may be less amount of fines resulting in the presence of a large number of voids within the die, leading to a reduction in tablet weight. Because of this, the tablet weight should be checked at given time intervals during production to avoid excessive weight variation.

iv) Content Uniformity:

This tests for dose variation in tablets that are of the same weight. Such variation arises from a non-homogenous distribution of drug in the tablet granulation. 20 tablets or such other numbers as may be indicated under the appropriate monograph are used for the assay. The tablets are crushed and analysed as may be stated in the individual monographs of the

official books. The limits of deviation in content from the stated amount are also given in the official books.

v) Thickness And Diameter:

They are both measured with micrometer calipers. Tablets of the same product should not vary in size as this will not only affect patient compliance but might also cause problems in packaging. This is because tablets of unequal size tend to block the channels of counting machinery, the container might also prove inadequate in holding the required number of tablets.

The thickness of tablets can vary due to (1) size segregation within the hopper which can lead to weight variation and consequently difference in tablet thickness if the same compression pressure is applied and (2) change in compression pressure. The diameter is controlled by the die and punches and so does not vary much. But the constant compression of tablets in a particular area of a die might result in a widening of that portion of the die with time resulting in the diameter of the tablet on formation being larger than the diameter at the top of the die. This can result in the crumbling of the tablet during ejection.

vi) Tablet Disintegration Test:

Drug dissolution from tablets occurs from the solid tablet, aggregates that are formed when the

tablets begin to break down and the fine particles that result from complete tablet disintegration. The dissolution of the drug from the fine particles is the most important and the rate limiting step in drug dissolution and absorption. The disintegration test is an attempt to evaluate the availability of the drug from the tablet.

The apparatus specified in the official books may differ in details but the principles are similar. Basically, the apparatus consists of a tube(s) closed at the bottom with a number 10 mesh screens. The tube(s) is attached to an arm and is raised and lowered at between 28-32 cycles per minute through a waterbath thermostated at $37^{o}C \pm 2$. At the top of the stroke, the mesh must just break the surface, while at the bottom of the stroke, the top of the tube must remain above the water level. The tablet(s) is placed in the tube and the machine is set in operation. The tablets steadily break up and pass through the mesh. To pass the test all the tablet(s) must pass through the mesh in 15 minutes.

Factors that make it difficult to correlate <u>in vitro</u> results with <u>in vivo</u> performance are:

agitation may be more turbulent than actual stomach conditions, plastic discs which are sometimes used to increase solid-solid contact may introduce errors by forcing materials through the mesh and the fact that the tablet disintegrates may not mean that it will dissolve and be absorbed.

vii) Dissolution Test:

The disintegration test, as a means of predicting drug bioavailability fails because of its inability to distinguish between fast and slowly dissolving particles. The dissolution test thus provides a means of determining the rate at which a drug goes into solution and so its rate and extent of absorption from the tablet formulation.

Both the USP and BP (1980) dissolution test apparatus consists of 4 main parts:

1. A water bath
2. A cylindrical stainless steel basket made of woven wire cloth.
3. A covered vessel with openings for withdrawing and replacing samples, inserting a thermometer and passing through the basket into the medium
4. A variable speed motor.

The temperature is maintained at 37 $\pm$ 0.5°C and the dissolution medium and volume is specified in the individual tablet monographs.

The dissolution medium is poured into the covered vessel and one tablet is placed in the basket. The basket is lowered into the medium and is situated 2cm above the bottom of the vessel and rotated at the rate specified in the monograph. Samples are withdrawn at fixed time intervals and analysed for drug content.

By plotting the percent drug dissolved versus time, the time taken for 50% of the drug to dissolve ($t_{50\%}$) can be determined, $t_{90\%}$ is also usually determined. The dissolution area (area under the curve) can also be measured and compared with the dissolution at any point in time to give the extent of dissolution.

A direct comparison of results obtained in the dissolution tests outlined above with *in vivo* conditions is not very easy (Levy, 1963;) since it is very difficult to design an apparatus that will exactly simulate *in vivo* conditions *in vitro*. Some of the sources of difference are (1) the pH of the medium might not be exactly the same as that of the GIT (gastro intestinal tract), (2) the temperature of the stomach might

actually be higher than the 37°C used for the in vitro test, depending on a lot of physiological and pathological conditions, (3) the intensity of agitation used for the test might be too mild or too vigorous in relation to the actual stomach conditions. Inspite of all these, the dissolution test still serves as a convenient means of testing to ensure that drug is released from tablet and that there is batch-to-batch uniformity of release pattern.

1.3 Disintegration And Disintegrants

A disintegrant is an agent added to compressed tablets for the purpose of causing them to break apart (disintegrate) in the fluids. Its major function is to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the mechanical body of the tablet. An ideal disintegrant is one that can cause the break up of a compressed tablet at the proper time and place within the alimentary tract, so that the active ingredients can be released to achieve maximum absorption at the fastest possible rate or as desired.

The disintegrant is very important in a conventional per oral tablet formulation. This is because the dissolution rate and consequently the rate and extent of

absorption may depend on the rate of disintegration of the tablet. Wagner, (1971) suggested that tablet dissolution is a sequential process of the disintegration of tablets into granules or primary particles and the dissolution of drug from them. Although Wood (1967) states that fast disintegration is not per se an indication of dissolution and biologic activity, it is generally recognised that a good disintegrant is a great asset in tablet dissolution and absorption.

Disintegrants have been classified chemically into starches, clays, celluloses, algins and gums by Feinstein and Bartilucci (1966) while Fakouhi et al (1963) based their own classification on mechanism of action of the disintegrants:

a) agents which react with moisture to constitute a foam,

b) effervescent substances which react with moisture to form a gas.

c) substances which react with moisture and swell.

The starches among which are corn, potato, wheat, rice, sago, cassava and cocoyam starch are undoubtedly the most popular class of disintegrants. Some of these starches, like corn starch and potato starch have been used for decades as disintegrants in the manufacture of

compressed tablets and today they are still the disintegrants of choice in most parts of the world. Many authorities consider starch as the best tablet disintegrating agent available and frequently use corn starch and potato starch as standards for evaluation of other disintegrants or in the evaluation of agents which might serve as disintegrants (Mital and Ocran, 1968; Khan and Rhodes, 1972, Nasipuri, 1979).

Some derivatives of starch are also used as disintegrating agents with some of them having better disintegrant properties than starch itself. One of these is sodium carboxymethyl starch which is able to swell 200 to 300 times in water without its granules rupturing. Unlike starch it is not hygroscopic and disintegration time is unaffected by ageing when it is used in compressed tablets.

Gums; both natural and synthetic are also used as disintegrating agents. They are used because of their ability to swell in water. Because of their tendency to become adhesive when wetted, they are capable of becoming <u>in situ</u> binding agents rather than disintegrants and so they are not commonly used. Examples of gums are locust bean gum, karaya gum, guar gum, tragacanth and agar. Methyl cellulose, sodium

carboxymethyl cellulose, alginates, polymers, cation exchange resins and synthetics like cross linked polyvinylpyrrolidone are all used as disintegrants although infrequently.

1.3.1 Incorporation of Disintegrants In The Tablet Formulation

Although there is complete agreement as to the usefulness of disintegrants in the formulation of compressed tablets, the mode of incorporation of the disintegrant in the tablet varies. Opinion is divided regarding the best method of addition, the main point of divided opinion is with regards to whether the disintegrating agent should be utilised intra- or extragranularly (i.e. whether it should be added before granulation or after granulation just before compression).

Some workers (Rubinstein and Bodey, 1976) add the total amount of disintegrating agent to granulation before compression arguing that the agent must be as dry as possible for efficient activity and that this state can be best controlled at this point in processing.

Others, add the disintegrant to the active ingredient and diluent during the preparation of the granules. This is based on the assumption that much finer particles are obtained during disintegration than

when the disintegrant is incorporated extranularly (Shotton and Leonard, 1972).

The method most commonly employed is to add part of the disintegrant to the powder formula prior to granulation, while the other part is added with the lubricant prior to compression. In a study of deaggregation of compressed tablets Rubinstein and Body (1976) using tablets of dibasic calcium phosphate containing varying proportions of intra- and extragranular maize starch found that the optimum starch combination that produced the maximum surface area in a tablet formulation was either 2.5% intragranular to 12.5% extragranular or 15% intragranular starch.

The proportion of disintegrant incorporated into a tablet formulation depends on the particular formulation although a range of 5-20% of the total granule weight is recommended. The specific disintegrant to be used also affects the quantity. In general, the higher the percentage of the disintegrant in the tablet formulation, the shorter is the disintegration time, but Commons et al (1968) investigating the influence of starch concentration on the disintegration time of tolbutamide found that

there appears to be a critical starch concentration for different granulation sizes above which disintegration time increases with further increase in proportion of disintegrant.

1.3.2 Mechanism Of Action Of Disintegrating Agents

The means by which disintegrants cause the rupture of tablets has been the source of much controversy among research workers.

In a review of the proposed theories explaining the mechanism of action of tablet disintegrants Billups and Cooper (1964) found that the most widely held opinion is that tablet disintegration is by absorption of water by the disintegrating agent and development of pressure within the tablet by swelling or expansion of the disintegrating agent. In their study, they concluded that while water absorption is a common qualitative characteristic of many disintegrating agents, it is not a qualitative measure of their effectiveness. Disintegrating agents with the highest rates of water absorption did not produce the fastest disintegration times. Some evidence supported the view that disintegrating agents with the highest rates of water absorption produced the longest disintegration times. Their results also showed that the amount of water

absorbed by corn starch, dried to a constant weight, after exposure to 98% relative humidity was only 0.5% in 50 minutes.

The following are some of the theories that have been put forward to explain the mechanism of action of disintegrants:

1) Swelling - Rupture Theory:

This theory states that a disintegrant, for example starch, when added to dry granules before compression, will absorb gastric fluid causing it to swell and mechanically disrupt the tablet. This is based on the observation by some investigators and generally accepted view that most disintegrating agents swell when exposed to water (King, 1976). Crisafi and Becker (1958) have demonstrated that starch will absorb about 20% of its weight of water when exposed to 95% relative humidity at 27°C. Patel and Hopponen (1966) found that corn starch dried for 2 hours at 110°C when suspended in water at 23°C, increased in volume by 78% within 5 seconds and also that in aspirin tablets where contact of starch grains is continuous in the interparticle spaces, disintegration, is rapid and effective, whereas where contact is not

continuous, disintegration is slowed and appears to depend on the degree of contact between starch grains and aspirin particles and on the size of interparticle spaces. These observations led to the conclusion that the primary mechanism of disintegration by starch in aspirin tablets is by a swelling action. Lowenthal and Wood (1973) postulated that the hydration of the hydroxy group and sorption of water could account for the slight swelling of 5-10% of starch obtained by Ingram and Lowenthal (1966) and went further to say that this volume of swelling could result in about 70% increase in volume and the swelling would take a few seconds. These two combined effects of the attachment of water molecules and the increase in volume of the starch grains cause sufficient force to break up the tablet.

Workers who held opposite views to the rupture theory have pointed out the observations that the extent of swelling of starch suspended in water is not enough to cause tablet disintegration and that while many substances swell to a greater degree than starch, these substances are poor disintegrants. Other materials do not swell but have good disintegrating properties, e.g. amylose (Manudhane et al, 1966).

Curlin (1955) testing the disintegration of aspirin tablets in cold water found by microscopic examination that the starch grains were not swollen after disintegration while Ingram and Lowenthal (1966) found that the swelling of the starch grains observed (5-10% increase in mean grain size) did not seem to be large enough to cause tablets to rupture, hence their conclusion that it did not seem possible that untreated starch will swell sufficiently at 37°C to cause tablet disintegration.

In tablets containing disintegrants which are adhesive in the hydrated state for example sodium carboxymethyl cellulose, the positive forces of penetration of water and swelling of particle must overcome the opposing forces of adhesion within the particles to produce tablet disintegration. When the opposing forces are equal to or greater than the positive forces the result is a longer disintegration time. Khan and Rhodes (1972) also found out that for disintegrants which are adhesive when in contact with water, the disintegration time of tablets containing these disintegrants decrease steadily with increasing concentration of disintegrants.

ii) 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 net work within the tablet and the higher the concentration of starch, the greater the number of capillaries formed. The capillaries are thought to promote the rapid absorption of water into the tablet and the subsequent break up of the tablet.

Commons et al (1968) using corn starch soaked in a saturated aqueous iodine solution and dried, found that the grains form continuous chains along the channel between the granules even at concentrations below those required to make the tablet disintegrate. It appears however that as the percentage of starch is increased, thicker chains of starch are formed in the pore channels thus enlarging them which will allow water to enter the tablet more readily and thus cause disintegration of the tablet more readily. Kerr (1950) states that starch in the natural state is insoluble in cold water but appears to absorb 25 to 30% water and does not swell appreciably. Crissafi and Becker (1958) have also

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.

The results of works quoted above makes Curlin's (1955) suggestion that the disintegrating effect of disintegrants is due to capillary action rather than swelling tenable.

This theory is not without criticism. Patel and Hopponen (1966) from results of their investigations concluded that capillary per se does not appear to 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 and this is substantiated by the results of work carried out but Ingram and Lowenthal (1966). Lowenthal and Wood (1973) using a scanning electron microscope to study the location and structure of starch grains in aspirin tablets reported that they did not find any channels or pores lined with starch grains in any of the surfaces examined which led them to propose that the thesis that starch grains act as a "wicking agent" and draw water into the tablet should be discarded. They were only able to observe occasional chains of starch grains which

were only one grain thick and of finite length and since they were few and isolated they could not have a significant effect on tablet disintegration.

The conclusion reached by Lowenthal and Burruss (1971) from the results of their study of the effect of disintegrants on mean pore diameter and porosity is that large mean pore diameter or porosity did not always give rapid disintegration time nor did small mean pore diameter or porosity imply poor disintegration. This also rules out the possibility that capillary is the only mechanism by which disintegrants act.

iii) Evolution of Gas

Effervescent tablets are based on their ability to evolve gas. The gas produced is carbon dioxide which is the product of the reaction 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 within the tablet until the pressure is high enough to cause the break-up of the tablet with either the dissolution or release of the carbon dioxide from the reaction medium.

1.3.3 Conclusion

The mechanism of action of disintegrating agents is complex and may be mediated through several unrelated phenomena, although it seems that in most cases, the principal mechanism of disintegration especially in starch is pressure exerted by increased volume in the presence of water with capillary possibly facilitating the rate of penetration of water.

The conditions required for rapid disintegration are sufficient starch agglomerates, low pressure, and presence of water (Lowenthal and Wood, 1973).

1.4 Binders

Binders are substances added to tablet formulations to impart cohesiveness and structural strength to the powdered material so that the tablets made from them can withstand handling processes.

A substance used as a binder when added in the right amount should impart just the degree of cohesiveness that will require minimum compression pressure to compact the granules to tablets.

There are various binders in use depending on the method of granulation to be used or whether manufacture is to be by direct compression or not. Those used in wet

granulation include acacia which is used in solutions with concentration ranging from 10 to 20% or even higher depending on how much water the mixed powders can tolerate. Gelatin must be used when warm since it hardens on cooling. Its dissolution is enhanced if it is first suspended in cold water and then heated in a water-bath. Starch is most useful when the drug is insoluble and in high concentrations. It is usually used in an amount equal to 2% of the formula, it is used as a paste prepared by suspending it in one to one and a half parts of cold water with the addition of four times as much boiling water. Other binders are methyl cellulose, sucrose, sodium carboxy methyl cellulose and polymers such as polyvinylpyrollidone (PVP).

These binders can also be added dry, blended with the diluents and drug and then activated by the addition of water or other solvents; although it is now known that the same binder added as a solution or mucilage is more effective than when added dry to the formulation before activation.

Dry binders are used in direct compression of tablets. Direct compression is a method of tablet

manufacture that does not involve the laborious and time-consuming step of granulation, its main objective is to produce pharmaceutically elegant tablets with the minimum cost and processing time; which usually involves the addition of various additives to impart suitable compression properties since most drugs cannot be easily compressed directly. Some of the agents added are dry binders which serve the same purpose as binders in the more common methods of tablet manufacture. Binders most commonly used for this purpose are microcrystalline cellulose, amylose and polyethyleneglycol (PEG).

The concentrations of liquid binders used varies depending on the nature of the binder and the powdered materials to be granulated. In turn, the concentration of the binder along with its nature and mode of incorporation influences the compression characteristics of the tablets to be prepared from the granules. It is therefore important to know the effects of these factors on tablet properties and take steps to eliminate those of them that are adverse.

The presence of binders in granules used for tablet manufacture has some effects on the properties of the tablets. Its most noticeable effect is on the

hardness and friability of the tablets which consequently affects the disintegration and dissolution rates of tablets. Jacob and Plein (1968) investigating the effect of increase in binder concentration on tablet properties found that it resulted in decreased dissolution rate of phenobarbital tablets. Shubair and Dingwall (1977) using three different drugs, showed that in vitro release levels of the drugs were affected by the amount of binder (starch mucilage). Other workers also reported that variation in starch mucilage concentration produced granules of different geometric surface area which will eventually affect dissolution rate since surface area is an important factor in the determination of dissolution rate. (Steiner et al, 1974).

Stanley-Wood and Shubair (1979) evaluating the effect of binder concentration on the compressibility, friability, granule size and size distribution together with the variation of surface area of granules produced by wet mixing granulation found that increasing the concentration of the mucilages up to 10%w/w resulted in variation in granule size distribution while at concentrations of 15 and 20%w/w mucilage there was a decrease in mean

granule size from the optimum size obtained at 10% w/w. They also found that at higher mucilage concentrations, the more viscous mucilages produced pasty masses which were not easily screened, which they explained as being due to a decrease in bond formations that also resulted in the production of a large amount of fines.

Sakr et al (1972) reported that as the concentration of binder (gelatin) increased in lactose tablet formulations, the friability of the tablets decreased while the disintegration and dissolution rates decreased.

The retardation effect on disintegration and dissolution rates are not the only effects of using excessive binder in tablet formulation. In a few extreme examples, excessive binder can result in tablet capping. Premature wear-out of tablet punches and dies is also another possible result of regular compression of formulations with excessive binder.

Inadequate addition of binders can result in the production of excessively soft tablets which will be unable to withstand handling effectively.

All these indicate that selection of binder and its concentration are important factors which should be properly controlled so that the medicament will be completely released for quick physiological availability.

1.5 Starch

Starch in its pure form is a white, amorphous, relatively tasteless solid which posesses no odour and is insoluble in cold water and in ordinary organic solvents such as alcohol, ether and acetone. Starches are markedly hygroscopic and will absorb water when equilibrated under normal atmospheric conditions until the amount present is 10-17% (Leach, 1965).

Under the microscope, starch is seen to consist of tiny, colorless, highly refractive particles, the size and shape of which are specific for each variety of starch. Under polarized light, most intact starch particles exhibit a dark cross whose centre is the hilum, this being the organic nucleus around which the granule has been formed, it may be placed centrally or nearer one end than the other. The starch particle also has striations (concentric rings) which are fine lines surrounding the hilum that result from the highly stratified structure of the majority of starch particles. The hilum often becomes replaced by a hollow fissure in commercial starches because of the removal of the crystalloid part of the amylose during the washing to which starches are subjected during preparation (Leach, 1965).

1.5.1 Structure

Reviews on starch chemistry (Greenwood, 1956; Goudah and Guth, 1965) show that it has now been established that starch is a polymolecular system. It is known to

consist of chains of ∝-D-glucopyranose units joined in the main by ∝-D(1-4)glucosidic bonds.

By fractionation into its simpler components (first carried out quantitatively by Schoch, 1945), it was found that starch is composed of two components which are chemically distinguishable - amylose and amylopectin with the common starches usually containing 20-25% amylose and 75-80% amylopectin while the waxy starches such as waxy maize starch, waxy rice and waxy sorghum starches consist of almost pure amylopectin with a very small fraction of amylose (less than 1%).

Amylose is a linear polymer composed of ∝-D-glucopyranose residues linked by ∝-D-(1-4) glucosidic bonds. Early methylation experiments indicated the presence of 0.2-0.4% of non-reducing end group in amylose which corresponds to a length of about 200-350 D-glucose residues. The result of this work also showed that the osmotically determined molecular weight of maize and potato amyloses agreed with a chain length of 200-350 D-glucose residues. They were thus the first to suggest that amylose is a linear molecule. Bear (1942) by studying the X-ray diagrams of amylose was able to determine the arrangement of the glucose units. He found that the glucose units were not arranged in a straight chain but rather were coiled in a spiral form with the length of each spiral being six D-glucose units.

Amylopectin, which is the major component of starch consists of high molecular weight multibranched polysaccharide composed of ∝-D-glucopyranose residues linked by ∝-D-(1-4) glucosidic bonds. The chains normally contain 20-25 D-glucose residues and are interlinked to form a ramified bush-like structure by means of ∝-D-(1-6)-glucosidic linkages.

Evidence regarding the manner in which the glucose units are combined in the two starch components have been obtained from methylation studies, such as the Haworth technique of methylation (Haworth and Machemer, 1932). This consists of treating the starch with dimethyl sulphate or methyl iodide in alkaline conditions. Until each free hydroxyl group in the starch molecule is converted into a methyl ester. The methylated starch chains are then split by hydrolysis with acid into methylated sugars, which are identified and estimated quantitatively. The positions occupied by the methyl groups in the fragments correspond with those of the unsubstituted hydroxyl groups in the original starch. The main product from both the amylose and amylopectin fractions is 2:3:6-tri-o-methyl-∝-D-glucopyranose which confirms the constitution as beinglong chains linked in the 1-4 position. Information on the extent of branching in the molecule can be obtained by determining the molecular weight of the polysaccharide and thus calculating the number of non-reducing ends per molecule.

The periodate oxidation method of Greenwood, (1956) is also another source of evidence regarding the manner in which glucose units are combined. It is based on the determination of the ratio of terminal to non-terminal D-glucose units in amylose or amylopectin by determining quantitatively the amount of formic acid produced on addition of periodic acid. One molecule of formic acid is produced from each non-reducing end unit and two molecules from each reducing end unit of a starch molecule, one molecule of formaldehyde is also produced from each reducing end unit.

These methods in conjunction with molecular weight determinations have enabled both the configuration and the degree of branching to be known.

The starch granule is composed of linear and branched starch molecules associated by hydrogen bonding either directly or through water hydrate bridges to form radially oriented crystalline areas of various degrees of order. An inter-connected three dimensional micellar lattice is formed by the participation of segments of individual molecules in several micellar areas (Leach, 1965).

1.5.2 Occurrence

Starch is one of the most widely distributed substances in nature, occurring in most plants and in most cases in abundant quantities. It is formed in the leaves

and other green plant parts from water, and carbon dioxide in the presence of light and chlorophyl. It is always extracted from those members of plants which contain reserve food stores, for example fruits, bulbs and tubers, because these are the only parts in which starch accumulates in sufficient quantity to make its extraction commercially viable.

Different plants use different structures for starch storage, thus in the preparation of starches for commercial purposes, many different plant parts are used as raw material. For example, potato starch from the tubers of Solanum tuberosum, cassava starch from the enlarged tubers of Manihot utilissima, wheat, maize and rice starches from cereals and sago starch from stems of the palms Merroxylon sagus and M. rumphii. The method used to separate the starch from the proteins and fibres which might also be present in the plant part depends on the structure and composition of the plant part.

The quantity of starch available in a given raw material differs from plant to plant, and even the same plant of different varieties contain different amounts of starch. Examples of quantity of starch present in some sources are, corn grains (71.5%), rice grains (90.2%), potato tubers (12.5%), cassava tubers (31%), arrowroot (25%) and sago (40%). These are average values.

The nature of the starch obtained also depends on the source of the starch and differs from plant to plant.

For example, starch derived from maize differs in particle size, shape, gelatinization temperature, amylose-amylopectin content, total lipid content, paste clarity and texture, taste and odour from wheat starch. Badenhuizen (1965) subdivided starch broadly into two groups according to their origin, either in organs that retain a high water content, or under conditions in which less water is available as in cases in which water content decreases during ripening. The first group includes starches that are deposited in tubers, bulbs, rhizomes, and unripe fruits. These have a B- or c- X-ray spectrum. In the second group are the cereal starches such as wheat starch and rice starch with an A-type X-ray spectrum. The importance of these differences depends on what the starch is to be used for. For example, the paste clarity, taste and odour of a given starch is very important if the starch is to be used in the food industry while it is unimportant if it is to be used as a disintegrant in the pharmaceutical industry.

1.5.3 Extraction

The method of extraction of starch from the raw material, (that is the plant part in which it is present) depends on the nature of such raw material. For example, the method used for the extraction of potato starch from the tubers of Solanum tubersosum differs from that used for the extraction of maize starch from the grains of zea mays, while it is similar to that used for cassava

starch extraction from the enlarged tubers of Manihot utilissima, since the raw materials are both underground storage organs.

There are some steps however which are the same in principle for different raw materials. These are cleaning of the material, a variety of procedures to release the starch from the cell and separating it from the other constituents of the plant part, and then finally drying the starch and reducing it to the desired size.

1.5.4 Uses Of Starch

Starch and products derived from it are very widely used in various facets of life. It is used in the pharmaceutical, food, paper and textile industries. The nature and properties of the starch used in these industries depend on the specific use for which the starch is required.

In the food industry, it is used as a thickner, filler, binder, stabiliser and as a source of high calorie. In the paper industry it is used to increase the strength of finished paper, improve appearance and erasibility and enhance surface characteristics. In the textile industry, it is used as a size to strengthen warp yarns, in finishing, in printing and as a component in finishes to glaze and polish sewing thread. Starch is also used as an adhesive.

Starch In The Pharmaceutical Industry:

Starch has a long history of usefulness in medicine and pharmacy. Starch has been found to be quite effective in drying-up dermatitis lesions, where there is a watery exudate as a result of which it is found as a component in such pharmaceuticals as dusting powders, pastes, ointments, and emulsions, apart from its action as a bulking agent in some of these preparations.

Starch finds its greatest and most important use in pharmacy in the manufacture of compressed tablets, a very important pharmaceutical dosage form. It is used as a binder, diluent, disintegrant and as a directly compressible vehicle.

a) as a diluent or bulking agent where it is used as a filler when the drug is required to be taken in very small doses. It is used for this purpose because it is bland, odourless and digestible.

b) as a binder, where it is used as a mucilage to 'glue' powders together to form granules and add to the cohesive strength already available in the bulking agent. Starch is used here because of its ability to form pastes.

c) as a disintegrant, to cause the tablet to break up. It is added dry for this purpose.

1.5.5 Properties Of Starch That Make It Useful In The Pharmaceutical Industry

The most important property of starch is its ability to swell in the presence of fluids and to produce a viscous paste when heated in water. The extent of changes induced by heating depends on the temperature and time involved (Greenwood, 1967) and is also greatly influenced by the starch species (Gunsel and Kanig, 1976).

The swelling of the starch particle is due to the penetration of water and subsequent hydration of the starch viscosity of the starch-water mixture is high because of the crowding effect of the swollen balloon-like particles.

The structure and nature of the starch particle makes this behaviour possible. The starch particle is composed of linear and branched starch molecules associated by hydrogen bonding either directly or through water bridges to form radially oriented micelles or crystalline areas of various degrees of order. An inter-connected 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 dependent on

the degree of association and the molecular arrangement) controls the behaviour of starch in water. (Leach, 1965). Subjecting the aqueous suspension of starch to the influence of heat weakens the micellar network within the particle by disrupting the hydrogen bonds, which permits further hydration and irreversible starch particle swelling (gelatinization). This process, according to Chabot et al, (1976) includes the loss of birefringence, leaching of amylose into solution and tangential swelling of the starch particle resulting in the formation of a small bladder. Initially some amylose is retained in the interior cavity, but rupture, collapse and dissolution of the swollen granule occur during prolonged heating.

As the starch particle swells, starch molecules that have been fully hydrated separate from the micellar network and diffuse into the medium. Evidence has been provided by Schoch (1945) to prove that in a dilute starch paste, an equilibrium is established so that the concentration of soluble starch in the water inside the swollen particle is the same as that in the surrounding aqeuous phase. The highly swollen particles

and their fragments adhere to each other and in effect form a matrix held together by associative bonding, thus it can be seen that the apparent viscosity of a starch paste is caused by the properties of individual swollen entities, presence of starch solubles, and the interaction or cohesiveness between swollen particles.

Hofstee (1953) by investigating the initial increase in viscosity of starch treated with heat and moisture or starch in 30% aqeuous glycerol suspension found that the extent of increase in viscosity during gelatinization is related to the water-absorbing powder of the starch particles. This relationship between moisture content and viscosity was also reported by Goering and DeHAAS (1972). They found that tuber starches had low pasting temperatures because they are formed under conditions of high moisture content and that pasting temperatures increase with increasing amylose content due to hydrogen bonding.

The individual starch particles in any given starch do not begin to swell at the same time but rather

over a temperature range of about 10°C. This is thought to be because gelatinization begins from portions of the granule where the bonding is weakest since the degree of bonding differs in individual particles of each starch species.

The addition of certain chemicals markedly alters the properties of starches. Properties affected include, gelatinization temperature range of starch paste, either enhancing gelatinization by accelerating the disruption of hydrogen bonds or inhibiting gelatinization by acting as desolvating agents. Chabot et al (1976) found that chemical modifications of corn, waxy maize and sorghum starches affect starch properties such as pasting temperature, starch particle swelling and the paste properties. This alteration of starch properties by addition of chemicals is important in the formulation of pharmaceuticals and should be taken into consideration in formulation studies since most drugs and adjuncts used in tablet formulation for example can have similar effects on starch. This is confirmed by the results of investigations carried out by Mansour and Guth (1968)

to determine the complexing property of some drugs with starch. They found that all the starches tested formed complexes with the drugs used. Amylopectin was found to be the main complexing component of starch. Chemicals such as sodium sulphate repress starch particle gelatinization while acids and hypochlorite reduce starch paste viscosity. On the other hand sodium nitrate lowers gelatinization temperature as does esters and ethers which increase particle swelling in addition.

On cooling, starch paste also has properties of interest. Starch pastes are physically unstable and thus tend to become less soluble on standing, a phenomenon which is referred to as retrogradation. Retrogradation is mainly due to the amylose fraction since amylopectin solutions in water are known to be relatively stable. Amylose, because of its long molecular chains and the numerous hydroxyl groups present in it has a great tendency for bonding between chains, thus producing bundles of amylose molecules and hence rigid gels and insoluble precipitates. The rate of retrogadation in a given starch paste depends on the amylose percentage in the starch, the method of preparation of the paste and the size of the amylose molecule. (Whistler and Johnson, 1948; Lansky et al, 1949). Goering et al (1975) also found that the pasting peak of starch paste was due to the breakdown of an amylose-fatty acid complex.

The paste forming property of starch is most important in the use of starch as a binder to form granules in the manufacture of compressed tablets.

The compressibility of starch is another property that is useful in the pharmaceutical industry. Most starches are poorly compressible alone and it is possible that poor adhesion between these agents and other tablet components is an asset in disintegration efficiency since "wicking" activity is enhanced (Gunsel and Kanig, 1976). Poor compressibility also increases the porosity of tablets. (Commons et al, 1968). All these properties (poor adhesion and increase in tablet porosity) are useful in the use of starch as a tablet disintegrant although the mechanism by which it does this is still unclear.

Starch is suitable for use as a diluent in pharmaceutical dosage forms because it is bland odourless and capable of digestion. It is used in tablets when the amount of medicament is too small to be compressed into tablets easily.

1.6 Research Into Local Sources Of Starch For The Pharmaceutical Industry

Recently, a lot of effort has been directed to the development of locally available raw materials for use in the pharmaceutical industry. This is in an attempt to rectify the negative trend whereby over 80% of drugs used in the country are imported as finished products and almost all the raw materials used for the local

production of the remaining 20% are imported (Olaniyi, 1985). Starch is one of these raw materials which are imported. The starches used commonly in the manufacture of tablets are maize starch obtained from Zea mays and Potato starch from Solanum tuberosum. Others that are also used are wheat starch from the grains of Triticum aestricum and rice starch from the grains of Oryza sativa. These starches are called the official starches since they are listed in the BP, USP and other pharmacopoeias.

The fact that it is not very easy to grow most of these plant sources of starch in Nigeria especially because of the climate, their importation will continue for as long as it continues to depend on them. This will be unjustifiable, since there are various plant sources of starch that are available abundantly in the country.

Cassava (Mannihot utilissima) tubers for example contain up to 81% of carbohydrates most of which is starch (Ketiku and Oyenuga 1972). The plant is locust resistant and does not require a particularly fertile soil, so it is planted under all manner of conditions and requires little attention during growth period (Childs). For these reasons, the growing of cassava should be cheap. This is further made easier in Nigeria

by the fact that large areas of the country have climate and rainfall conditions ideal for its cultivation ensuring very good harvest (Ugwu, 1978). This is why as far back as 1960, Nigeria had a production figure of 9-10 million tonnes of cassava (Ekandem, 1962). The tubers of Yam (Diascorea spp) also contain a high percentage of starch. Ketiku and Oyenuga, (1973) found that up to 78% of the total carbohydrate content of the tubers was starch. The production of yam is even higher than that of cassava. Ekandem, (1962) stated that production exceeded 13 million tonnes. There are various varieties of yam grown in Nigeria - Diascorea rotundata, D. cayenensis and D. alata - some of which are not popularly eaten which makes them ideal for use as sources of starch for the pharmaceutical industry. The Diascorea species are known to tolerate many soil and climatic conditions and most of them are even drought tolerant (Martin and Gaskins). This is why they are grown in virtually all parts of the country.

The rhizome of cocoyam, Colocasia esculenta is also another possible source of pharmaceutical starch. Cocoyam is very widely distributed in the country and is very easy to cultivate since it does not require much care during growth. In some cases it even grows in uncultivated areas. Because the climatic conditions of

most parts of the country are suited to the growth of this plant, Nigeria produces about 40% of the total world production of cocoyam (Onwueme, 1978). Cocoyam has a major advantage over cassava and yam tubers as sources of pharmaceutical starch, in that it is not as widely eaten as the others.

1.6.1 Survey Of Work Done On Local Starches:

One of the earliest reported work on the use of locally available starches as pharmaceutical raw materials was by Mital and Ocran (1968). They extracted starches from yam and cassava tubers and analysed them; the starches were found to conform with B.P standards for starch. The disintegration properties of the starches were then studied by incorporating them in tablet formulations using lactose, sodium hydrogen carbonate and calcium carbonate as organic and soluble and insoluble inorganic substances. They found that cassava and yam starches showed promising results with regard to the percentage of 'fines' and the moisture content of granules as compared to the potato starch. The disintegration time of tablets prepared with cassava and yam starches was somewhat lower than that

of the reference disintegrant while the friability and hardness of the tablets proved that cassava and yam starches were as good as the potato starch.

Nasipuri (1975) reported that cassava starch was as good as potato starch when used as binder and disintegrant in the formulation of tablets. In an unpublished work, Billi (1975) found that cassava starch could be effectively used as a disintegrant and binder in the preparation of chloroquine phosphate tablets.

Nasipuri (1979a) investigated the use of cocoyam starch as tablet binder and disintegrant using sulphadimidine and chlorpheniramine maleate. His results showed that cocoyam starch is as good a binder as potato starch or acacia at the concentrations used. It was also found that cocoyam starch could be said to be a better binding agent than acacia in terms of disintegration properties of tablets on ageing, while cocoyam starch had virtually the same dissolution rate characteristics as potato starch when used as binder/disintegrant. It was thus concluded that cocoyam starch may be used as a binder as well as a disintegrant for the formulation of tablets containing both soluble and insoluble drugs. It was also found to

be as good as potato starch with respect to its binding and disintegrating properties and slightly better than acacia with respect to its binding property particularly after ageing.

Nasipuri (1979b) evaluated the use of yam starch obtained from the tubers of Diascorea rotundata as tablet binder and disintegrant using sulphadimidine and Promethazine Hydrochloride. From the results obtained, it was concluded that yam starch can be used as a binder as well as a disintegrant for the formulation of tablets containing both soluble and insoluble organic drugs. It was found to be as good as potato starch with respect to its binding and disintegrating properties and slightly better than gum acacia as binder for its ability to give a higher dissolution rate.

Yam and cassava starches have also been investigated as diluents by Jaiyeoba and Opakunle (1978a). They found that these starches were suitable for this purpose. They also investigated these starches as glidants and again found them to be suitable (Jaiyeoba and Opakunle, 1978b).

Using plantain starch obtained from Musa paradisiaca, Esezobo and Ambujam (1982) found that plantain starch can be used both as a tablet binder and disintegrant in the

preparation of tablets. They compared the effect of plantain starch on the physical properties of paracetamol and chloroquine tablets with those of tablets prepared with maize starch. They concluded that plantain starch was a better binder since it gave harder, glossier and less friable tablets than maize starch but that it was a poorer disintegrant.

Recently, (Deshpande and Panya, 1987) sorghum starch has also been investigated as tablet binder and disintegrant. The starch was found to be suitable for such use both in the formulation of tablets of organic and inorganic medicinal agents.

1.7 Statement Of Objective

Starch is widely used as a binder and disintegrant in the manufacture of tablets. Various workers have shown that the type and concentration of binder and disintegrant affect the properties of granules and their tablets (Levy, 1963; Underwood and Cadwallader, 1972), Pilpel et al,(1978), Esezobo, 1986; Odusote and Nasipuri, 1987.

Starches are obtained from different sources. Some non-official starches found in abundant quantities in Nigeria have been tested and found to be useful as tablet binders and disintegrants. These include yam

starch (Mital and Ocran, 1968; Nasipuri, 1979a). Cassava starch (Nasipuri, 1975), cocoyam starch (Nasipuri, 1979b) and sorghum starch (Deshpande and Panya, 1987). These efforts have only established the possibility of using these starches in the pharmaceutical industry. It is however still necessary to investigate the effects of these starches on the properties of granules and their tablets and also see their advantages and disadvantages relative to each other. The objectives of this work therefore are:

i) To investigate the effects of some local starches (cocoyam, cassava, and yam) on the properties of granules and their tablets.

ii) To compare the effects of these starches on granule and tablet properties to those of official maize starch.

iii) To explain the differences, if any, in the nature and extent of effects of the different starches on the granule and tablet properties by investigating some fundamental properties of starch.

A soluble organic drug, promethazine Hcl and an insoluble organic drug, sulphadimidine were used in the formulation of tablets. These drugs are also representative of low and high dose drugs respectively.

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials

1. Sulphadimidine Powder (ICI)

It occurs as white or creamy-white crystals or powder and is either odourless or almost odourless. Sulphadimidine is only very slightly soluble in water and practically insoluble in ether, but is soluble in dilute mineral acids and in aqueous solutions of alkali hydroxides and carbonates.

Like the other Sulphonamides, it is used mainly in the treatment of acute uncomplicated urinary tract infection, although it can also be used in the treatment of other infections by susceptible organisms. The usual dose range is 2 to 6g daily, in divided doses.

2. Promethazine hydrochloride (May and Baker)

It is a white or faintly yellowish, odourless, crystalline powder. It is highly soluble in water (soluble in 0.6 part of water) and is practically insoluble in ether.

It has antihistaminic actions and is therefore used in allergic conditions. It also has sedative

properties. The usual dose range is 20 to 50mg daily in single or divided doses.

Promethazine HCl is sensitive to light and should be protected from light.

3. Maize Starch (May and Baker)
4. Lactose (May and Baker)
5. Talc
6. Magnesium Stearate

} Hopkin and William, Essex, England.

7. Cassava, Coaoyam and Yam Starches.

Method of Preparation Of The Local Starches

The fresh tubers of Diascorea rotundata Mannihot utilissima and the rhizome of Colocasia esculenta (yam, cassava and cocoyam respectively) were washed and peeled. They were out into small pieces, washed and then grated. The grated mass was reduced to a fine pulp using a blender after mixing with sufficient quantity of water. The pulp was passed through a 180um sieve with the addition of enough water to ensure a good recovery of starch. The starch was allowed to settle and then washed several times with 0.1N sodium hydroxide to neutralise the slight acidity. Excess alkali was removed by washing several times with distilled water. On standing yam and cassava pulps for about 6 hours and

cocoyam pulp for 12 hours it was possible to decant the clear supernatant fluid with insignificant loss of starch. The tightly packed starch was collected and air-dried on a laboratory bench overnight. The dried starch was ground to fine powder (passed through 180um sieve) using a pestle and mortar.

2.2 Methods

2.2.1 Investigations Of The Starches

i) Microscopic examination of starches: A small quantity of the extracted starches was mounted on a slide in glycerol. The size of the starch grains were measured. Other properties of the starch grains examined were the position of the hilum, shape of the grains, the nature of the striations and the nature of occurrence (single or compound) of the grains.

ii) Identification test of the starches: The B.P. (1980) test for identifying starch was used. 1g of each of the starch as was boiled with 15ml of water, then cooled, iodine solution was then added, a blue colour which disappeared on warming and reappeared on cooling indicated a positive identification of starch.

iii) Test of acidity of the starches: To 10g of each of the starches was added 100ml of 70% alcohol which was neutralised to phenolphtalein solution, the containers were shaken well during one hour, filtered and 50ml of the filterate titrated with 0.1N NaOH, using phenolphtalein solution as indicator. The B.P. (1980) requires that not more than 2.0ml of 0.1N sodium hydroxide be used.

iv) Moisture content determination of the starches: 2.0g of each of the starches was weighed into tared evaporating dishes. They were then placed in an oven at 105°C and dried to constant weight. Determination were carried out in duplicate.

v) Determination of swelling power: Starch powders were granulated using water as binder. The wet mass was forced through a mesh of size 1.6mm. The granules were dried at 80°C to constant weight in a hot air oven. Tablets were prepared using the same compression pressure with a 12mm punch and die set. The dimensions and weight of the slugs were measured. Two tablets each of the four different starches were placed in a desiccator at 98% relative humidity at room temperature for 5 days. The relative humidity was maintained at 98% by placing a saturated solution of lead

nitrate at room temperature in the desiccator (Odusote and Nasipuri, 1987). The percent increase in volume of tablet after 5 days was calculated and taken as the swelling power of the starches.

vi) Moisture sorption capacity: 10g of each of the starches was weighed and spread evenly in a petri-dish. The samples were exposed to 98% relative humidity at room temperature in a desiccator. The samples were weighed daily until they attained a constant weight. The difference between the initial and final weights was calculated and expressed as a percentage. This was taken as the moisture sorption capacity.of the starches.

vii) Determination of Starch mucilage viscosity: A Ferranti-Shirley viscometer (Ferranti Limited, Manchester) was used. It consisted of a rigidly constrained plate and a cone which is driven through an electromechanical torque dynamometer by an electronically controlled motor. The cone speed can be continuosly varied up to 100 r.p.m. The cone speed is indicated directly on the scale of a ten-turn potentiometer graduated in 1000 divisions. A water jacket beneath the plate

rapidly brings the small volume of sample fluid to equilibrium. The equipment can measure a viscosity range of 0.03 to 30,000poises. There are 3 different cones available for use with this equipment - a large cone (7cm diameter), medium (4cm diameter) and small (2cm diameter). The plate temperature was maintained at the desired level by pumping water from a thermostatically controlled temperature water bath into the water jacket. Tap water was also used as cooling water.

5%w/w, 7.5%w/w and 10%w/w mucilages of cassava, cocoyam, yam and maize starches were prepared. These were the concentrations of the starches used as binder in granulation. The viscosities of these mucilages were then measured at 40°C (the temperature at which they were used as binder) using a large cone, because of the thickness of the mucilages. The cone speed was varied from 10 r.p.m to 100 r.p.m.

The following equation was used to calculate the viscosity of the sampe for each speed, (Ref. Operating manual).

$$\underset{\text{(poise)}}{\text{Viscosity}} = \frac{\text{Cone Constant} \times \text{Instrument Reading} \times \text{Range}}{\text{Speed}} \quad \text{--(3)}$$

The large cone constant is 1.26 while the range used was x4.

Notes on the Equation:

Viscosity = $\frac{\text{Shear Stress}}{\text{Shear rate}}$. The instrument reading indicates the torque on the cone which is the same as the shear stress, while the speed is a measure of the shear rate. Therefore, viscosity

= K . $\frac{\text{Instrument Reading}}{\text{Speed.}}$

Where K is a constant that accounts for the nature of the apparatus used in determining the viscosity, (in this case, the cone which is used to measure the shear stress). The value of K changes depending on the cone angle and radius. K is given by,

$$\frac{3(\text{Cone angle})}{2\pi(\text{cone radius})} = \text{Cone constant}$$

The range is a multiplying factor on the instrument, the value of which can be chosen by the operator depending on the nature of the sample to be tested.

The results obtained were plotted to give shearing rate versus shearing stress to show the relative flow curve characteristics of the different starch mucilage at the same concentration.

The viscosity of the pastes at a fixed speed of 50rpm was measured at different temperatures. Graphs of viscosity versus temperature were plotted for the different starches at different concentrations.

viii) Determination of starch true density: The method of Schoch and Leach (1964) was used. 5g of the starch was weighed into a 50ml specific gravity bottle which was previously calibrated with distilled water. Xylene was carefully poured into the bottle and allowed 15 minutes to condition at room temperature. The starch was gently stirred with a glass rod to release entrapped air and again left to condition. This process was repeated until no further bubbles were released. The specific gravity bottle was then filled up and the lid carefully replaced. The outside of the bottle was wiped dry and the bottle weighed. The density was calculated from the difference in weight as shown in Table 1.

2.2.2 Preparation Of Granules

The wet granulation method of massing and screening was used. The amounts of materials used are as shown in Table 2. The powders were dry-mixed for 5 minutes in a

Table 1: Calculation of specific gravity of starch

	Cassava	Cocoyam	Yam	Maize
Weight of starch in air (g)	5.070	4.989	5.906	5.019
Weight of Xylene by full Pycnometer (g)	41.336	43.328	42.727	41.758
Weight of Starch + Xylene	46.406	48.317	48.633	46.777
Weight of immersed Starch + Xylene	43.684	45.547	44.815	43.869
Weight of Xylene displaced by Starch (g)	2.722	2.770	3.818	2.908
Loss of Weight in water (g)	3.170	3.220	4.440	3.380
Specific gravity of Starch	1.60	1.55	1.33	1.49

Specific gravity of Xylene = 0.86

$$\text{Loss of Weight in water} = \frac{\text{Weight of Xylene displaced by Starch}}{\text{Specific gravity of Xylene}}$$

$$\text{Specific gravity of Starch} = \frac{\text{Weight of Starch in air}}{\text{Loss of weight in water}}$$

Endecotts test sieve shaker. The weighed amount of granules was placed on the top sieve and shaken for 15 minutes. The weight of granules retained on each sieve and the fines collector were taken.

ii) Moisture content: 5g of granules was dried to constant weight in a hot air oven at 105°C. The difference between the initial and the final weight was expressed as a percentage of the moisture content of the granules.

iii) Flow time: An Erweka flowability tester was used. It measured the time required for 100ml of granules to pass through an orifice.

iv) Bulk density: (Method of Stanley-Wood and Shubair, 1978). 30g of each granules was gently and slowly poured through a short-stemmed glass funnel into a 100ml graduated glass cylinder. The orifice of the funnel stem was aligned with the 100ml mark. The volume occupied by the granules was read to the nearest 0.5ml and the bulk density calculated in gm/ml.

Tapped density: The graduated cylinder was dropped 20 times from a height of about 2.54cm onto a wooden bench and the volume recorded. The tapped density was calculated in gm/ml.

v) Percent compressibility: (Stanley-Wood and Shubair, 1978). The % compressibility was calculated from the difference between the tapped and the bulk densities divided by the tapped density and the ratio expressed as a percentage.

2.2.4 Compression Of Granules

Granules of size greater than 150 microns and less than 1000 microns were compressed into tablets, after the exodisintegrant and lubricant had been added (Tables 4a and b). Tablets were compressed on a power-driven single punch tablet press. The machine was set to produce flat bevelled-edged 12mm diameter Sulphadimidine tablets and 9mm Promethazine hydrochloride tablets at the rate of 30 tablets per minute. The compression pressure setting was 3 units for Promethazine Hcl and 5.5units for Sulphadimidine.

2.2.5 Tests On Tablet Properties

i) Hardness: A Monsanto hardness tester was used. It indicates in kg the force required to crush the tablet. The mean of six determination was calculated.

ii) Friability: Tablets were subjected to friabilation in an Erweka friabilator at 25 r.p.m. for 4 minutes. The weight of 20 tablets before and after

Table 2: Calculation of Packing Fraction Of Tablets

Packing fraction (P_f) = $\frac{\text{Bulk density}}{\text{True (Particle) density}}$

Bulk density of a tablet = $\frac{\text{Weight}}{\text{Volume}}$

Volume = $\pi r^2 h$

r = radius of the tablet

h = thickness of the tablet.

True density (ρ_{AB}) can be calculated as below,

$\frac{1}{\rho_{AB}} = \frac{\eta_A}{\rho_A} + \frac{\eta_B}{\rho_B}$

ρ_A, ρ_B = Densities of the components

$\frac{W_A}{W_A+W_B}$, $\frac{W_B}{W_A+W_B}$

η_A, η_B = Weight fraction of the components A and B.

W_A = Weight of the components present in the tablet.

W_A+W_B, = Total tablet weight.

Density of Sulphadimidine, 1.54

Density of Lactose , 1.53

Density of Promethazine , 1.69

mortar using a pestle in the case of Sulphadimidine. For Promethazine HCl, the powders were dry-mixed in a tumble mixer for 15 minutes. The starch mucilages were prepared by suspending the weighed amount of starch powder in a small amount of water (to prevent the formation of clumps), then boiling water was added to the suspension with continuous heating and stirring of the starch until a mucilage was formed.

The mucilage was added to the powder mix and mixing continued using a pestle and mortar, while the mucilage was added. This was continued for about 10 minutes. The moistened mass was forced through a 1.60mm screen using the Erweka oscillating granulator. The granules were dried at $40^{o}C$ for 4 hours in a hot air oven. They were then passed through the same 1.6mm screen.

2.2.3 Characterisation Of Granules

1) Size analysis: 100g of the granules were used for the analysis. The sieve method of measurement was used. Six sieves of aperture sizes 1000um, 600um, 500um, 355um, 250um and 150um were used. They were arranged in a stack with the sieve with the largest pore size at the top, and the smallest pore size at the bottom. The stack was mounted on an

friabilation was taken. The percent loss in weight was calculated to obtain the friability. The mean of two determinations was calculated.

iii) Diameter/Thickness: A vernier caliper was used to measure the diameter and thickness in mm.

iv) Packing Fraction: The packing fraction of each of the tablets was calculated as shown in Table 2.

v) Disintegration time: Six tablets were assessed at the same time in a B.P. (1980) disintegration test apparatus containing distilled water as medium at a temperature of 37 $\pm$ 2^{o}C. The mean of three such determinations was calculated.

vi) Dissolution rate: A modified BP dissolution rate test apparatus was used. The medium was 1000ml of 0.1N HCl for Sulphadimidine tablets while for Promethazine HCl tablets it was 300ml of distilled water. One tablet was placed in a basket which was then immersed in the medium. A rotation speed of 100 r.p.m was used. The temperature of the medium was thermostatically maintained at 37 $\pm$ 0.5^{o}C. At appropriate time intervals samples of the dissolution medium were withdrawn through a plug of cotton wool (for filteration) and suitably diluted for

spectrophotometric determination. Drug determination was made at 244mm for Sulphadimidine and 249nm wavelength for Promethazine at which wavelength lactose (diluent in Promethazine tablets) did not absorb. A Unicam SP 8-100 UV Spectrophotometer was used. The determinations were carried out twice in each case. The mean of the determinations was calculated. The Beer-Lamberts curve for Sulphadimidine and Promethazine is as shown in Figs. 1 and 2 respectively.

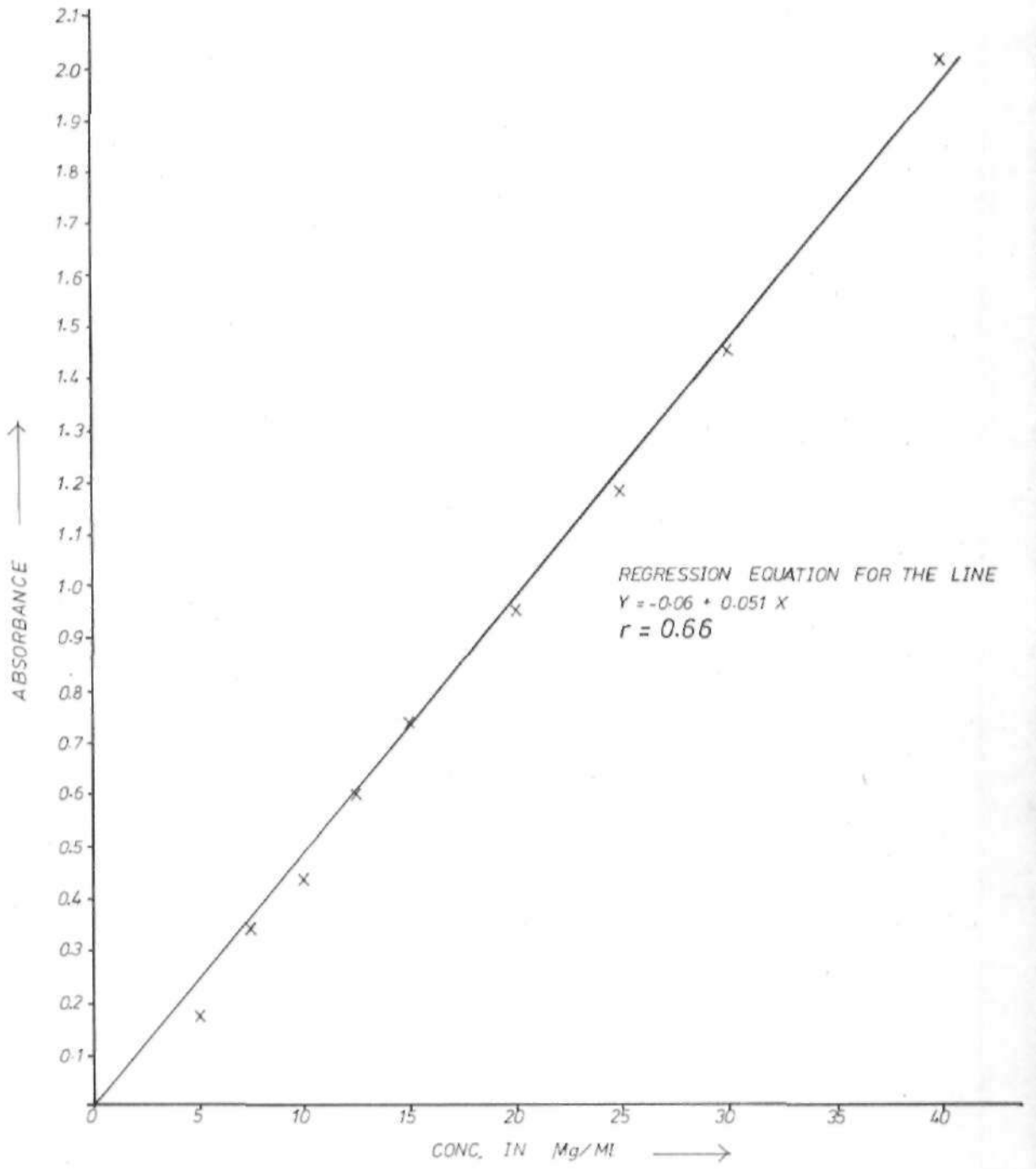


FIG. 1: BEER-LAMBERT's CURVE OF ABSORBANCE Vs. CONC. FOR SULPADIMIDINE AT λ MAX 244 nm USING UV SPECTROPHOTOMETER.

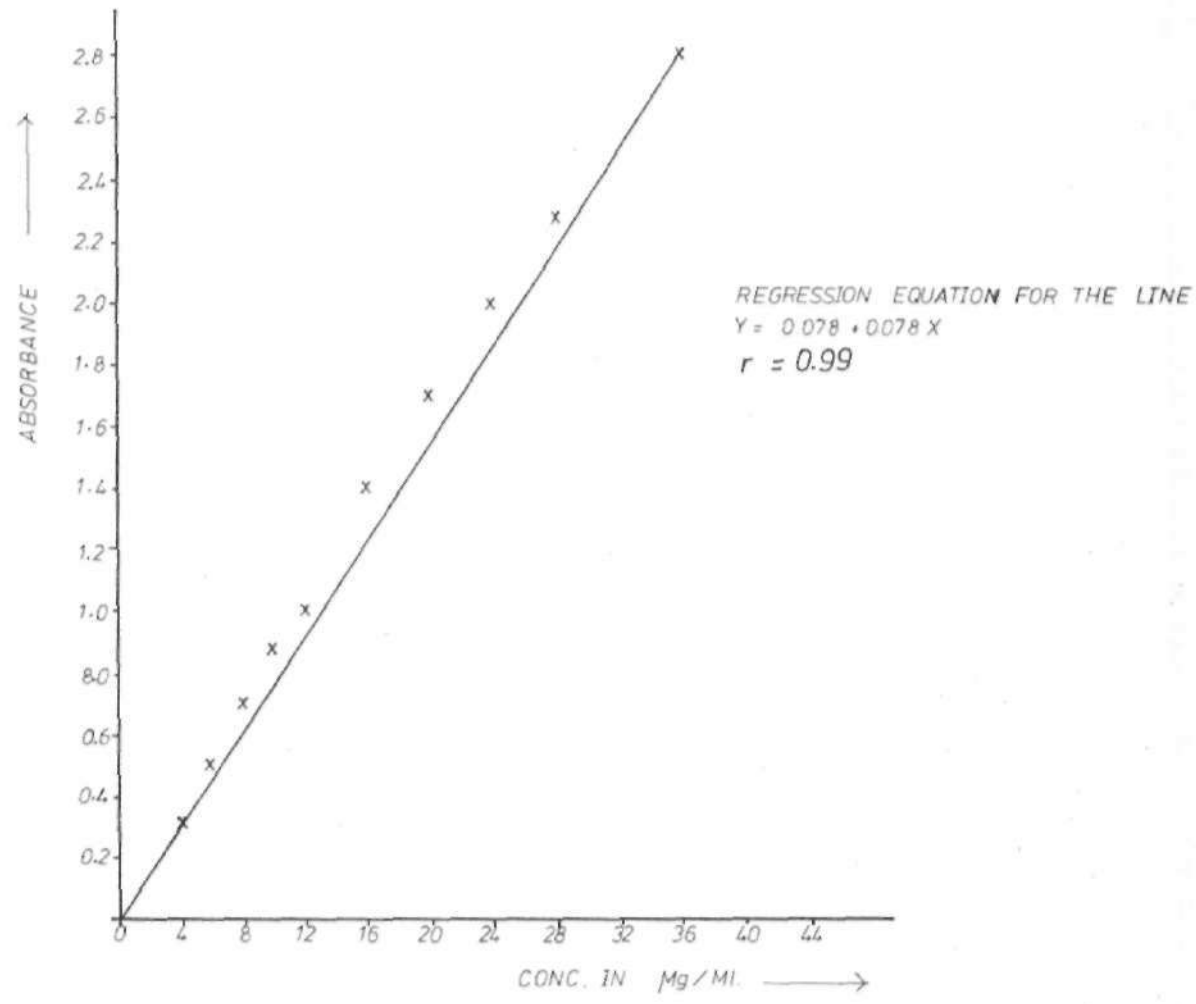


FIG 2: BEER-LAMBERT'S CURVE OF ABSORBANCE Vs. CONC. FOR PROMETHAZINE HYDROCHLORIDE AT λ MAX 249 nm. USING UV SPECTROPHOTOMETER.

TABLE 3: Results Of Investigations Of Starches Used In Tablet Formulation

	CASSAVA	COCOYAM	YAM	MAIZE
TEXTURE	Fine	Fine	Fine	Fine
COLOUR	Very White	White	White	White
ODOUR	Odourless	Odourless	Odourless	Odourless
GRAIN SIZE um (average)	3.24 to 22.68 (11.01)	1.62 to 8.10 (3.84)	11.34 to 43.74 (29.60)	5 to 22.5 (12.74)
HILUM (Position)	Central	Central	Tip of grain	Central
OCCURRENCE	Compound	Single	Single	Compound
SHAPE	Round	Polyhedral	Ovoid	Round
DENSITY (gm/ml)	1.60	1.55	1.33	1.49
MOISTURE SORPTION CAPACITY (%)	18.98	16.88	19.55	14.35
SWELLING POWER (%)	27.34	23.11	26.85	20.33
MOISTURE CONTENT(%)	8.6	8.8	7.7	9.2
IDENTIFICATION TEST (BP)	ALL THE	STARCHES PASSED	THIS	TEST
TEST OF ACIDITY (BP)	" "	" "	"	"

TABLE 4a: Sulphadimidine Tablet Composition

(i) Varying binder concentration, while keeping disintegrant concentration constant.

	Per tablet	Quantities Used
Sulphadimidine	500mg	100g
Starch powder	2.5%w/w	2.5g
Starch mucilage	5%w/w, 7.5%, 10%	1g, 1.5g, 2g (dry binder weight)
Starch powder	2.5%w/w	- *
Talc/Mg Stearate(1:1)	0.25%w/w	- *

(ii) Varying disintegrant concentration, while keeping binder concentration constant.

	Per tablet	Quantities Used
Sulphadimidine	500mg	100g
Starch powder	2.5%, 5%, 7.5%w/w	2.5g, 5g, 7.5g
Starch mucilage	7.5%w/w	1.5g(dry binder weight)
Starch powder	2.5%, 5%, 7.5%w/w	*
Talc/Mg Stearate(1:1)	0.25%w/w	*

TABLE 4b: Promethazine HCl Tablet Composition

(i) Varying binder concentration, while keeping disintegrant concentration constant.

	Per tablet	Quantities Used
Promethazine HCl	10mg	10g
Starch Powder	1.25%w/w	2g
Lactose Powder	150mg	150g
Starch mucilage	5%, 7.5%w/w 10%w/w	0.4g, 0.6g, 0.8g
Starch Powder	1.25%w/w	*
Talc/Mg Stearate (1:1)	0.25%w/w	*

(ii) Varying disintegrant concentration, while keeping binder concentration constant.

	Per tablet	Quantities Used
Promethazine HCl	10mg	10g
Starch Powder	1.25%, 2.5% 5%w/w	2g, 4g, 8g
Lactose Powder	150mg	150g
Starch mucilage	7.5%w/w	0.6g
Starch Powder	1.25%, 2.5%, 5%	*
Talc/Mg Stearate (1:1)	0.25%w/w	*

*The amounts of exodisintegrant (starch powder) and lubricant were calculated as percentages of the actual granule weight after dry-screening of the granules

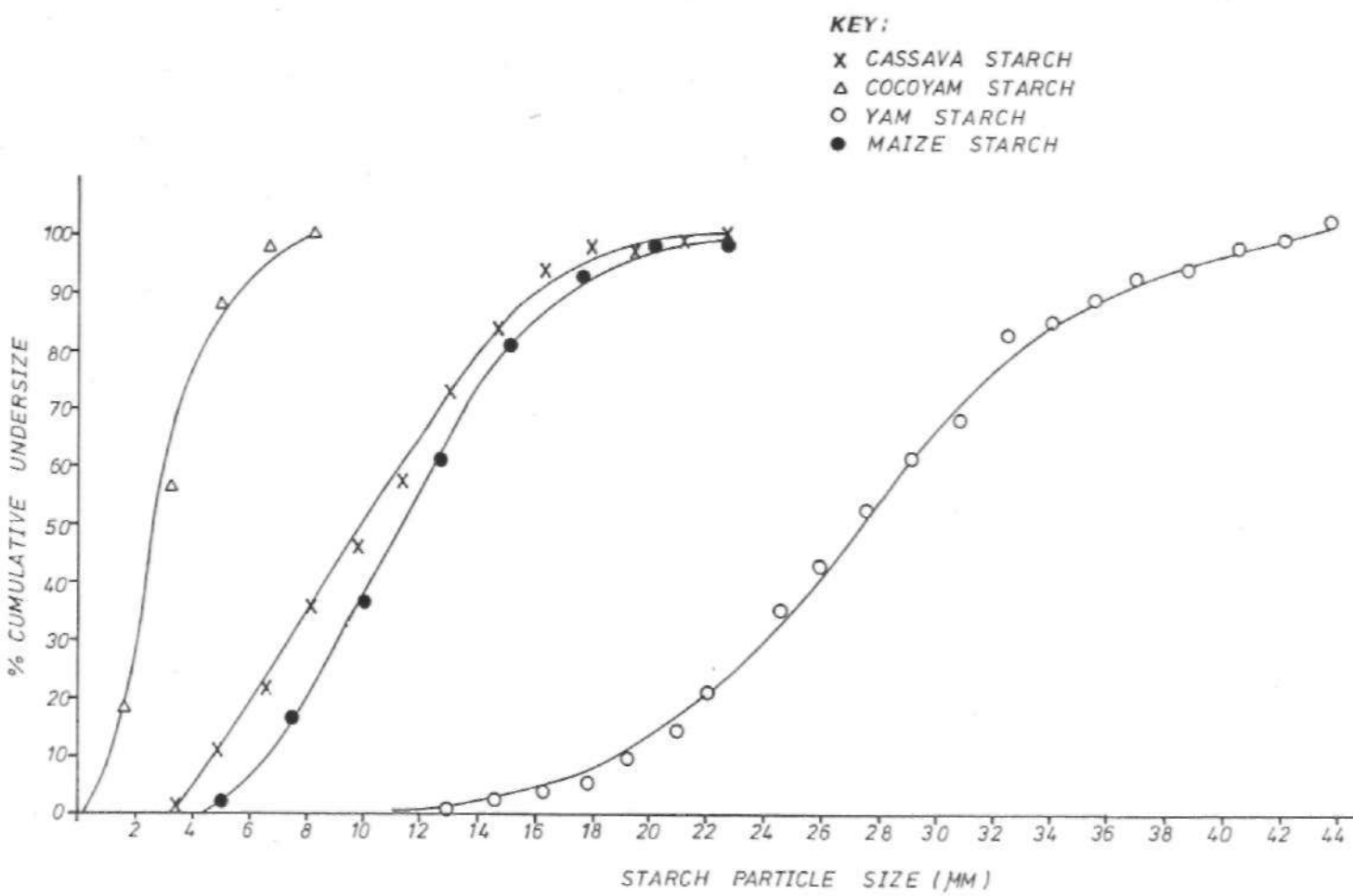


FIG.3: STARCH PARTICLE SIZE DISTRIBUTION.

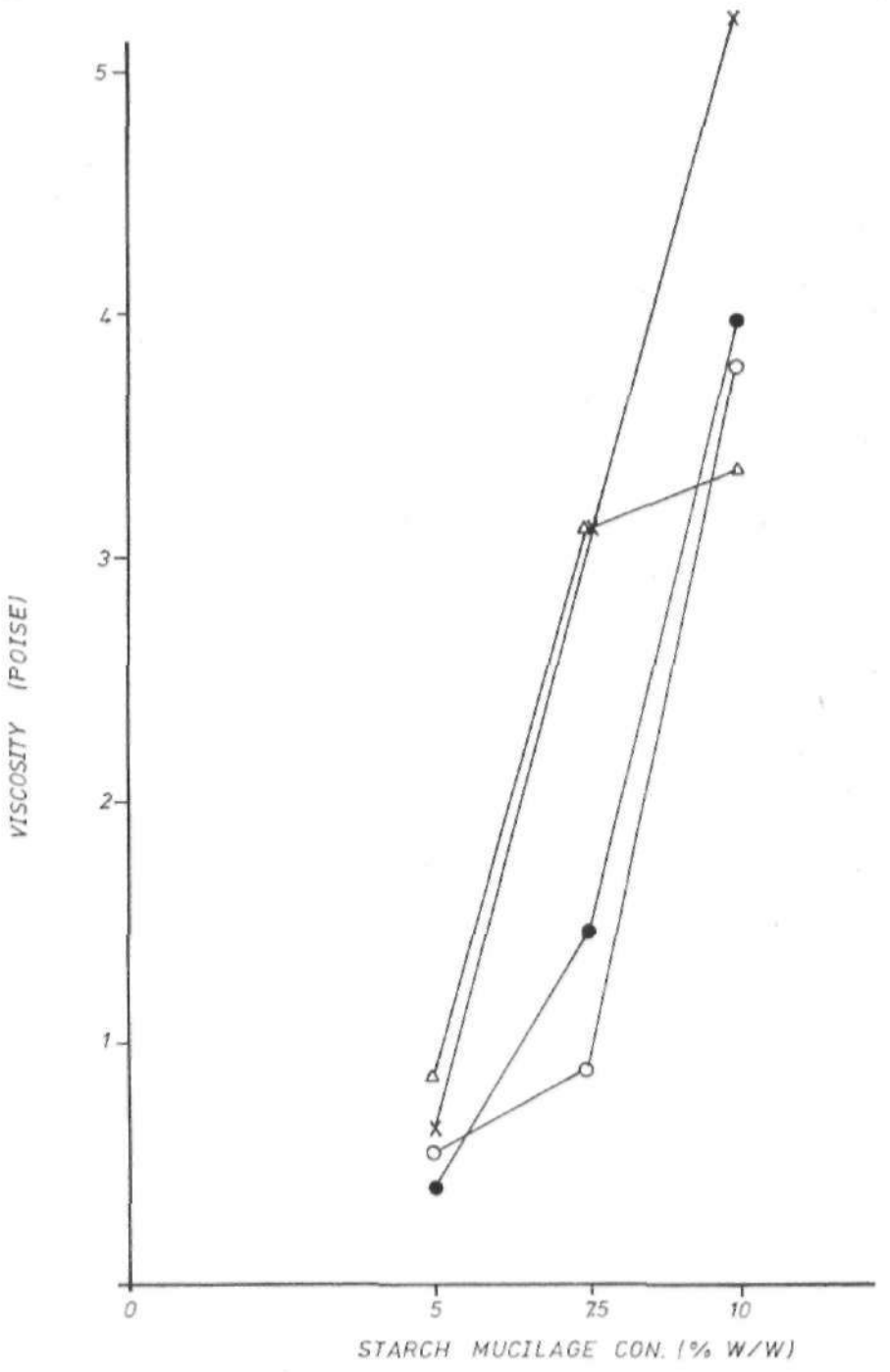


FIG. 4 : EFFECT OF CONCENTRATION ON THE VISCOSITY OF STARCH MUCILAGE.

KEY:

X — CASSAVA STARCH
△ — COCOYAM STARCH
○ — YAM STARCH
● — MAIZE STARCH

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Tests On Starches

Fig. 3 shows the particle size distribution of the various starches used. The distribution was similar for all the starches - few of the particles had very small and very large sizes relative to the average particle size, while the majority of the particles were in between. The result shows that cocoyam starch had the smallest particles while yam starch had the biggest. Both the size and distribution of the cassava and maize starch particles were similar.

Fig. 4 shows that the apparent viscosity of the starch mucilages increased with increase in the concentration of the mucilage. The increase in apparent viscosity between 7.5% and 10%w/w was higher than that between 5% and 7.5%w/w for all the starches except cocoyam. This was because as the concentration of starch in the mucilage increased, the 'crowding effect' of the disrupted starch grains increased thus increasing the difficulty with which the mucilage was flowing. This effect was more pronounced at the 10%w/w mucilage concentration as compared to the other concentrations used, because of the large amount of starch grains present which severely restricted the space available

for flow of the particles. The case of cocoyam was an exception probably because of the stringy nature of the pastes formed, which is usually more pronounced at higher concentrations.

At 5%w/w mucilage concentration, cocoyam starch was the most viscous, followed by cassava, yam and maize starches respectively (Appendix 6A). At 7.5%w/w concentration, the ranking order of apparent viscosities was cassava cocoyam maize yam. The apparent viscosity values of cassava and cocoyam were the same and were much higher than those of maize and yam at this concentration (Appendix 6B). At 10%w/w mucilage concentration (Appendix 6C), cassava starch mucilage was the most viscous, with its apparent viscosity being much higher than those of other starches whose values were almost same. Cocoyam starch had the lowest apparent viscosity at this concentration.

The viscosity of starch paste can be affected by the grains swelling power, the ability of granule fragments to serve as cross-linking sites for the polymeric exudate that comprises most of the paste (Myers and Krauss, 1965), the nature and amount of the exudate and the extent of the polymeric sheet formed after granule rupture. The net effect of these factors

is to impede the flow of a fluid and also increase the molecular forces of attraction of which viscosity is a measure in fluids. All these factors can also interact to cause the change in ranking order of viscosities with changing mucilage concentration.

The effect of temperature on starch paste viscosity was also investigated. The results obtained show that viscosity of all the different starch pastes used at the three different concentration levels decreased with increase in temperature (Appendices A, B, C). This can be attributed to the events that occur in a starch suspension when temperature is increased. When an aqeuous suspension of starch is heated, the individual grains gelatinize and swell freely until they imbide virtually all the water available around them. As a result, the swollen grains become increasingly susceptible to disintegration by mechanical shear as in the cone and plate viscometer. The bonding forces within the grain also become more tenuous thus making the grain more fragile towards thermal or mechanical breakdown.

Maximum viscosity of the paste is achieved when the increase in structural viscosity caused by swollen starch aggregates is counter balanced by the decrease in viscosity resulting from disintegration and

solubilization of the starch. The latter effect becomes more pronounced and predominates as heating continues and consequently the viscosity of the paste decreases gradually.

Since the swelling power, nature of paste and strength of paste structure (factors which affect paste viscosity) varies from starch to starch, the extent and rate at which the viscosity decreases with increased temperature will differ among the various starches. This was found to be the case (Appendices A, B and C).

Increasing the temperature, did not affect the ranking order of the starches relative to each other, the order remained the same at the different temperatures.

The flow characteristics of all the starches were similar at all the mucilage concentrations used (Appendices 6A, B and C). The plot of shearing rate versus shearing stress produced curves that indicated that the flow of the mucilages was pseudoplastic. The rate of increase of shearing stress was less than that of shearing rate which is further confirmation that the mucilages are pseudoplastic. The curved rheogram obtained, as for other pseudoplastic substances results from a shearing action on the long chain molecules of the material. As the shearing stress increases, the

normally disarranged molecules begin to align their long axes in the direction of flow. This orientation reduces the internal resistance of the material and allows a greater rate of shear at each successive shear stress. Some of the solvent associated with the molecules may be released resulting in the lowering of viscosity. In the case of a plastic body, flow cannot take place until the applied stress exceeds the force of flocculation which causes particles to adhere together when flow is initiated, the particle layers move relative to the adjacent layers; the material then behaves like a Newtonian body.

Relationship of viscosity to binding capacity:

Viscosity is a measure of the resistance of a fluid to flow: the higher the viscosity the greater the resistance. It can also be described as a measure of the viscous forces of mutual attraction between molecules of a fluid with the viscosity increasing as the molecular forces increase (McKennell, 1960). The viscosity of starch mucilages will therefore affect their ability to bind particles together. Up to a limit, the higher the viscosity, the higher will be the binding capacity of the mucilage. The viscosity of binder also affects its handling properties. A very thick (highly viscous)

mucilage will not be easily pourable. It will also be difficult to effectively disperse it in the powder mix, thus decreasing its binding capacity.

3.2 Tests On Granules And Tablets

Figs. 5 and 6 shows the effect of binder type on the granule size distribution of promethazine and sulphadimidine at 5%w/w binder concentration. The results show that both the type and concentration of starch used as binder affects the granule size distribution of both soluble (Promethazine) and insoluble (Sulphadimidine) drugs. Generally, with all the starches used, most of the granules were within the 500 microns and 1000 microns size range. This indicates that all the starches formed many strong and stable bridges between the drug particles. Similar results were obtained at the other binder concentrations used (See Appendices 2 and 4).

For Sulphadimidine, the amount of granules within the 500 microns and above (large-sized) size range produced using different starches was in the order, maize cassava yam cocoyam at 5%w/w binder concentration while at 7.5%w/w concentration the order was cocoyam > cassava > maize > yam and at 10%w/w it was cassava > maize > cocoyam > yam. For Promethazine, the

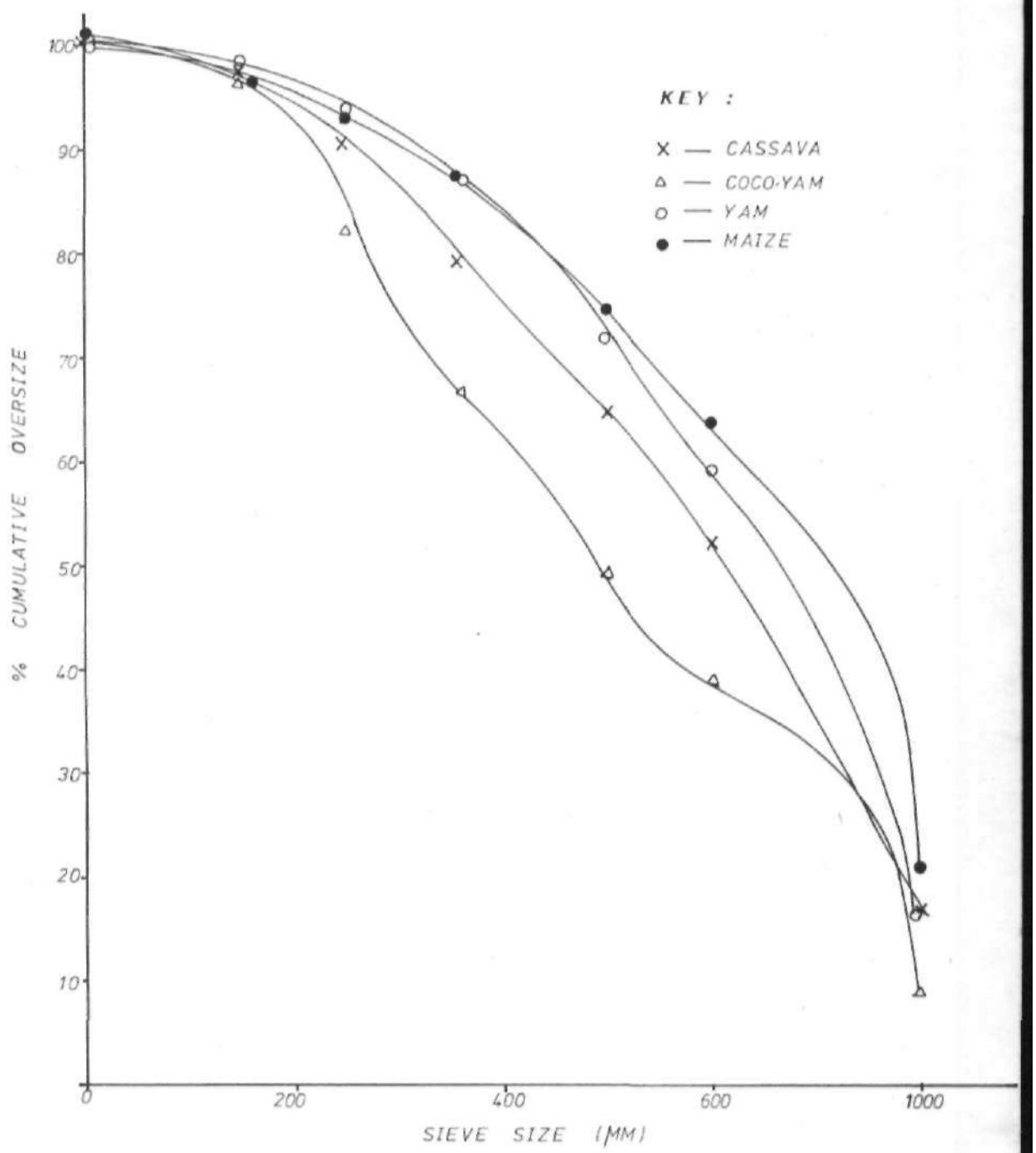


FIG. 5 : GRANULE SIZE DISTRIBUTION OF PROMETHAZINE USING 5 % W/W STARCH MUCILAGE AS BINDER.

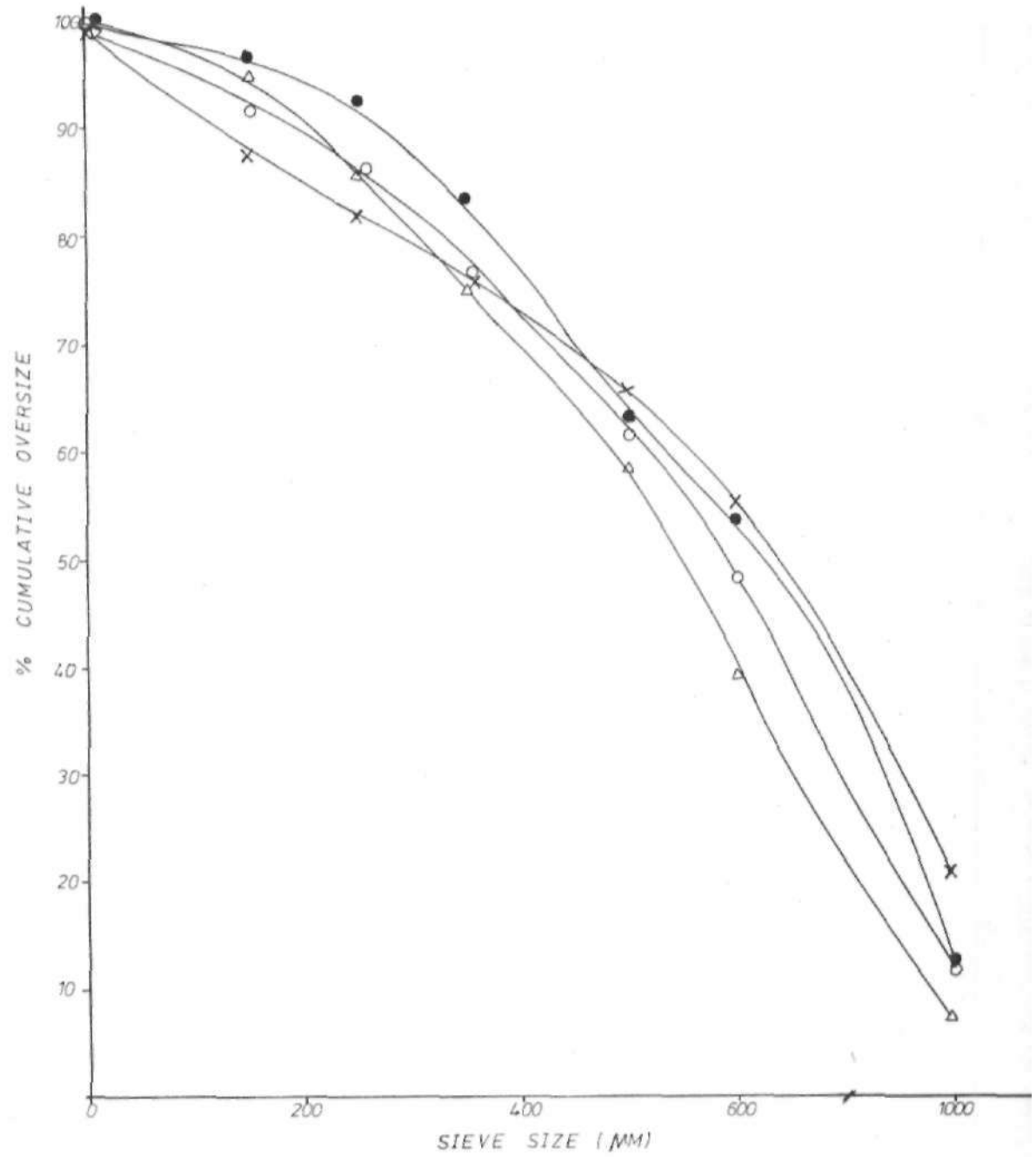


FIG.6 : GRANULE SIZE DISTRIBUTION OF SULPHADIMIDINE USING 5 % W/W MUCILAGE OF EACH STARCH AS BINDER.

order was maize> yam > cassava> cocoyam at 5%w/w binder concentration, cassava> yam> maize > cocoyam at 7.5%w/w and cassava yam cocoyam maize at 10%w/w. Since in all cases the same amount of starch was used at the same concentrations, to eliminate the solvent effect (Nasipuri and Akala, 1986) the differences in amount of large-sized granules produced is attributable to the differences in the binding capacity of the various starches. It was observed that the ranking order among the starches depended not only on the concentration of binder but also on the nature of the drug. This explains why none of the starch properties determined could be used separately to explain the ranking orders. The starches that produced the highest amount of large-sized granules may have formed the highest number of strong solid bridges by having the highest penetration, covering and wetting ability since these are the processes by which increase in granule size occur (Davies and Gloor, 1971; Carstensen et al, 1976).

On the whole, the amount of large-sized granules increased with increase in binder concentration for both drugs. This was due to the formation of more and stronger bonds in the presence of more concentrated starch mucilages. Granulations of Promethazine with

maize starch were exceptions to this general trend; the amount of large-sized granules decreased as binder concentration increased.

With respect to fines production, granulations made with cocoyam starch as binder were peculiar (Appendices 2 and 4). This is probably because of the stringy nature of pastes it produces (Goering and DeHAAS, 1972), its small size and low amylose content relative to the other starches (Table 1 and Appendix 1). The amylose content is important because it is the amylose fraction of starch that gives it its binding property since it leaches out of the starch particle to from thread-like structures (Chabot et al, 1976) that could enhance binding action.

The granule size distribution was similar for all the starches used when equal concentrations were used (Appendices 2 and 4). The only exception was Promethazine granulation made with 5%w/w cocoyam starch as binder (Figure 5), where the amount of granules of size 500 microns and above was significantly lower than for the other starches. Conversely, it had the highest amount of granules within the 150 microns to less than 500 microns size range. This implies that cocoyam starch produced relatively small sized granules. This could be

because of its low amylose content which will reduce the thickness of the solid bridges formed. This effect will be most pronounced at the low concentrations such as 5%w/w and with soluble drugs such as Promethazine.

Figs. 7 and 8 show that the type of starch used as disintegrant affects the granule size distribution. The disintegrant concentration also affects the size distribution as can be seen in Appendices 3 and 5. This could have been because some portion of the starch was wetted during granulation and thus acted as binder thereby changing the granule size distribution. Since the amount of starch wetted will depend on the source of starch, the trend of changes in the size distribution of granules with change in disintegrant concentration will be unpredictable. Results obtained in this work supports this suggestion. For example, the amount of large-sized granules of Promethazine decreased with increase in disintegrant concentration when cassava starch was used, while it increased with increase in disintegrant concentration when cocoyam starch was used. The magnitude of the changes was also inconsistent.

The moisture content of all the granulations were all below or equal to 5%w/w (1.93 to 5.25%w/w). The forces in operation (pendular, funicular and capillary) will thus be expected to be similar (Pilpel, 1971).

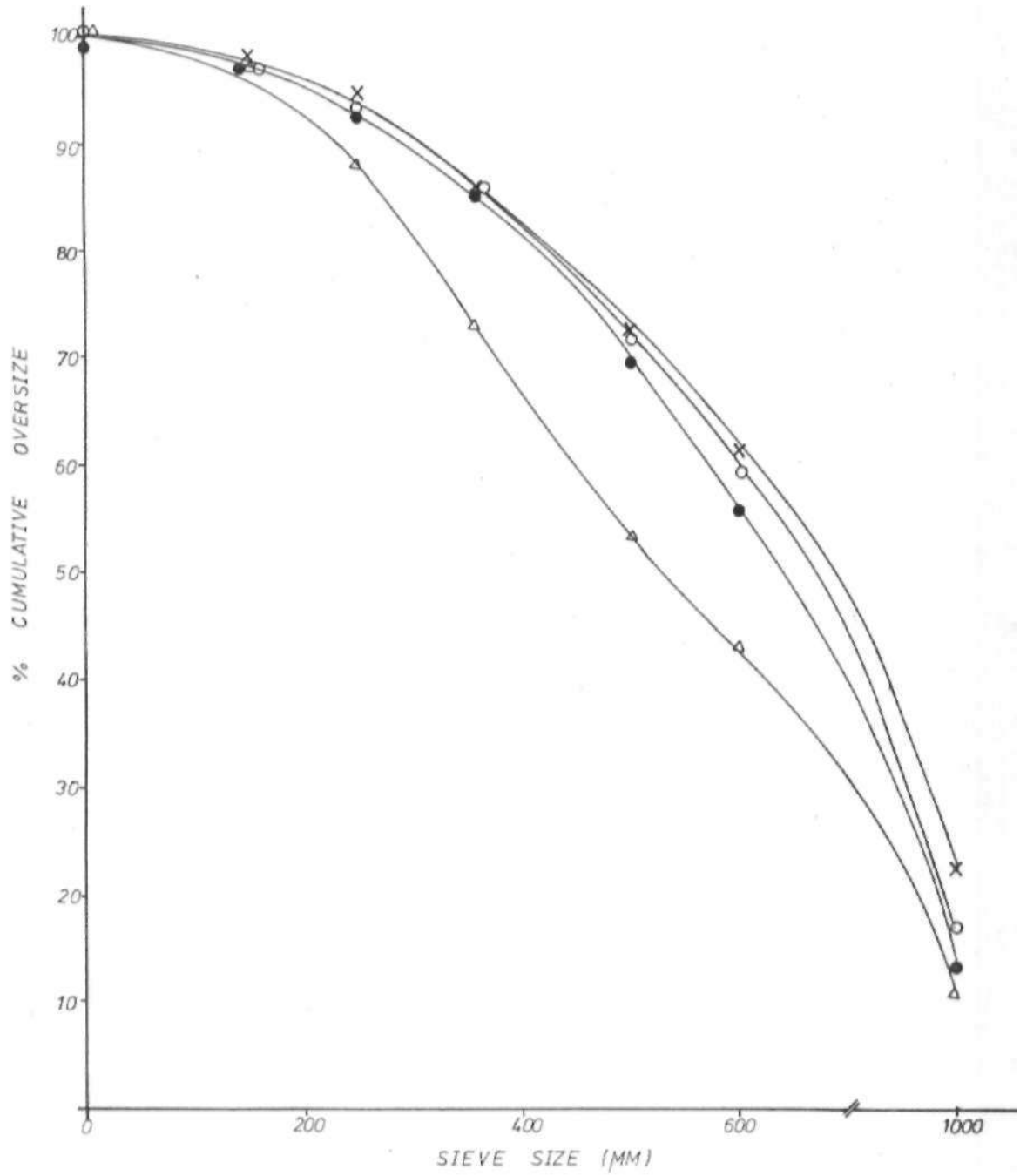


FIG. 7: GRANULE SIZE DISTRIBUTION OF PROMETHAZINE USING 2.5% W/W STARCH AS DISINTEGRANT.

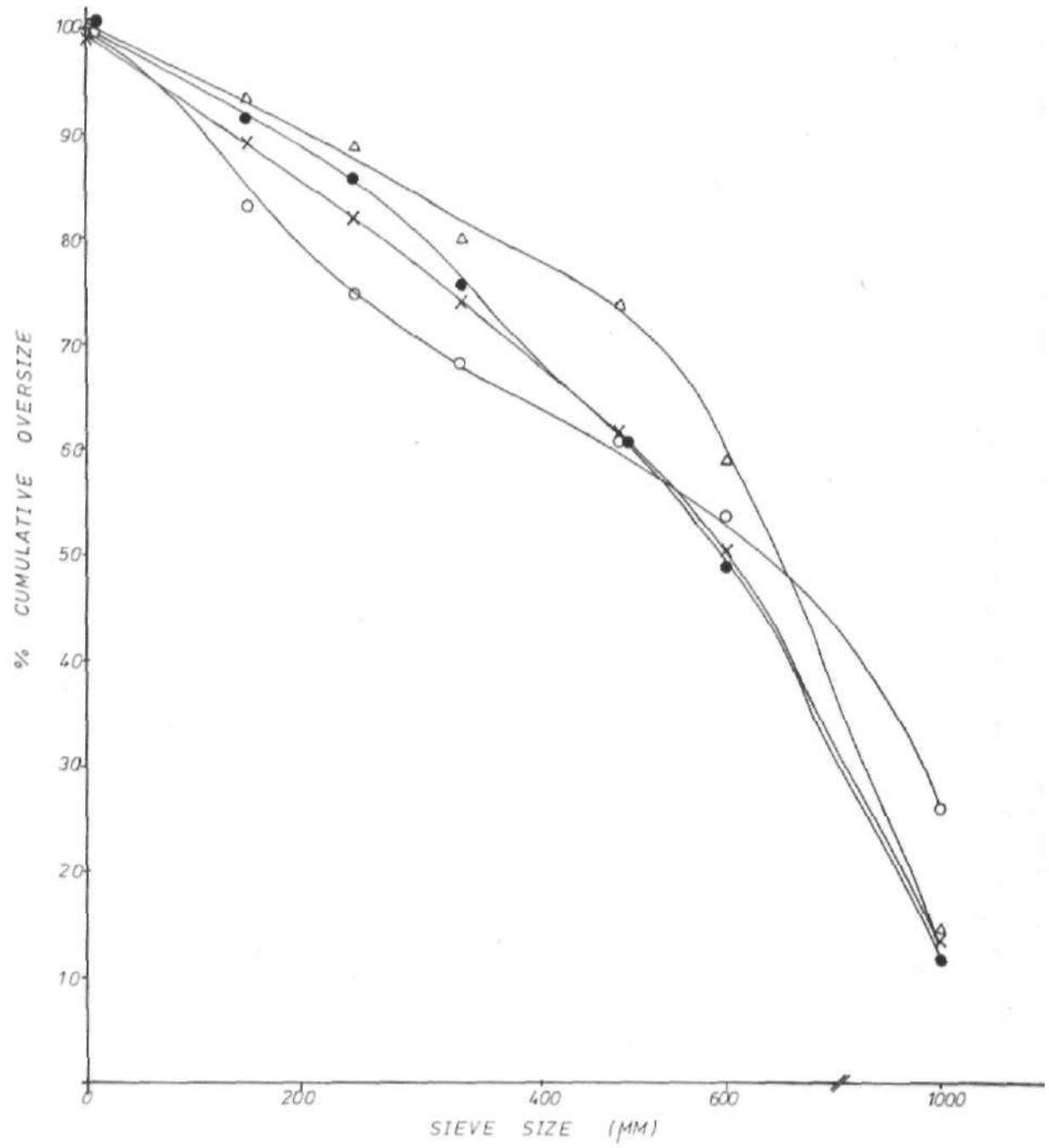


FIG.8 : GRANULE SIZE DISTRIBUTION OF SULPHADIMIDINE USING 5% W/W OF EACH STARCH AS DISINTEGRANT.

Tables 5 and 6 show that the bulk and tapped densities of granules generally decreased as binder concentration increased, for both Sulphadimidine and Promethazine granulations. In a few cases the values remained constant. The decrease in bulk and tapped densities with increase in binder concentration is due to the formation of larger sized granules. These had more inter-granular voids for a given granule weight and therefore low density values. A rise in density value as was seen for maize starch granulations between 7.5%w/w and 10%w/w (Tables 8b and c) could be an indication that large but fragile granules were formed.

Tables 5, 6, 7 and 8 show the compressibilities of the various granulations of Sulphadimidine and Promethazine using different starches at different concentrarions. The results indicate that compressibility which is a measure of the ability of a material to be reduced in volume under pressure is affected by the type and concentration of starch used as binder and disintegrant. Tablet volume after compression did not have any relationship to compressibility values because of the plastic and elastic relaxation that occur after compression.

TABLE 5a: Properties Of Sulphadimidine granules Using 5%w/w Starch Mucilage as binder

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	% COMPRESSIBILITY
a	1.93	11.48	0.44	0.57	22.81
b	3.69	9.36	0.47	0.58	18.97
c	3.59	11.34	0.43	0.59	10.17
d	2.43	9.40	0.50	0.60	16.67

TABLE 5b: 7.5%w/w Starch Mucilage as binder

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	% COMPRESSIBILITY
a	2.45	11.70	0.44	0.55	20
b	2.5	10.44	0.44	0.54	18.52
c	2.67	11.88	0.43	0.52	17.31
d	2.7	11.00	0.43	0.53	18.87

TABLE 5c: 10%w/w Starch Mucilage as binder

	% MOISTURE CONTENT	FLOWABILITY	BULK DENSITY	TAPPED DENSITY	% COMPRESSIBILITY
a	2.67	10.74	0.44	0.55	20
b	4.00	11.54	0.43	0.53	18.87
c	5.25	9.42	0.42	0.51	17.65
d	2.93	13.00	0.43	0.53	18.87

KEY TO ALL TABLES

a - Cassava Starch as binder
b - Cocoyam Starch as binder
c - Yam Starch as binder
d - Maize Starch as binder

TABLE 6a: Properties Of Promethazine granules using 5%w/w Starch Mucilage as binder

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	3.44	12.28	0.53	0.58	8.62
b	3.13	11.32	0.49	0.57	14.04
c	3.31	12.20	0.50	0.56	10.71
d	3.25	13.08	0.53	0.57	7.02

TABLE 6b: 7.5%w/w Starch mucilage as binder

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	3.12	12.64	0.54	0.60	10
b	3.37	10.40	0.52	0.57	8.77
c	3.24	12.76	0.50	0.55	9.09
d	3.14	12.92	0.51	0.55	7.27

TABLE 6c: 10%w/w Starch mucilage as binder.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	3.89	13.08	0.54	0.60	10
b	3.26	12.76	0.49	0.56	12.5
c	3.64	14.32	0.50	0.55	9.09
d	3.86	13.28	0.48	0.52	7.69

TABLE 7a: Properties Of Sulphadimidine granules using 5%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	2.41	11.62	0.44	0.55	20
b	2.57	10.40	0.44	0.54	18.52
c	2.59	11.92	0.43	0.52	17.31
d	3.32	11.36	0.43	0.53	18.87

TABLE 7b: 10%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	2	10.29	0.41	0.48	14.58
b	2.25	11.82	0.40	0.45	11.11
c	4.11	10.13	0.40	0.46	13.04
d	2.54	11.86	0.40	0.46	13.04

TABLE 7c: 15%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	2.84	6.80	0.42	0.54	22.22
b	3.14	5.86	0.40	0.47	14.89
c	2.38	11.19	0.40	0.46	13.04
	3.68	11.46	0.40	0.46	13.04

TABLE 8a: Properties Of Promethazine granules using 2.5%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	3.12	12.64	0.54	0.60	10
b	3.37	10.40	0.52	0.57	8.77
c	3.24	12.76	0.50	0.55	9.09
d	3.14	12.92	0.51	0.55	7.27

TABLE 8b: 5%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	3.7	13.32	0.48	0.52	7.69
b	3.66	13.68	0.47	0.52	9.62
c	3.11	13.72	0.48	0.53	9.43
d	3.66	12.68	0.46	0.50	8.00

TABLE 8c: 10%w/w Starch as disintegrant.

	% MOISTURE CONTENT	FLOWABILITY (SECS)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	% COMPRESSIBILITY
a	4.26	13.24	0.45	0.49	8.16
b	3.44	15.28	0.47	0.50	6.00
c	3.46	14.44	0.45	0.49	8.16
	3.49	12.44	0.47	0.51	7.84

The flow times of Promethazine granulates increased as the binder and disintegrant concentrations increased (Tables 6 and 8). This is probably due to the increase in granule size with increase in binder and disintegrant concentration. Davies and Gloor (1972) have also found a similar relationship between granule size and flow time.

The ranking orders for flow time of Sulphadimidine granules shown in Tables 5a, b and c were similar to those obtained when the percentage of fines produced by the granulates with each of these starches as binder (Appendices 4a, b and c). Although fines can have glidant effects, depending on their proportion they could also cause an increase in flow time. This is because of their very small size, at which the cohesive forces between the particles become significant.

Fig. 9 and 10 graphically illustrate the effect of the various starches used as binder at different concentrations on the hardness of Sulphadimidine and Promethazine tablets. Increasing the binder concentration resulted in a corresponding increase in tablet hardness. Esezobo and Ambujam (1982); Nasipuri and Akala (1986) and Esezobo (1986) have all made similar reports with different starches. This is because more bonds are formed in the presence of more starch as binder. The amount of bonding that occurs between particles due to asperity melting and

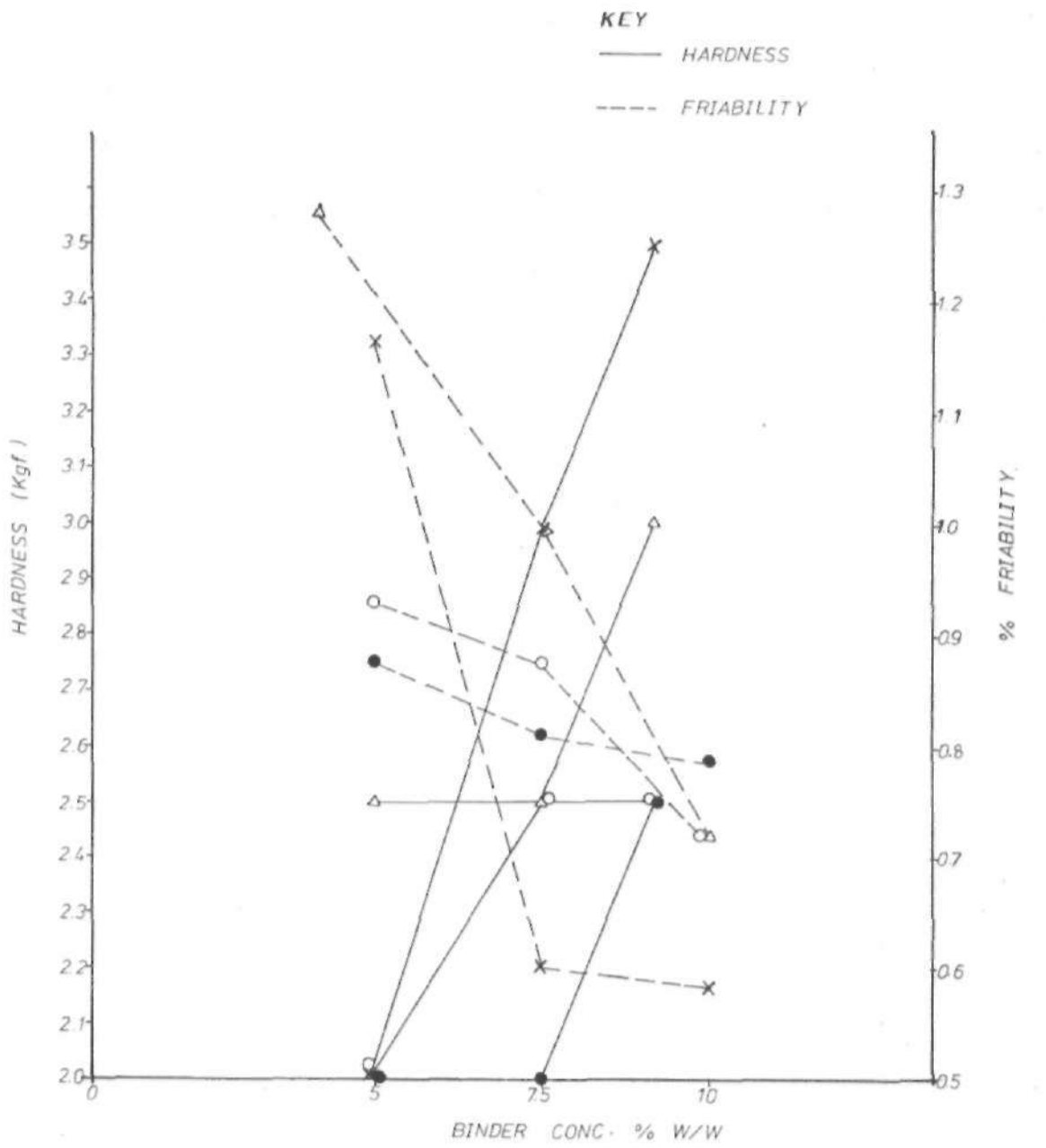


FIG.9 : EFFECT OF BINDER CONCENTRATION ON PROMETHAZINE TABLETS HARDNESS AND FRIABILITY.

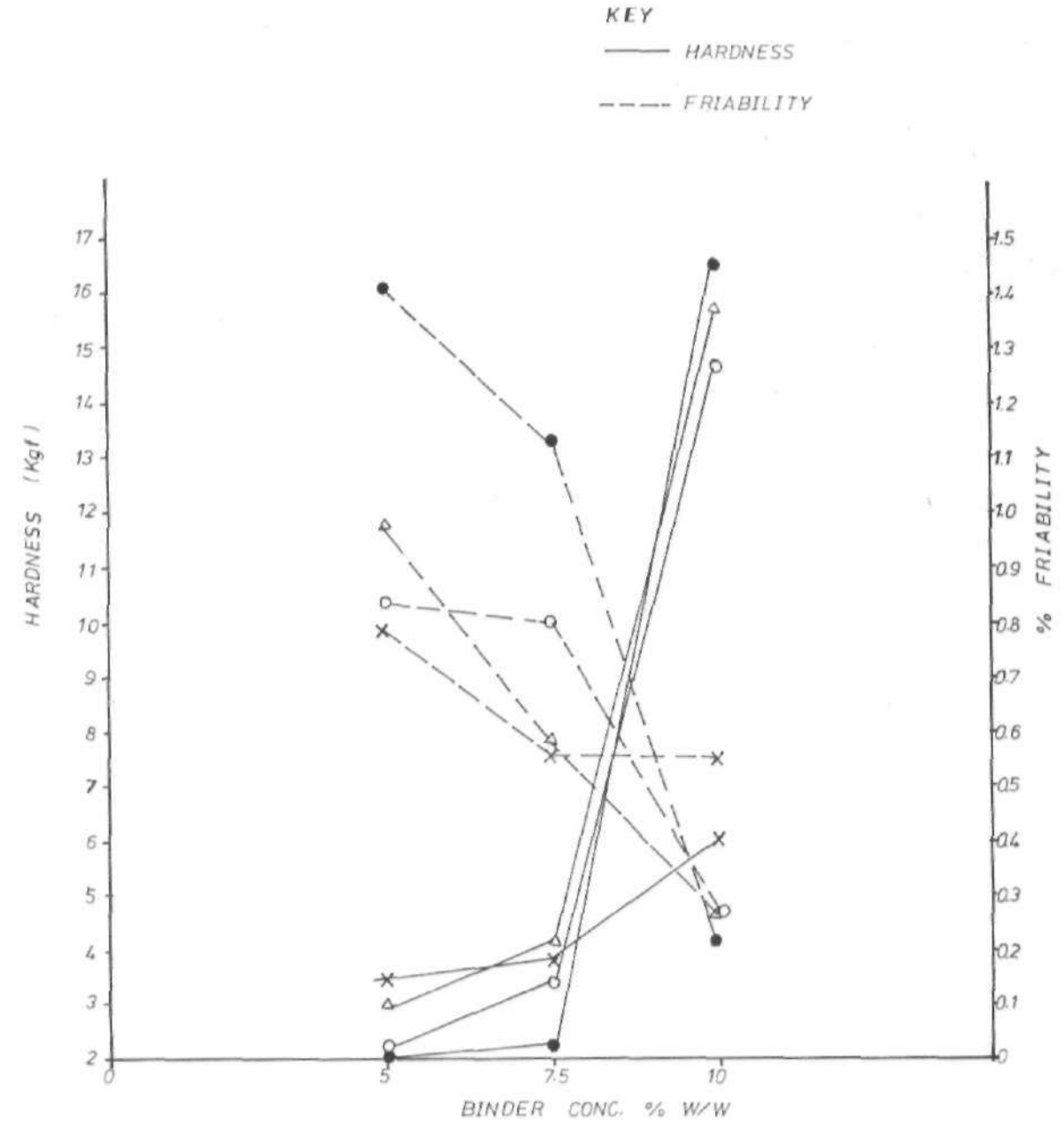


FIG.10: EFFECT OF BINDER CONCENTRATION ON SULPHADIMIDINE TABLETS HARDNESS AND FRIABILITY.

plastic and elastic deformation of the particles and consequently the hardness of the tablets, depends on the compressing force and the amount of binding agent present (York and Pilpel, 1973). Since the compressing force was same for all the batches, the increase in tablet hardness observed can be attributed to the amount and the type of binding agent used.

Changing the binder concentration did not have much effect on the hardness of Promethazine tablets.

The type of starch used as disintegrant and its concentration affected the hardness of both Promethazine and Sulphadimidine tablets. The effect did not follow any definite pattern (Tables 11 and 12). The effect of disintegrant type and concentration on tablet hardness could have been due to the small proportion of the disintegrant that is wetted and acts as binder. Since the amount wetted is not definite, its effect on hardness will also be unpredictable.

The poor compressibility of starch and its inability to adhere to itself and other materials in the tablet in the dry state could be another reason. This is because starch will thus reduce the amount of solid bonds that are formed between drug particles. This effect will increase in the quantity of dry starch present in the formulation.

TABLE 9a: Properties Of Sulphadimidine tablets using 5%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.79	3.5	4	452.39	1,22	1.54	0.79
b	0.98	3	4.15	469.35	1.17	1.54	0.76
c	0.83	2.17	4	452.39	1.22	1.51	0.81
d	1.41	2	4.5	508.94	1.08	1.54	0.70

TABLE 9b: 7.5%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.56	3.67	3.35	378.88	1.45	1.54	0.94
b	0.58	4.17	3.20	361.92	1.52	1.54	0.99
c	0.80	3.46	3.30	373.22	1.47	1.51	0.97
d	1.13	2.33	4	452.39	1.22	1.54	0.79

TABLE 9c: 10%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (mg/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.55	6	3.30	373.22	1.47	1.54	0.97
b	0.27	15.83	3.36	380.01	1.47	1.54	0.97
c	0.28	14.67	3.30	373.22	1.47	1.51	0.97
d	0.22	16.50	3.25	367.57	1.50	1.54	0.97

TABLE 10a: Properties of Promethazine tablets using 5%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	1.17	2	2.10	133.60	1.24	1.54	0.81
b	1.28	2.5	2.17	138.05	1.20	1.54	0.78
c	0.93	2	2.44	155.23	1.07	1.55	0.69
d	0.88	2	2.41	153.32	1.08	1.54	0.70

TABLE 10b: 7.5%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS (kgf)	THICKNESS	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.60	3	2	127.23	1.30	1.54	0.84
b	1.00	2.5	2.2	139.96	1.19	1.54	0.77
c	0.87	2.5	2.12	134.87	1.23	1.55	0.79
d	0.81	2	2.42	153.95	1.08	1.54	0.70

TABLE 10c: 10%w/w Starch mucilage as binder

	% FRIABILITY	HARDNESS	THICKNESS	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.58	3.5	2.49	158.41	1.05	1.54	0.68
b	0.72	3	2.30	146.32	1.13	1.54	0.73
c	0.72	2.5	2.22	141.23	1.18	1.55	0.76
d	0.79	2.5	2.51	159.68	1.04	1.54	0.68

TABLE 11a: Properties Of Sulphadimidine tablets using 5%w/w Starch as disintegrant

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.52	4.35	3.65	412.60	1.33	1.54	0.86
b	0.61	5.17	3.50	395.64	1.39	1.54	0.90
c	0.76	4	3.37	380.95	1.44	1.51	0.95
d	0.94	3.33	3.80	429.55	1.28	1.54	0.83

TABLE 11b: 10%w/w Starch as disintegrant.

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	1.30	6.42	4.14	467.99	1.18	1.54	0.77
b	0.79	5.40	4.29	484.94	1.13	1.54	0.73
c	0.46	8	4.25	480.42	1.15	1.51	0.76
d	0.52	6.20	4.26	481.55	1.14	1.54	0.74

TABLE 11c: 15%w/w Starch as disintegrant.

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	1.06	6.25	4.30	486.07	1.13	1.54	0.73
b	0.68	5	4.25	480.42	1.15	1.54	0.76
c	0.71	7	4.50	508.68	1.08	1.51	0.72
d	0.79	5.5	4.20	474.77	1.16	1.54	0.75

TABLE 12a: Properties of Promethazine tablets using 2.5%w/w Starch as disintegrant.

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.60	3	2	127.23	1.30	1.54	0.84
b	1.00	2.5	2.2	139.96	1.19	1.54	0.77
c	0.87	2.5	2.12	134.87	1.23	1.55	0.79
d	0.81	2	2.42	153.95	1.08	1.54	0.70

TABLE 12b: 5%w/w Starch as disintegrant.

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTION
a	0.66	2.55	2.28	145.05	1.17	1.54	0.76
b	0.80	3.17	2.23	141.87	1.20	1.54	0.78
c	0.68	2.0	2.30	146.32	1.16	1.55	0.75
d	0.84	2.5	2.40	152.68	1.11	1.54	0.72

TABLE 12c: 10%w/w Starch as disintegrant.

	% FRIABILITY	HARDNESS (kgf)	THICKNESS (mm)	VOLUME (mm^3)	BULK DENSITY (gm/ml)	TRUE DENSITY (gm/ml)	PACKING FRACTIO
a	0.62	2	3	190.85	0.93	1.54	0.60
b	0.89	2	2.29	145.68	1.22	1.54	0.79
c	0.72	2.5	2.47	157.13	1.13	1.55	0.73
d	0.80	2	3.03	192.76	0.92	1.54	0.60

Fig. 9 and 10 show the effect of both the type and concentration of starch mucilage on the friability of Sulphadimidine and Promethazine tablets. There was a general decrease in the friability of the tablets with increase in binder concentration. Tablet hardness increased with increase in binder concentration. This result is as expected since like hardness, friability is a measure of the interparticulate cohesiveness which increases with increase in binder concentration.

The packing fraction of the various tablets were calculated. Packing fraction is a measure of how closely packed the particles (granules) in a tablet are. The packing fraction increased with increase in binder concentration while changing the disintegrant concentration did not have much effect on the packing fraction of both Sulphadimidine and Promethazine tablets. Maize starch as binder in Promethazine tablets at 7.5%w/w concentration (Table 10b) and as disintegrant at 2.5%w/w concentration (Table 12a) produced tablets with exceptionally low packing fractions.

Fig. 11 shows the disintegration times of Promethazine tablets using different starches as binders at different concentrations. The results indicate that with all the starches used, the disintegration time of tablets increased as the binder concentration increased,

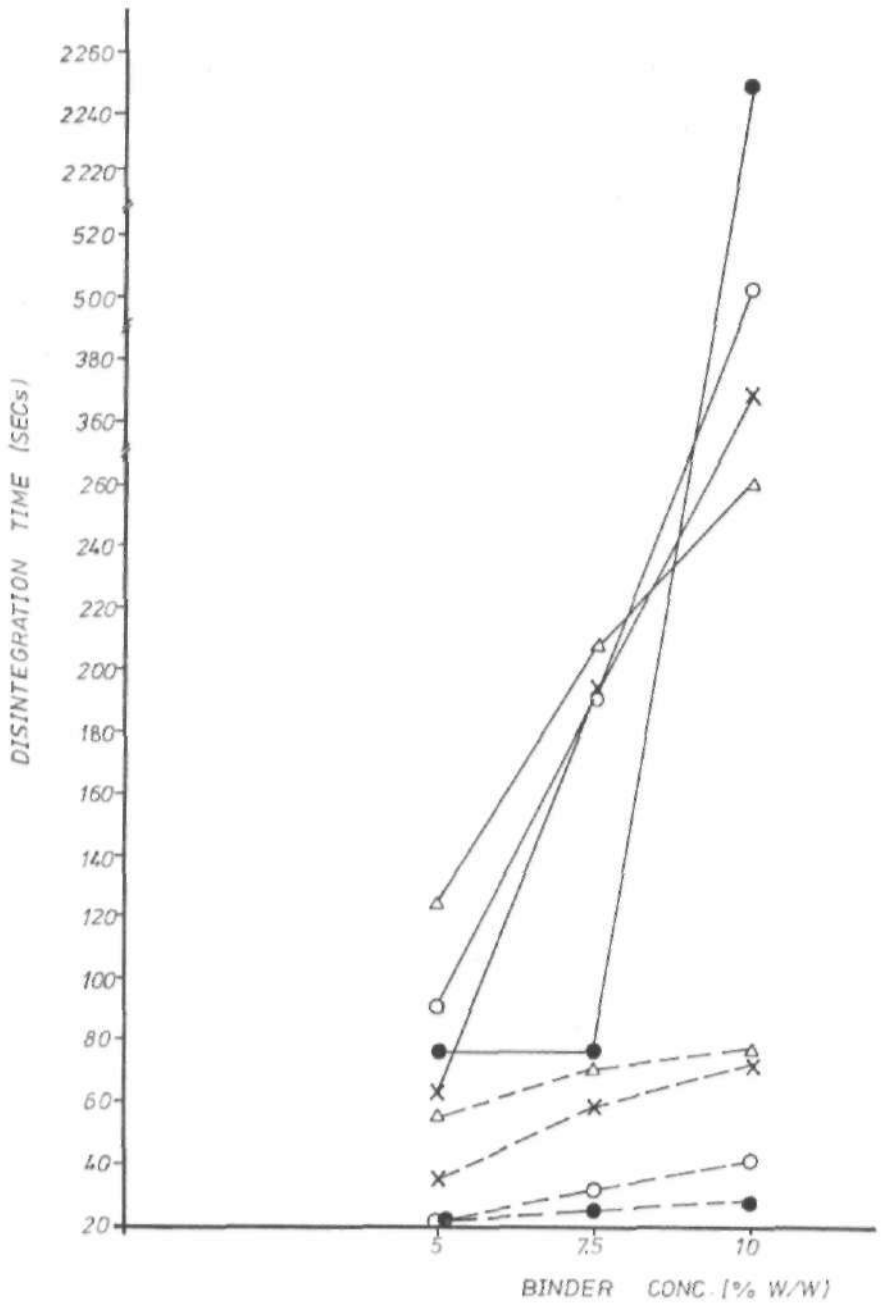


FIG. 11 : EFFECT OF BINDER CONCENTRATION ON TABLET DISINTEGRATION TIME.

KEY:

——— SULPHADIMIDINE

– – – – PROMETHAZINE

the magnitude of which depended upon the type of starch. Similar results were obtained for Sulphadimidine tablets. This is because as the binder concentration increases, the number and strength of the bonds formed between the drug particles increase. The resulting harder tablets are more difficult to penetrate by the disintegration medium and the bonds more difficult to break, hence the extended disintegration time. The nature and strength of the bonds will depend on the properties of the starches hence the difference in the increases in disintegration time when different starches were used.

The increase in disintegration time of Promethazine tablets between 5% and 7.5%w/w binder concentration was much higher than that between 7.5%w/w and 10%w/w. Yam starch was the only exception. Since the disintegration medium has to penetrate the tablet to break it up, the thickness of the mucilagenous barrier formed around the particles by the binder will affect the disintegration time. The thickness of this layer increased substantially between 7.5%w/w and 10%w/w with yam starch rather than between 5% and 7.5%w/w as for the other starches. The change in viscosity of yam starch mucilage between 5% and 7.5%w/w being the lowest as compared to the other starches

as opposed to its change between 7.5% and 10%w/w being the highest supports this suggestion (See Fig. 4).

The increase in the disintegration time (Fig. 17) and packing fraction of Sulphadimidine tablets with increase in binder concentration was highest for maize starch between 7.5% and 10%w/w. This confirms the deduction already made from the result of hardness tests that the bonds formed at this concentration (10%w/w) by maize were the strongest. When compared with the results in Fig. 10, the disintegration time of Sulphadimidine tablets formulated with cocoyam starch as binder was unexpectedly low. Since it has already been stated that cocoyam starch formed very strong bonds, this results could be an indication of very good disintegrating properties. Similar although less obvious results were obtained with yam starch as binder.

At 5%w/w binder concentration, Promethazine tablets formulated with yam and maize starches as binders had the shortest disintegration time with cocoyam having the longest (Fig. 11). At 7.5%w/w, the order was cocoyam yam maize. The order was same at 10%w/w concentration since all the ranking orders were virtually same at all concentration; they must be due to some fundamental property of the starches. The orders correspond with that for swelling power of the starches which is presumably the fundamental property.

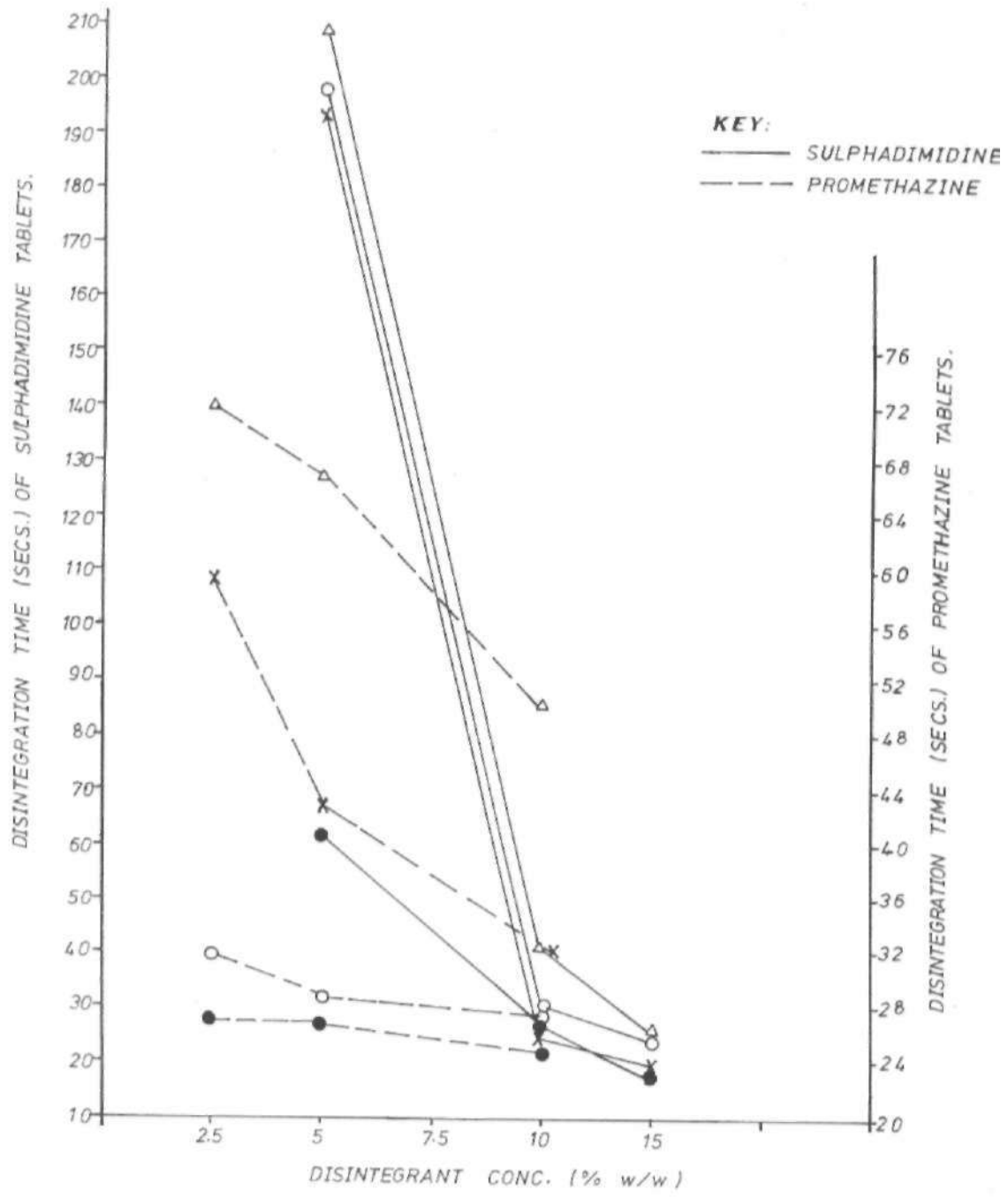


FIG. 12 : EFFECT OF DISINTEGRANT CONC. ON TABLET DISINTEGRATION TIME.

Fig. 12 shows that disintegration times of both Promethazine and Sulphadimidine tablets decreased with increase in disintegrant concentration. The type of starch had more effect on Promethazine tablet disintegration than its concentration; the converse was true for Sulphadimidine tablets. The result for Promethazine tablets could be an indication that swell-rupture is the major process by which these tablets disintegrate. This is because swelling power is a fundamental property of a starch which is greatly influenced by the species of the starch (See Table 3).

At all the disintegrant concentration levels used, maize starch consistently produced Promethazine tablets with the shortest disintegration time followed by yam, cassava and cocoyam in that order. It corresponds to the order for swelling power of the starches (See Table 3).

Based on the swell-rupture theory, the decrease in disintegration time with increase in disintegrant concentration is because as the amount of starch available increases with increased concentration. This then means that there are more starch particles swelling, resulting in faster tablet disintegration. Using the capillary theory on the other hand, the presence of more

starch results in the formation of thicker chains in the pore channel thus enlarging the pores; there will also be more of the chains. This allows water to enter the tablet more easily and cause tablet rupture more readily. Increased starch concentration also fulfils one of the three conditions for rapid disintegration outlined by Lowenthal and Wood (1973). This condition is the presence of sufficient starch agglomerates. As the starch concentration increases, the number and size of such agglomerates will increase resulting in faster tablet disintegration. The two other conditions are: (i) pressure used to form the tablet (since the greater the pressure used, the greater is the fusion of the tablet ingredients and the greater the force needed to disrupt the tablet) and (ii) the presence of water.

At 5%w/w disintegrant concentration, Sulphadimidine tablets formulated with maize starch as disintegrant had the fastest disintegration rate, followed by cassava, yam and cocoyam starches respectively. The order was the same at 15%w/w disintegrant concentration, while at 10%w/w concentration the order was cassava > maize > yam > cocoyam. These ranking orders were similar to that for the swelling power of these starches, so the swell-rupture theory can be used to explain the order (Leach, 1965).

The change in disintegration time of Sulphadimidine tablets with increase in disintegrant concentration from 10%w/w to 15%w/w (Fig. 18) as compared to that obtained between 5%w/w and 10%w/w was very small. Between 10 and 15%w/w disintegrant concentration, the change in tablet disintegration time was approximately same for all of the four starches. This might be an indication that the starches had attained their maximum disintegrating power.

The effect of varying binder concentration on Promethazine tablet dissolution times is shown in Figs.13, 14 and 15. The results show that both the type and concentration of binder affects dissolution time of Promethazine tablets. The type and concentration of disintegrant also affects the dissolution time of tablets (Figs.16, 17 and 18). Similar results were obtained for Sulphadimidine tablets (Figs. 19 to 24).

The t_{50} and t_{90} values for the Promethazine tablets increased as the binder concentration increased Table 13a) from 5%w/w to 7.5%w/w. Similar results have been reported by Jacob and Plein (1968), Sakr et al (1972) and Esezobo and Pilpel (1976). It can be attributed to the increase in the number and strength of the bridges formed with increase in binder concentration resulting in an increase in the time taken to break them down and release the drug

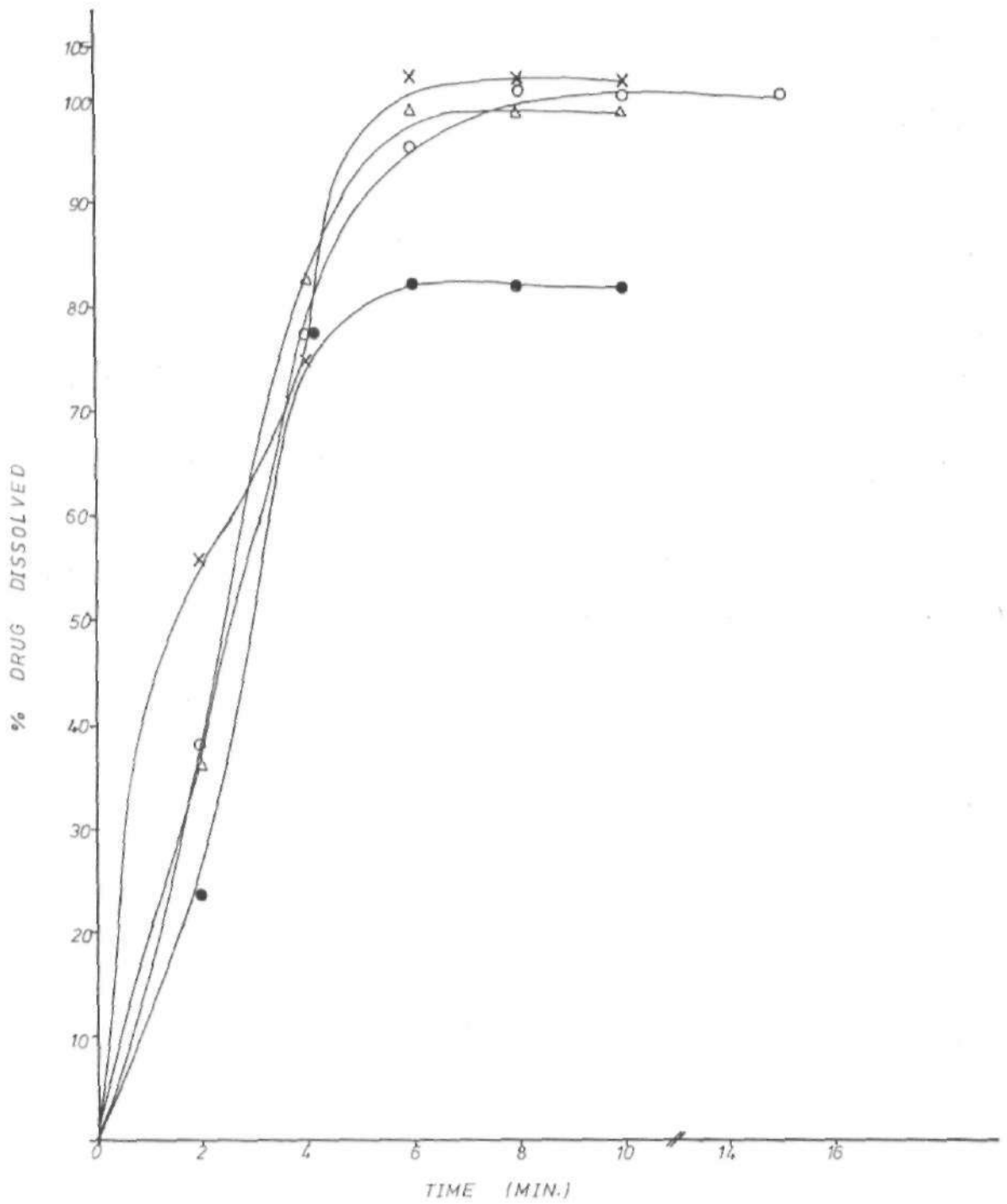


FIG. 13: DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 5% W/W STARCH AS BINDER.

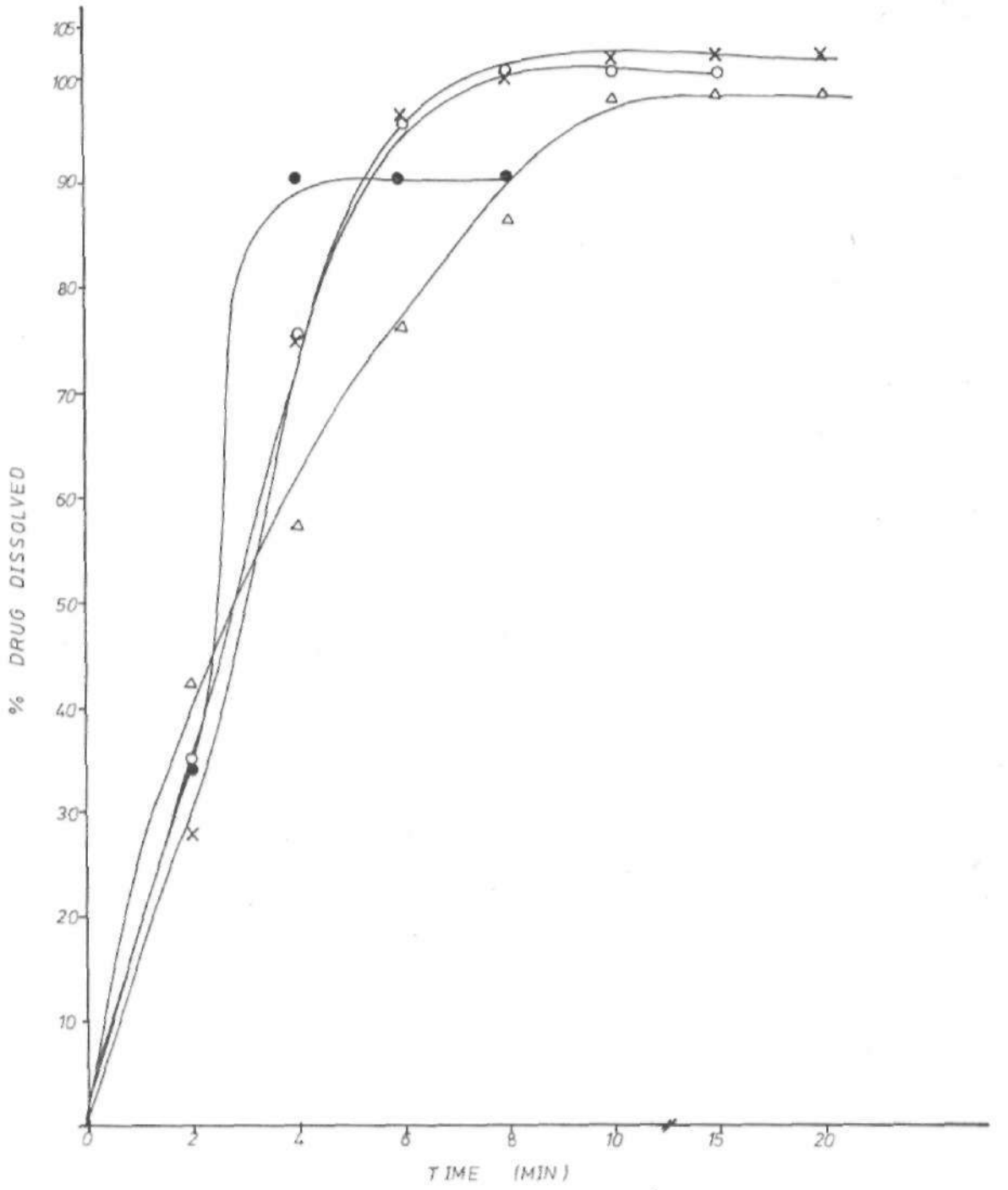


FIG.14 : DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 7.5 % W/W STARCH AS BINDER.

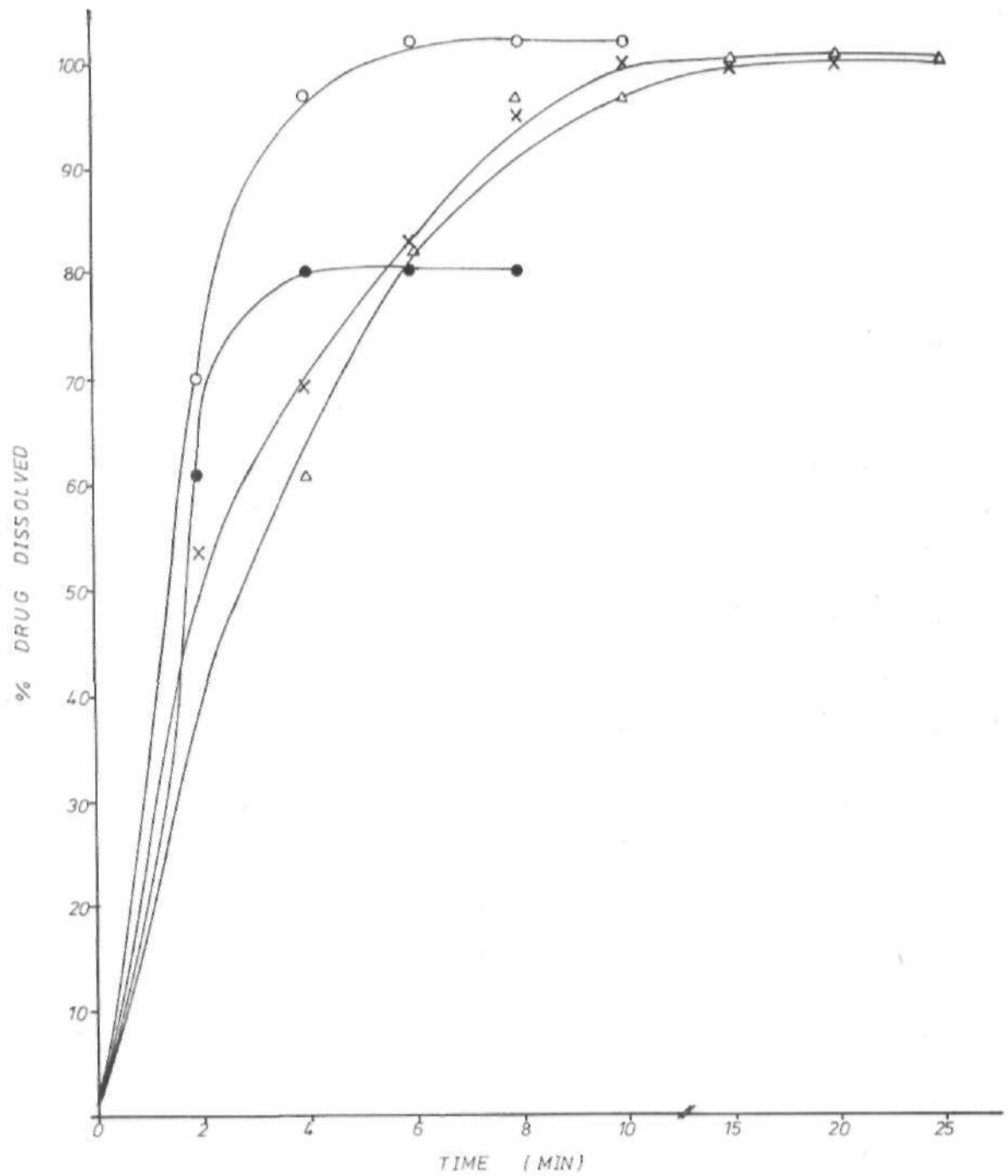


FIG.15: DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 10 % W/W STARCH AS BINDER.

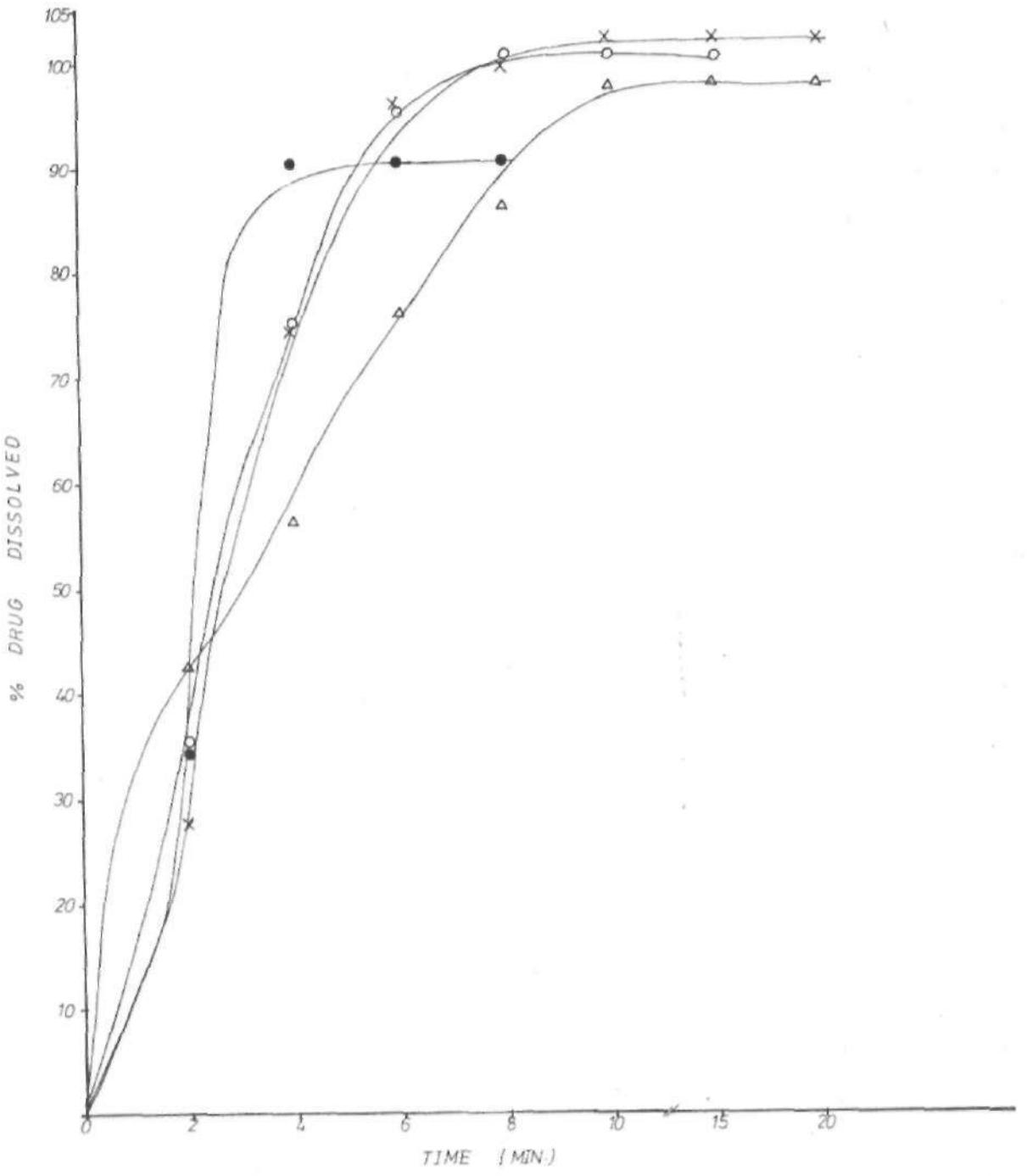


FIG.16 : DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 2.5% W/W STARCH AS DISINTEGRANT.

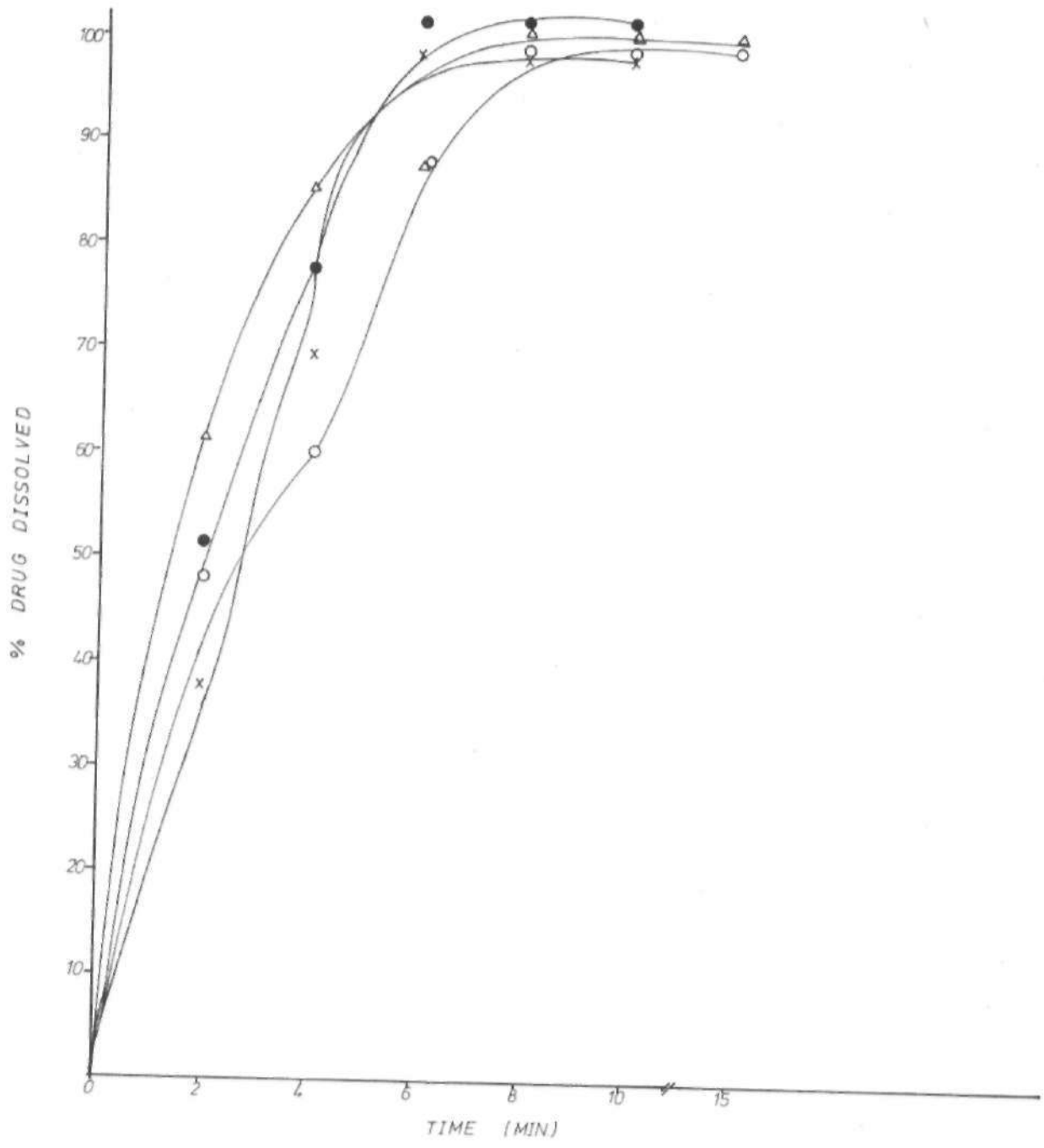


FIG.17 : DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 5% W/W STARCH AS DISINTEGRANT.

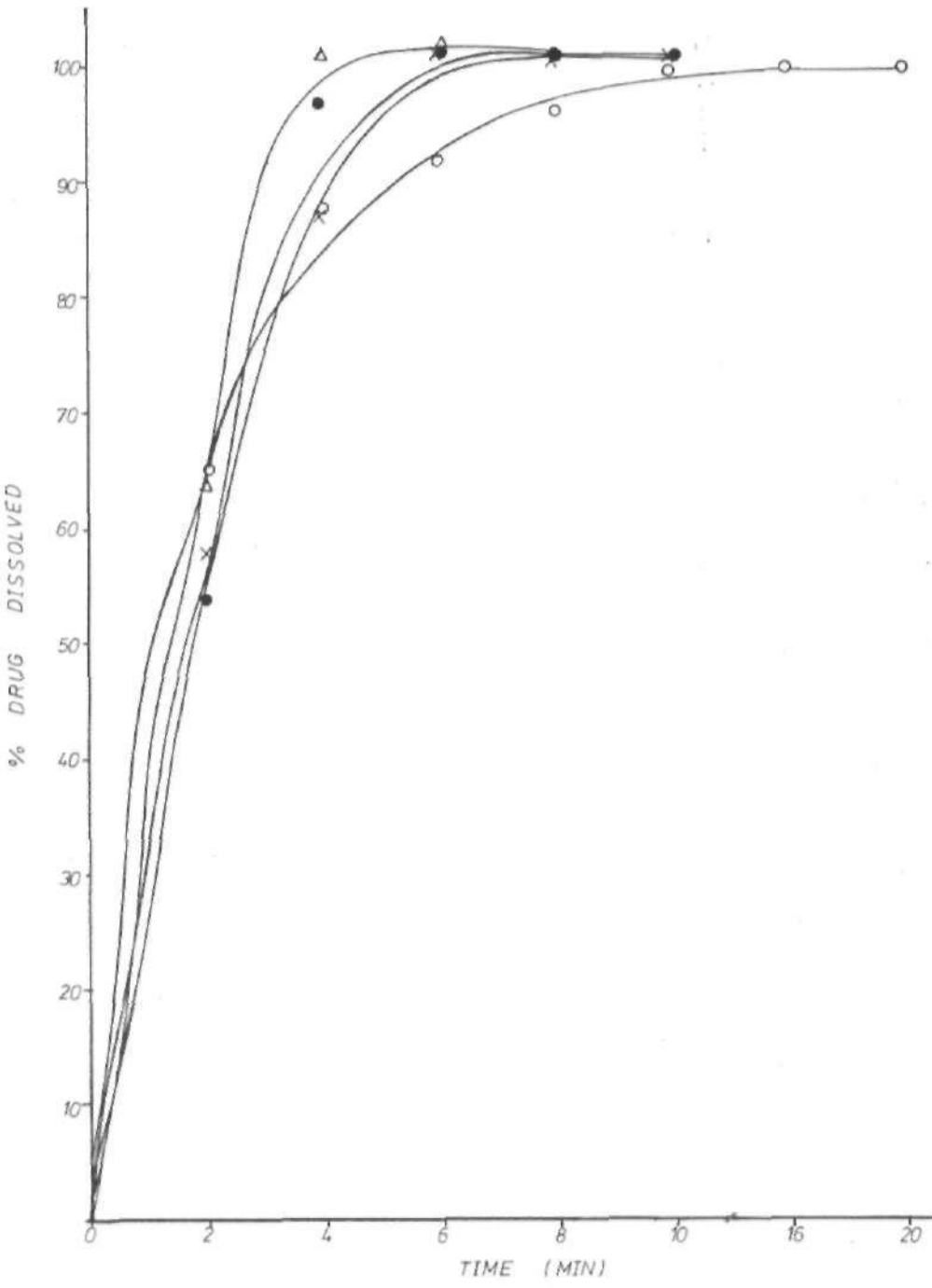


FIG.18: DISSOLUTION RATE PROFILES FOR PROMETHAZINE TABLETS USING 10 % W/W STARCH AS DISINTEGRANT.

TABLE 13a: Effect of binder type and concentration on the dissolution of Promethazine tablets.

Binder Conc.	5%w/w		7.5%w/w		10%w/w	
	T_{50}	T_{90}	T_{50}	T_{50}	T_{50}	T_{90}
a	1.5	4.5	3.1	5.3	2	7
b	2.45	4.6	2.85	8	1.6	7.2
c	2.6	5	2.85	5.4	1.4	3.1
d	3	-	2.5	4.5	1.8	-

TABLE 13b: Effect of disintegrant type and concentration on the dissolution of Promethazine tablets.

Disintegrant Conc.	2.5%w/w		5%w/w		10%w/w	
	T_{50}	T_{90}	T_{50}	T_{90}	T_{50}	T_{90}
a	2.7	5.5	2.7	4.65	1.7	4.2
b	3	8.1	1.35	4.65	1.35	3.9
c	2.5	5.2	2.7	6.5	1.1	5.3
d	2.1	4.8	2	4.8	1.4	2.95

a - Cassava starch

b - Cocoyam "

c - Yam "

d - Maize "

All T_{50} and T_{90} values are in minutes.

content. It is also possible that starch (as binder) may have been distributed as a thin film around the granules and may form a mucilagenous barrier when finished tablets are placed in water (Huber et al, 1964). The thickness of the barrier will be proportional to the concentration of starch present which increases the dissolution time.

The t_{50} values of Promethazine tablets decreased as binder concentration increased from 7.5% to 10%w/w. This was unexpected and could be due to the interaction of the factors that could influence tablet dissolution (Yen, 1963). This interaction could result in unpredictable effects on the dissolution rate of tablets. Such factors include particle size and capillary space size (Adeyemi and Pilpel, 1984) and starch grain size (Underwood and Cadwallader, 1972). Packing fraction also decreased between 7.5% and 10%w/w binder concentration (Tables 10b and c). This decrease could have resulted in faster penetration and eventual disruption of the tablet by the dissolution medium.

At 5%w/w binder concentration (Table 13) cassava and cocoyam starches produced Promethazine tablets with the shortest dissolution time; followed by yam and maize starches. This ranking order is the reverse of that of the apparent viscosities of these starches at this

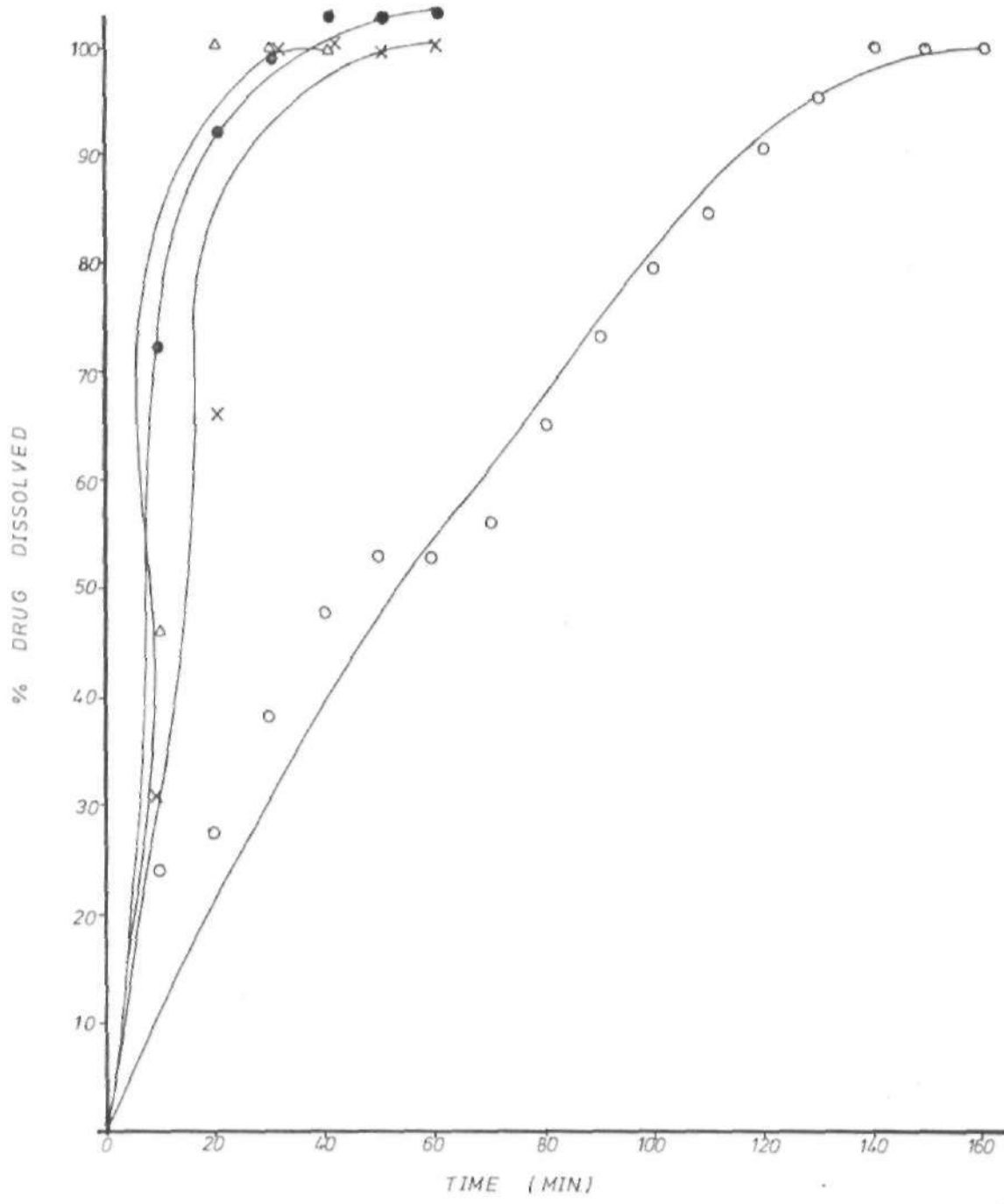


FIG. 19 : DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 5% W/W STARCH MUCILAGE AS BINDER.

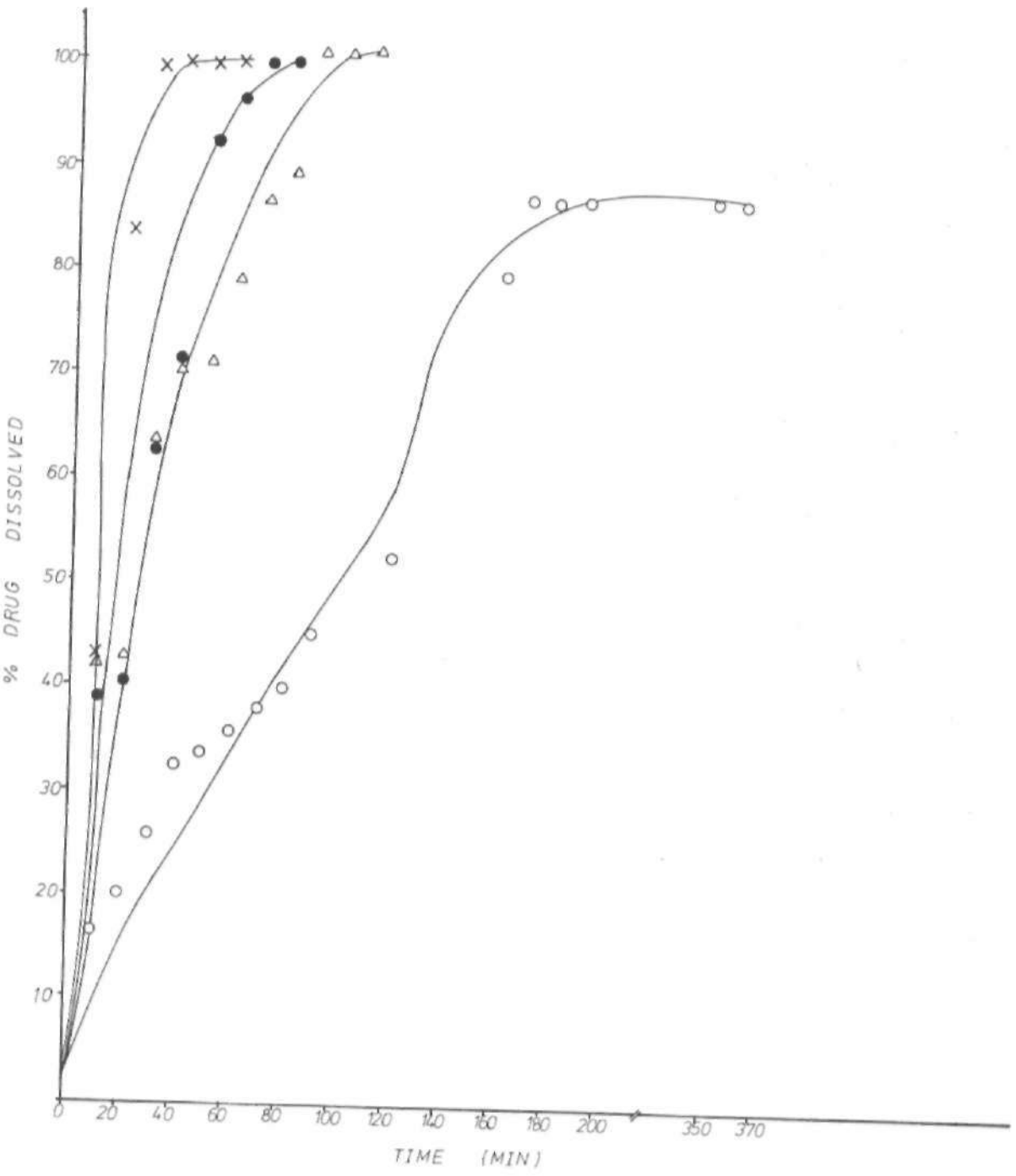


FIG. 20: DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 7.5 % W/W STARCH MUCILAGE AS BINDER.

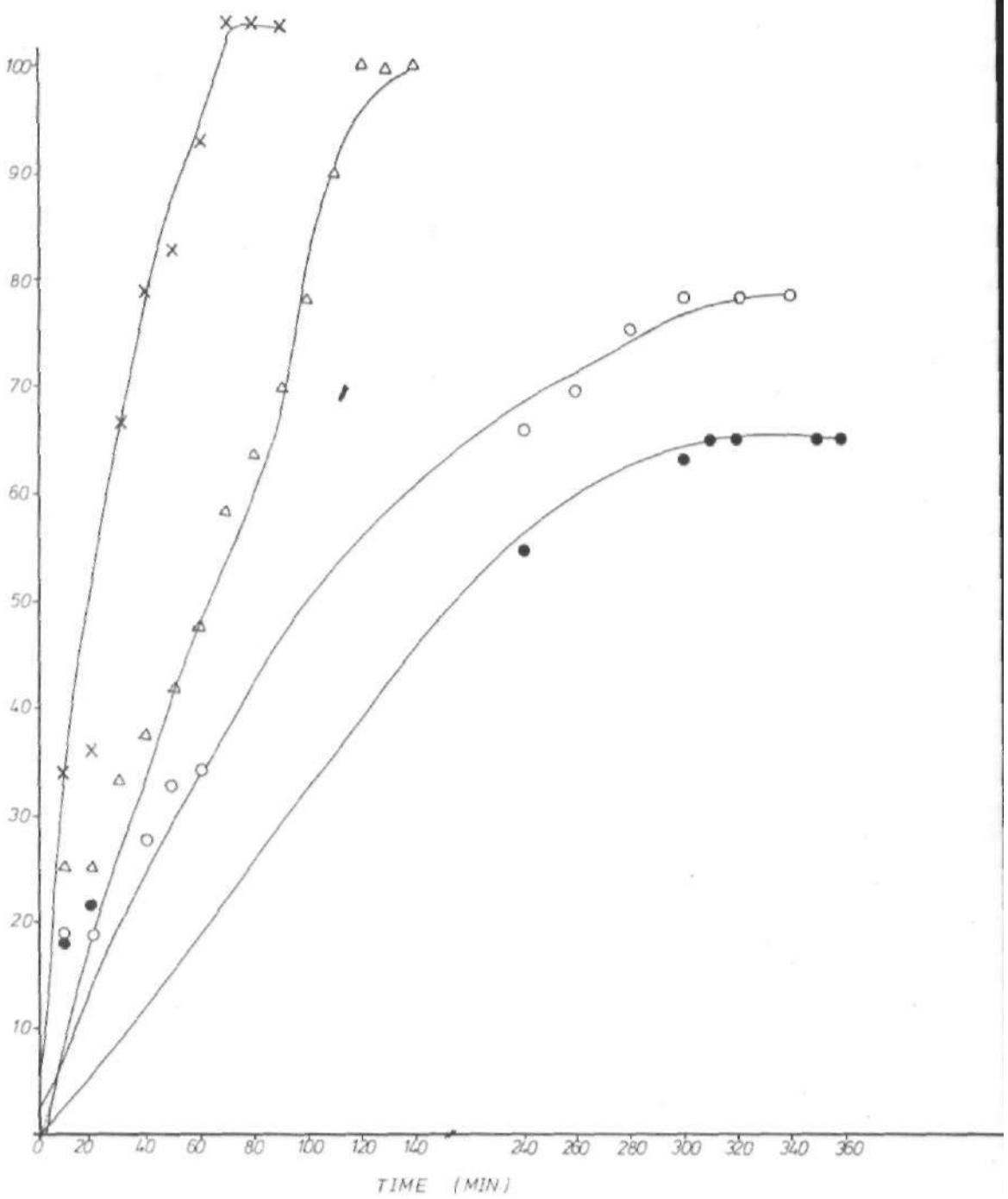


FIG. 21 : DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 10% W/W STARCH MUCILAGE AS BINDER.

TABLE 14a: Effect of binder type and concentration on the dissolution of Sulphadimidine tablets

Binder Conc.	5%w/w		7.5%w/w		10%w/w	
	T_{50}	T_{90}	T_{50}	T_{90}	T_{50}	T_{90}
a	15	25	10	18	18	52
b	9	16	20	69	64	110
c	54	115	100	-	100	-
d	7	18	16	46	154	-

TABLE 14b: Effect of disintegrant type and concentration on the dissolution of Sulphadimidine tablets

Disintegrant Conc.	5%w/w		10%w/w		15%w/w	
	T_{50}	T_{90}	T_{50}	T_{90}	T_{50}	T_{90}
a	10	24	8	17	4	17.5
b	18	70	31	59	20	46
c	90	-	9.5	32	9.5	28
d	18	48	6	43	5.5	30

a - Cassava Starch

b - Cocoyam "

c - Yam "

d - Maize "

All T_{50} and T_{90} values are in minutes.

concentration. This is because as the viscosity of the mucilage increases, 'lumps' of the starch are formed resulting in the presence of aggregates of unbound drug particles which can dissolve more easily than the bound ones. At 7.5%w/w concentration, the dissolution rate was in the order maize > cassava > yam > cocoyam. This was again quite similar to the order for viscosity. At 10%w/w concentration the order was yam > cassava > cocoyam > maize. This order has no relationship with viscosity because all the starches already have very thick highly viscous mucilages, thus eliminating their individual differences.

Increasing the disintegrant concentration resulted in decrease in the dissolution time of Promethazine tablets (Table 13b). Similar results have been reported by Pilpel et al (1978). This could have been because of the more rapid and thorough disintegration of granules with increase in disintegrant concentration (Levy, 1963). At 2.5%w/w disintegrant concentration, maize had the lowest dissolution time, followed by yam, cassava and cocoyam respectively (Fig. 16). A similar ranking order was obtained for the swelling power of the starches. At 10%w/w disintegrant concentration the order was yam > cassava > cocoyam > maize. From the dissolution rate profiles (Figs. 13 to 18) the dissolution rate of

Promethazine tablets formulated with all the starches were similar when the same amount of binder or disintegrant was used. The initial release was very high with all the tablets releasing 100% of their drug content within 15 minutes except in two cases where maize starch did not release up to 100%.

At a binder concentration of 5%w/w, Sulphadimidine tablets prepared with maize starch had the fastest dissolution rate followed by cocoyam, cassava and yam respectively. At a concentration of 7.5%w/w, the order was cassava> maize> cocoyam> yam while at 10%w/w concentration, it was cassava> cocoyam> yam = maize. At a binder concentration of 7.5%w/w starch, Sulphadimidine tablets formulated with yam starch could only release about 88% of their drug content and 79% at 10%w/w concentration. Those formulated with maize starch were only able to release 66% after 6 hours (Table 14a). These tablets were very hard relative to the other tablets (Table 13) with hardness values as high as 16 Kgf. This could have contributed to the delay in dissolution.

Sulphadimidine tablets formulated with yam starch as binder had the poorest dissolution rate properties at all the concentrations used. This is similar to

results obtained by Iwuagwu et al (1986) with white yam starch. They explained that it was due to the formation of very strong bonds between the drug and the starch particles. The size of the yam starch particles might also account for this behaviour. Underwood and Cadwallader (1972), suggested that tablets containing a starch with large particles have a smaller starch particle ratio (less starch separating individual drug particles), so that aggregates of the drug may form. On the other hand, starches with small granule size separate the drug particles and do not allow as much aggregate formation resulting in faster dissolution. Yam starch particles are large size (29.6um) relative to the other starches (See Table 3). The general similarity in the dissolution times of the tablets formulated with the other starches confirms this (Table 14a). At a concentration of 10%w/w binder, Sulphadimidine tablets formulated with yam and maize starches released only 79% and 65.59% respectively of their total drug content after 6 hours. This could have been due to the formation of many strong interparticulate bonds as shown by their hardness and friability values in Fig. 10. Although having similar values of hardness and friability, cocoyam released 100% of its drug content in _ hours.

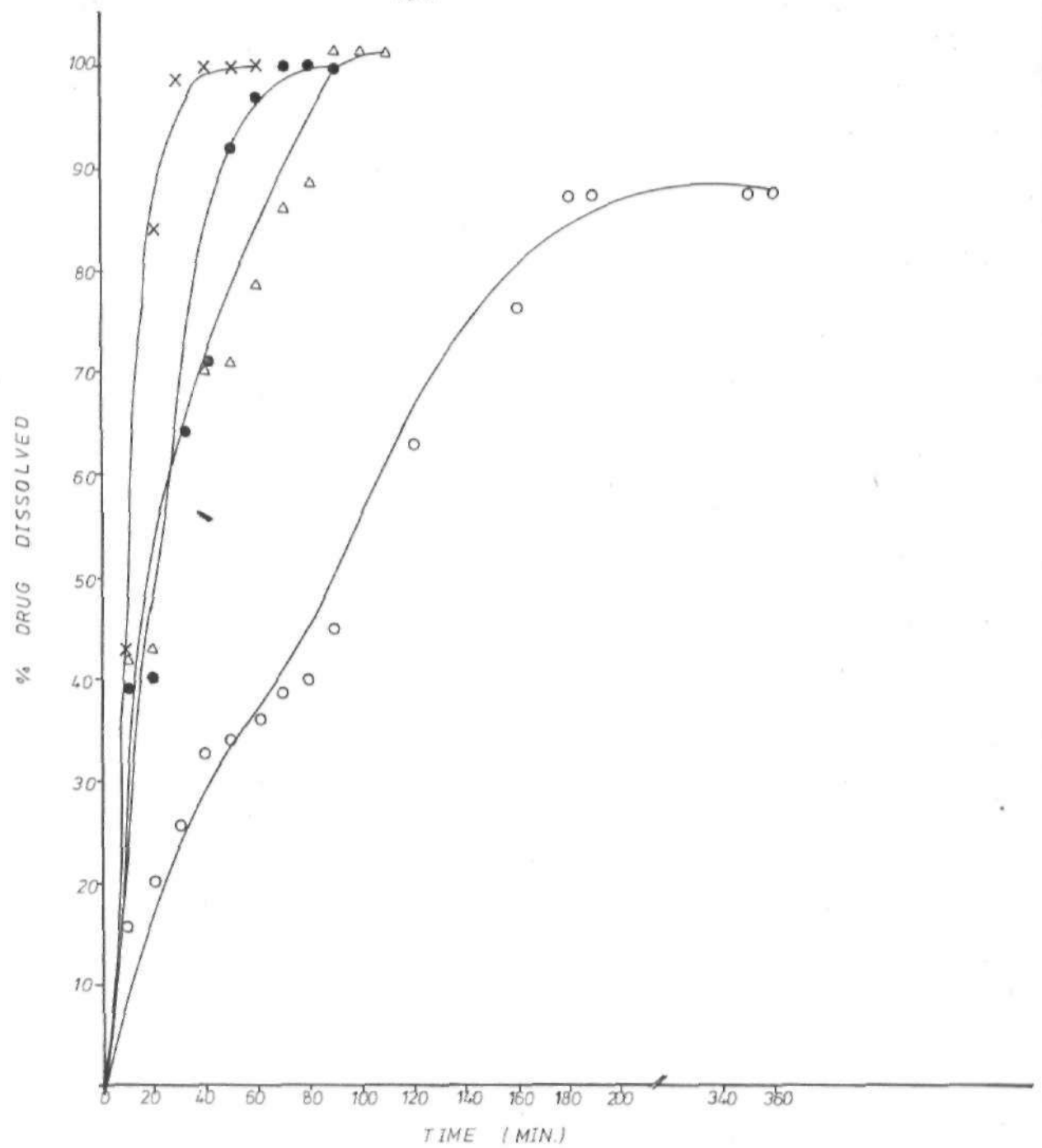


FIG.22: DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 5 % W/W STARCH AS DISINTEGRANT.

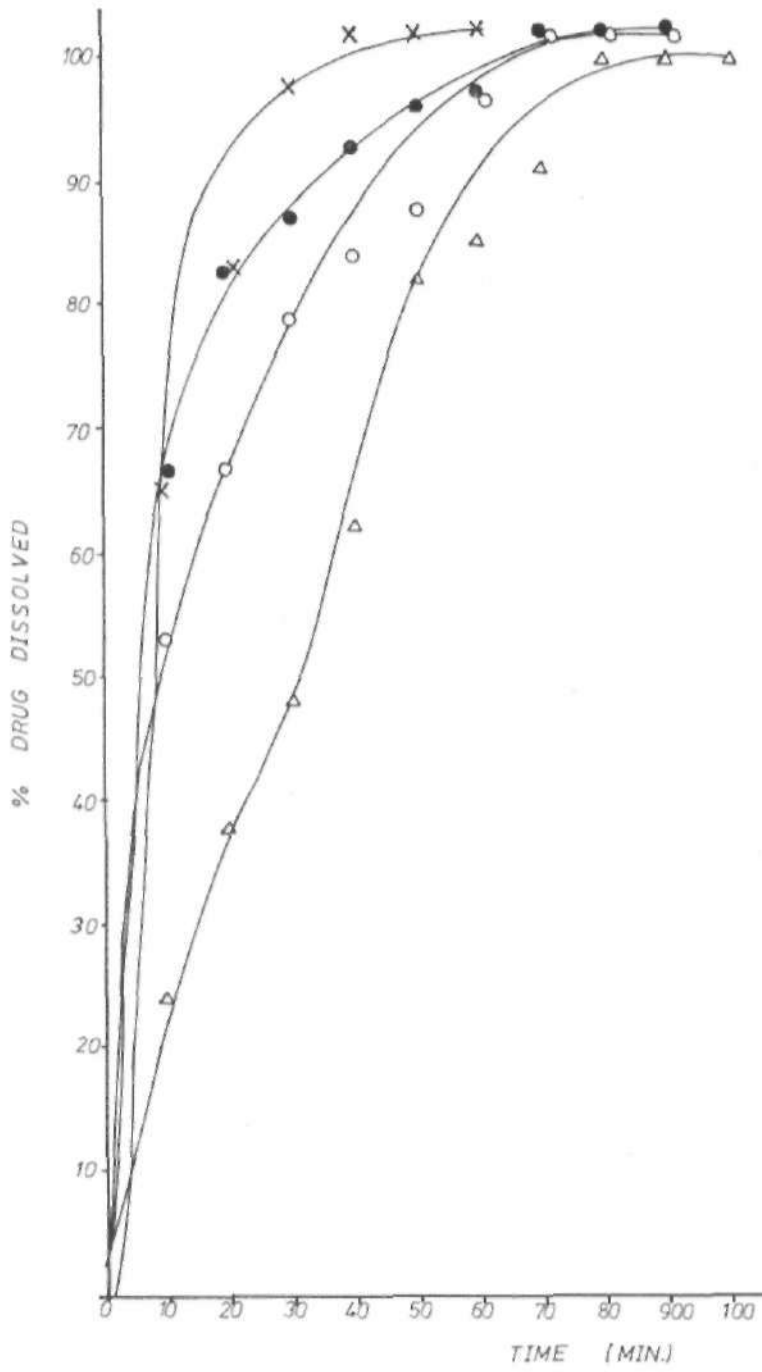


FIG. 23: DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 10% W/W STARCH AS DISINTEGRANT.

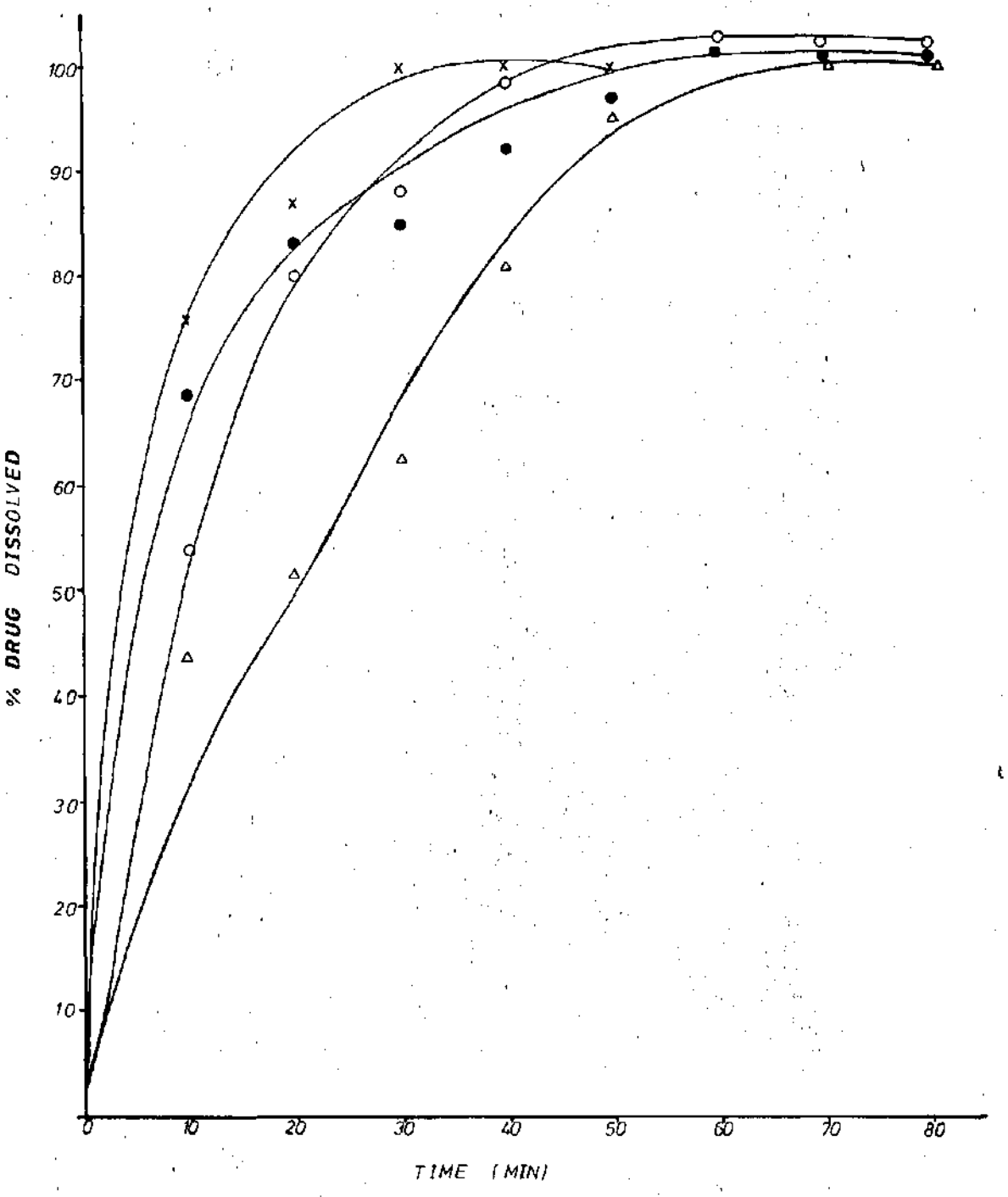


FIG. 24 : DISSOLUTION RATE PROFILES OF SULPHADIMIDINE TABLETS USING 15 % W/W STARCH AS DISINTEGRANT.

Figs. 22, 23 and 24 show that the ranking orders for dissolution rate among the starches used as disintegrant for Sulphadimidine tablets were the same at all the disintegrant concentration levels. The order was cassava> yam> maize> cocoyam. This neither corresponds to that obtained for moisture sorption capacity nor swelling power of the starches as would have been expected. This means that starches when incorporated in tablet formulations behave differently from when they are present alone. These differences in behaviour are due to the complex physico-chemical nature of tablet formulations, since such factors as moisture content, nature and strength of forces holding particles together, plastic and elastic relaxation all influence the properties of a tablet.

Disintegration and dissolution times generally increased with increase in the packing fractions of the tablets. This was the case with both Sulphadimidine and Promethazine tablets. This is because as the granules pack more closely, the time taken for the medium (disintegration/dissolution medium) to penetrate the tablets increases thus increasing the time required to break down the tablet. There were a few exceptions to this general trend. This is because very little swelling of the starch particle will result in the break down of the tablet if the granules are very tightly packed.

CHAPTER 4

SUMMARY AND CONCLUSION

The results obtained show that the type of starch used as binder or disintegrant in tablet formulations affects the properties of granules and tablets. The comparative effects of the starches tested on the properties of granules and tablets differed depending on the property being tested, the concentration of starch used and the nature of the drug.

In general, increasing the concentration of starch mucilage binder produced an increase in the size of granules. It also resulted in an increase in the hardness, disintegration and dissolution times of the tablets while it decreased their friability. These effects were observed with all the starches and in tablet formulations of both soluble and insoluble drugs.

In some cases, the fundamental properties of the starches such as swelling power, starch mucilage viscosity and particle size could completely explain the effects of the starches on granule and tablet properties relative to each other. In other cases, the fundamental properties of the starches could not completely explain the results when used singly. This is due to the complex physico-chemical nature of tablets and the unpredictable interaction of their excipients.

The local starches compared well with the official maize starch at various concentrations of binder and disintegrant under the same experimental conditions.

Each of the local starches could be used as an excipient (binder or disintegrant) in the formulation and production of tablets.

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APPENDIX 1

AMYLOSE - AMYLOPECTIN CONTENT OF STARCHES.

	Cassava	Cocoyam	Yam	Maize
AMYLOSE %	17+	12.8°	17.8*	26+
AMYLOPECTIN	83	87.2	82.2	74

Sources:

+ The Starch Chemistry and Industry by J.W. Knight Pages 7 - 11

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APPENDIX 2a: SIZE DISTRIBUTION OF PROMETHAZINE GRANULES USING 5%w/w STARCH AS BINDER.

Sieve size µm	Weight of granules retained on sieve (gm)				% Retained on Sieve				Cumulative % Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	16.04	9.061	16.06	20.182	16.54	9.39	16.52	20.65	16.54	9.39	16.52	20.65
600	34.67	28.662	41.492	42.032	35.74	29.69	42.69	43.00	52.28	39.08	59.21	63.65
500	11.862	10.03	12.382	10.756	12.23	10.39	12.74	11.00	64.51	49.47	71.95	74.65
355	14.82	16.524	14.636	12.284	15.28	17.12	15.06	12.57	79.79	66.59	87.01	87.22
250	10.522	15.484	6.902	6.02	10.85	16.04	7.10	6.16	90.64	82.63	94.11	93.38
150	6.982	13.672	3.782	3.382	7.20	14.16	3.89	3.46	97.84	96.79	98.00	96.48
Fines	2.106	3.112	1.946	3.10	2.17	3.22	2.00	3.17	100.01	100.01	100	100.01

KEY:

a - Cassava Starch as binder

b - Cocoyam Starch as binder

c - Yam " " "

d - Maize " " "

APPENDIX 2b: SIZE DISTRIBUTION OF PROMETHAZINE GRANULES USING 7.5%w/w STARCH AS BINDER

Sieve size µm	Weight of granules retained on sieve (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	21.934	10.102	17.24	12.970	22.41	10.48	17.24	13.32	22.41	10.48	17.24	13.32
600	38.24	31.336	41.036	41.852	39.06	32.50	42.29	42.97	61.47	42.98	59.53	56.29
500	10.958	10.910	12.268	12.960	11.19	11.32	12.64	13.31	72.66	54.30	72.17	69.60
355	13.276	17.982	14.208	15.118	13.56	18.65	14.64	15.52	86.22	72.95	86.81	85.12
250	8.142	14.268	6.964	7.930	8.32	14.80	7.17	8.14	94.54	87.75	93.98	93.26
150	3.764	9.782	3.582	3.808	3.85	10.15	3.69	3.91	98.39	97.90	97.67	97.17
Fines	1.582	2.032	2.250	2.768	1.60	2.11	2.32	2.84	99.99	100.01	99.99	100.01

APPENDIX 2c: SIZE DISTRIBUTION OF PROMETHAZINE **GRANULES** USING 10%w/w STARCH AS BINDER

Sieve size µm	Weight of granules retained on sieve (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	24.598	14.238	16.696	8.070	25.43	14.50	17.03	8.37	25.43	14.50	17.03	8.37
600	37.714	38.628	41.382	33.030	38.98	39.33	42.22	34.27	64.41	53.83	59.25	42.64
500	9.506	12.600	12.054	12.622	9.83	12.83	12.30	13.10	74.24	66.66	71.55	55.74
355	11.402	16.828	14.074	17.768	11.79	17.14	14.36	18.44	86.03	83.80	85.91	74.18
250	6.56	9.308	7.172	12.696	6.78	9.48	7.32	13.17	92.81	93.28	93.23	87.35
150	4.388	4.738	3.954	8.338	4.54	4.83	4.03	8.65	97.35	98.11	97.26	96
Fines	2.582	1.864	2.690	3.854	2.67	1.90	2.74	4.00	100.02	100.01	100	100

APPENDIX 3a: SIZE DISTRIBUTION OF PROMETHAZINE GRANULES USING 2.5%w/w STARCH AS DISINTEGRANT

Sieve size μm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	21.934	10.102	16.728	12.970	22.41	10.48	17.24	13.32	22.41	10.48	17.24	13.32
600	38.24	31.386	4.036	41.852	39.06	32.50	42.29	42.97	61.47	42.98	59.53	56.29
500	10.958	10.910	12.268	12.960	11.19	11.32	12.64	13.31	72.66	54.30	72.17	69.60
355	13.276	17.982	14.208	15.118	13.56	18.65	14.64	15.52	86.22	72.95	86.81	85.12
250	8.142	14.268	6.964	7.930	8.32	14.80	7.17	8.14	94.54	87.75	93.98	93.26
150	3.764	9.782	3.582	3.808	3.85	10.15	3.69	3.91	98.39	97.90	97.67	97.17
Fines	1.582	2.032	2.250	2.768	1.60	2.11	2.32	2.84	99.99	100.01	99.99	100.01

KEY:

a - Promethazine granules using Cassava Starch as disintegrant

b - " " " Cocoyam " " "

c - " " " Yam " " "

d - " " " Maize " " "

APPENDIX 3b: SIZE DISTRIBUTION OF PROMETHAZINE GRANULES USING 5%w/w STARCH AS DISINTEGRANT

Sieve size µm	Weight of granules retained on Sieve (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	14.222	16.430	20.636	9.454	14.66	16.64	21.15	9.66	14.66	16.64	21.15	9.66
600	29.866	35.630	40.990	26.396	30.79	36.09	42.00	26.98	45.45	52.73	63.15	36.64
500	11.048	12.002	11.900	10.850	11.39	12.16	12.19	11.09	56.84	64.89	75.31	47.73
355	17.420	16.128	13.264	17.488	17.96	16.34	13.59	17.88	74.80	81.23	88.90	65.61
250	17.310	13.238	8.276	20.700	17.85	12.40	8.48	21.16	92.65	93.63	97.38	86.77
150	5.152	3.616	1.020	9.132	5.31	3.66	1.05	9.34	97.96	97.29	98.43	96.11
Fines	1.976	1.670	1.500	3.804	2.04	1.69	1.54	3.89	100	98.98	99.97	100

APPENDIX 3c: SIZE DISTRIBUTION OF PROMETHAZINE GRANULES USING 10%w/w STARCH DISINTEGRANT

Sieve size µm	Weight of granules retained on Sieve (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	10.288	18.338	15.728	11.932	10.44	18.45	16.12	12.24	10.44	18.45	16.12	12.24
600	25.90	40.408	33.680	28.834	26.27	40.65	34.52	29.59	36.71	59.10	50.64	41.83
500	12.142	12.990	11.050	11.246	12.32	13.07	11.33	11.54	49.03	72.17	61.97	53.37
355	21.566	16.020	15.738	16.940	21.87	16.12	16.13	17.38	70.90	88.29	78.10	70.75
250	21.838	9.652	14.170	17.774	22.15	9.71	14.52	18.24	93.05	98.00	92.62	88.99
150	5.184	1.300	4.570	6.814	5.26	1.31	4.68	6.99	98.31	99.31	97.30	95.98
Fines	1.672	0.690	2.64	3.914	1.70	0.69	2.71	4.02	100.01	100	100.01	100

APPENDIX 4a: SIZE DISTRIBUTION OF SULPHADIMIDINE GRANULES USING 5%w/w OF EACH STARCH AS BINDER

Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	21.8809	7.7075	11.561	12.5295	22.13	7.94	11.90	12.76	22.13	7.94	11.90	12.76
600	32.0899	30.0493	35.6973	40.0845	32.45	30.94	36.74	40.82	54.58	38.88	48.64	53.58
500	11.1130	18.7325	13.0915	14.9153	11.24	19.29	13.47	15.19	65.82	58.17	62.11	68.77
355	9.2378	16.5075	13.2913	14.9923	9.34	17.00	13.68	15.27	75.16	75.17	75.79	84.04
250	6.7983	12.0325	9.4950	8.5723	6.88	12.39	9.77	8.73	82.04	87.56	85.56	92.77
150	6.1314	7.0075	6.4435	3.9473	6.20	7.22	6.63	4.02	88.24	94.78	92.19	96.79
Fines	11.6267	5.0833	7.5888	3.1473	11.76	5.23	7.81	3.21	100	100.01	100	100

KEY:

a - Sulphadimidine granules using cassava starch as binder and disintegrant

b - Sulphadimidine granules using cocoyam starch as binder and disintegrant

c - Sulphadimidine granules using yam starch as binder and disintegrant

d - Sulphadimidine granules using maize starch as binder and disintegrant.

APPENDIX 4b: SIZE DISTRIBUTION OF SULPHADIMIDINE GRANULES USING 7.5%w/w OF EACH STARCH AS BINDER

Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	13.0632	14.2599	25.2825	12.291	13.26	14.49	26.00	12.59	13.26	14.49	26.00	12.59
600	37.0529	44.3644	26.8325	34.8335	37.61	45.08	27.60	35.69	50.87	59.57	53.60	48.28
500	11.8113	14.9902	7.4530	13.3585	11.99	15.23	7.67	13.69	62.86	74.8	61.27	61.97
355	11.6181	5.7153	7.3825	13.7310	11.79	5.81	7.59	14.07	74.65	80.61	68.86	76.04
250	8.0166	8.3467	6.6075	9.7723	8.14	8.48	6.80	10.01	82.79	89.09	75.66	86.05
150	6.8775	4.9301	7.5705	6.3923	6.98	5.01	7.79	6.55	89.77	94.1	83.45	92.60
Fines	10.0858	5.8124	16.0825	7.2288	10.24	5.91	16.54	7.41	100.01	100.01	99.99	100.01

APPENDIX 4c: SIZE DISTRIBUTION OF SULPHADIMIDINE GRANULES USING 10%w/w OF EACH STARCH AS BINDER

Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	21.7460	29.12	11.7504	36.2395	22.32	30.06	1.89	37.11	22.32	30.06	11.89	37.11
600	38.5563	31.8903	34.4363	28.1223	39.53	32.93	34.85	28.80	61.85	62.99	46.78	65.91
500	10.8450	7.6410	14.5697	6.7625	11.12	7.89	14.75	6.93	72.97	70.88	61.53	72.84
355	10.5200	6.9000	15.1213	6.6048	10.79	7.12	15.30	6.76	83.76	78	76.83	79.60
250	6.3245	4.6973	10.5515	5.2723	6.48	4.85	10.68	5.40	90.24	82.85	87.51	85
150	4.0988	10.0115	6.7126	6.2570	4.20	10.34	6.79	6.41	94.44	93.19	94.30	91.41
Fines	5.4515	6.5973	5.6681	8.3938	5.59	6.81	5.74	8.60	100.03	100	100.04	100.01

APPENDIX 5a: SIZE DISTRIBUTION OF SULPHADIMIDINE GRANULES USING 5%w/w STARCH AS DISINTEGRANT

Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	13.0632	14.2599	25.2825	12.291	13.26	14.49	26	12.59	13.26	14.49	26.00	12.59
600	37.0529	44.364	26.8325	34.8335	37.61	45.08	27.6	35.69	50.87	59.57	53.60	48.28
500	11.8113	14.9902	7.4530	13.3585	11.99	15.23	7.67	7.69	13.69	62.86	74.8	61.97
355	11.6181	5.7153	7.3825	13.7310	11.79	5.81	7.59	14.07	74.65	80.61	68.86	76.04
250	8.0166	8.3467	6.6075	9.7723	8.14	8.48	6.80	10.01	82.79	89.09	75.66	86.05
150	6.8775	4.9301	7.5705	6.3923	6.98	5.01	7.79	6.55	89.77	94.1	83.45	92.60
Fines	10.0858	5.8124	16.0825	7.2288	10.24	5.91	16.54	7.41	100.01	100.01	99.99	100.01

KEY:

a - Sulphadimidine granules using Cassava Starch as binder & Disintegrant

b - " " " Cocoyam " " " "

c - " " " Yam " " " "

d - " " " Maize " " " "

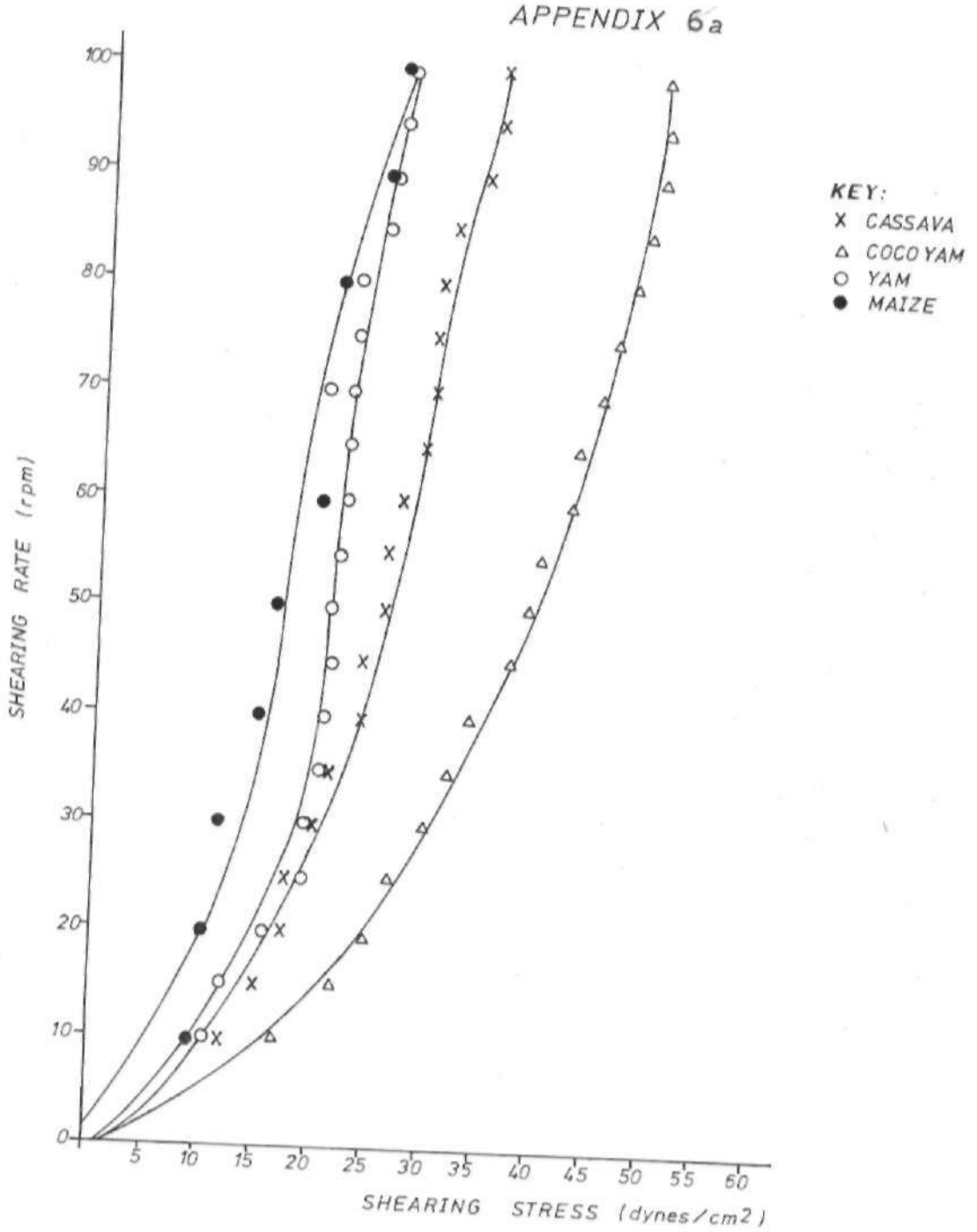
APPENDIX 5b: GRANULE SIZE DISTRIBUTION OF SULPHADIMIDINE USING 10% STARCH AS DISINTEGRANT

Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	14.2197	17.4511	13.6031	18.3957	14.46	17.65	13.95	18.92	14.46	17.65	13.95	18.92
600	33.8676	35.4293	31.1048	37.1901	34.44	35.03	36	38.25	48.90	52.68	49.95	57.17
500	11.4564	19.4977	11.2823	20.2139	11.65	19.72	11.57	20.79	60.55	72.40	62.52	77.96
355	9.4700	8.1669	8.7665	6.9519	9.63	8.26	8.99	7.15	70.18	80.86	70.51	85.11
250	15.8718	9.3138	13.5544	7.5158	16.14	9.42	13.90	7.73	86.32	90.28	84.41	92.84
150	8.3686	6.3476	7.7036	5.5712	8.51	6.42	7.90	5.72	94.83	96.70	92.31	98.56
Fines	5.0939	3.2925	7.5085	1.3904	5.18	3.33	7.70	1.43	100.01	100.03	100.01	99.99

APPENDIX 5c: SIZE DISTRIBUTION OF SULPHADIMIDINE GRANULES USING 15%w/w STARCH AS DISINTEGRANT

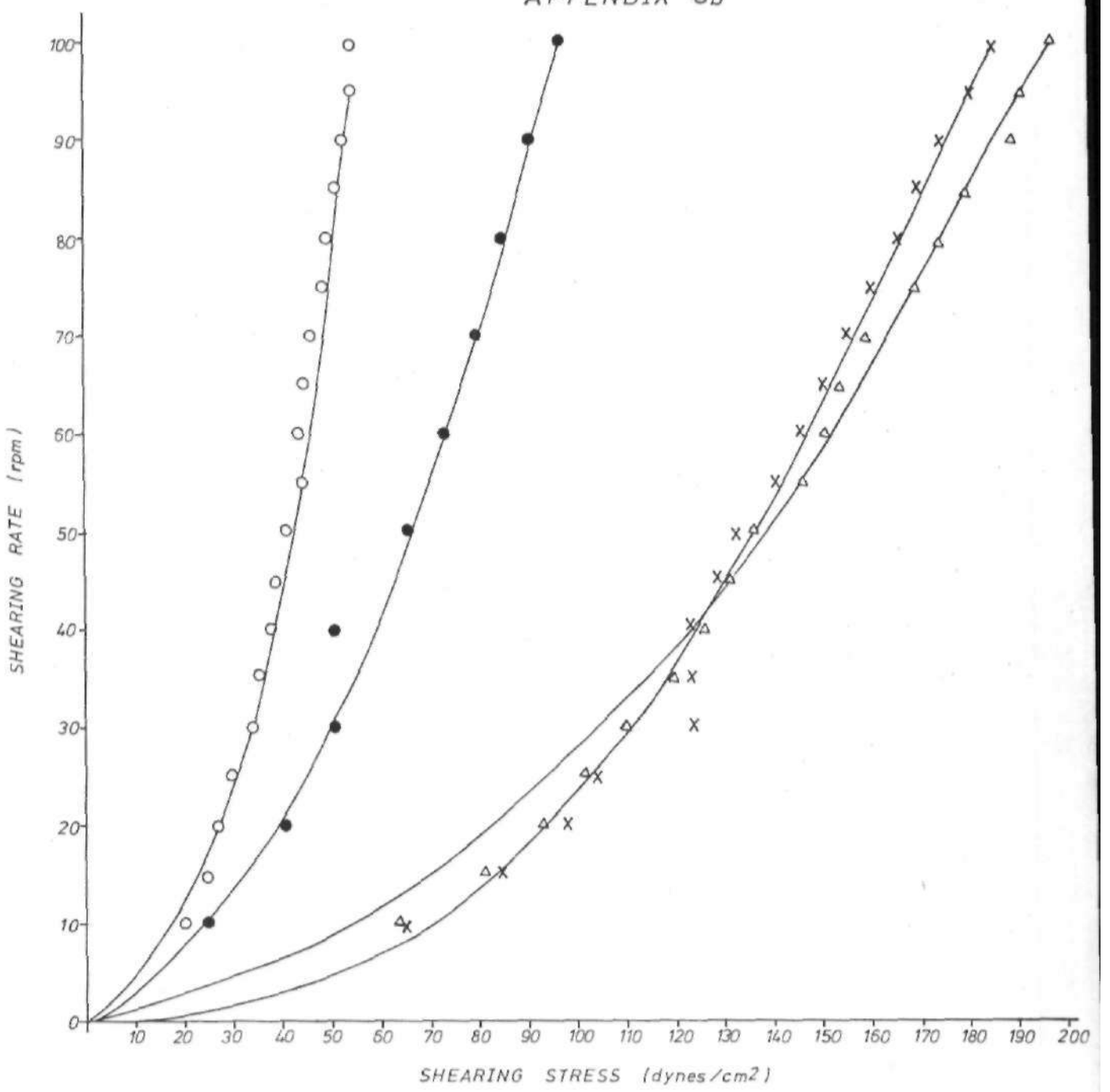
Sieve size µm	Weight of Granules (gm)				% Retained on Sieve				% Cumulative Oversize			
	a	b	c	d	a	b	c	d	a	b	c	d
1000	13.3557	16.2463	15.2309	16.5144	13.53	16.49	15.47	16.99	13.53	16.49	15.47	16.99
600	30.0267	28.5123	38.8993	38.404	30.42	28.94	39.51	37.28	43.95	45.43	54.98	54.27
500	11.4698	20.266	12.1788	21.3258	11.62	20.57	12.37	21.94	55.57	66.90	67.35	75.94
355	12.0028	5.2217	9.5599	7.5428	12.16	5.30	9.71	7.76	67.73	71.3	76.71	83.7
250	16.03	13.8128	9.7568	7.5428	16.24	14.02	9.91	7.76	83.97	85.32	86.62	91.46
150	9.0021	8.2365	7.9945	6.804	9.12	8.36	8.12	7	93.09	93.68	94.74	98.46
Fines	6.8207	6.2266	5.1787	1.4969	6.91	6.32	5.26	1.54	100	100	100	100

APPENDIX 6a



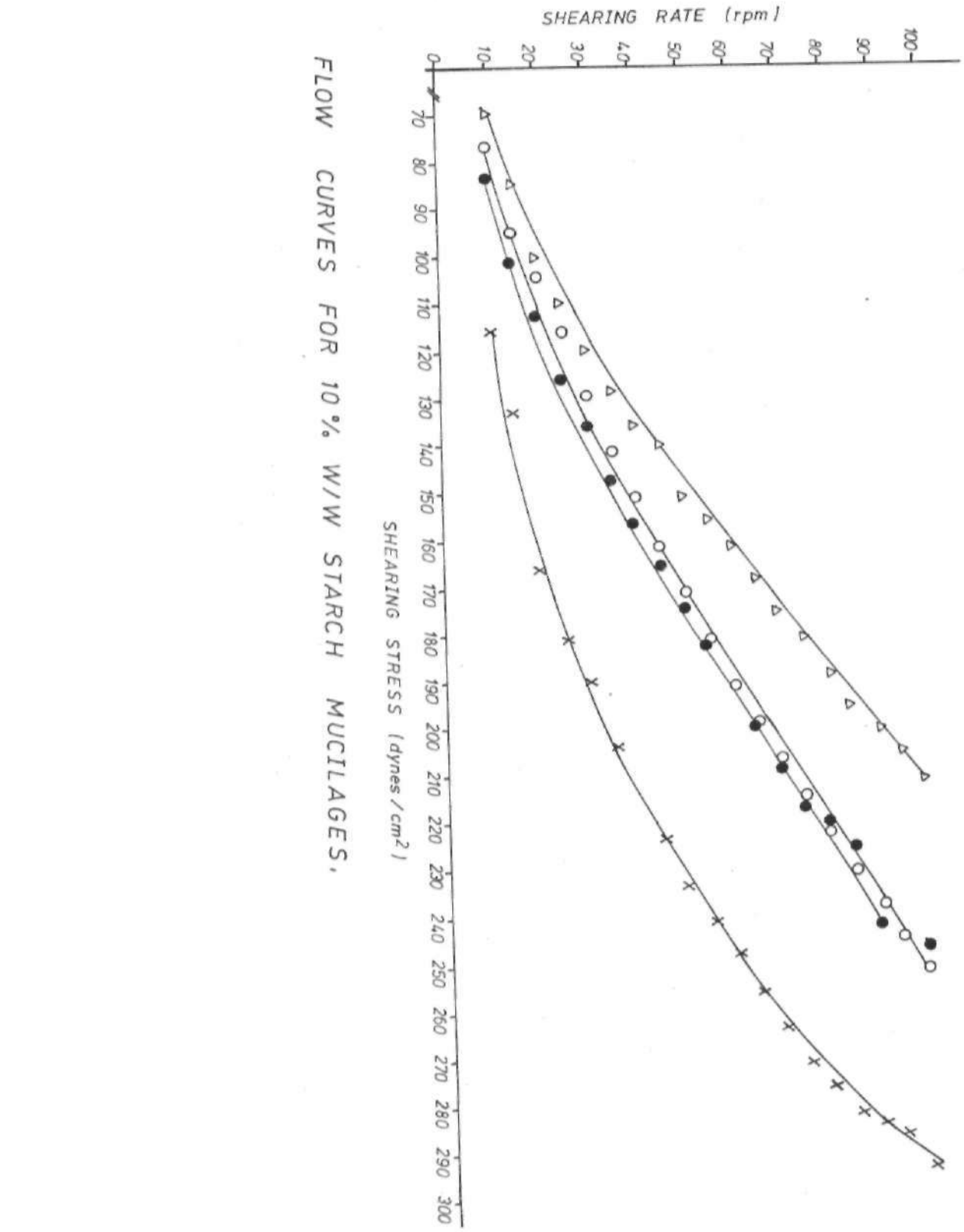
FLOW CURVES FOR 5 % W/W STARCH MUCILAGES .

APPENDIX 6b



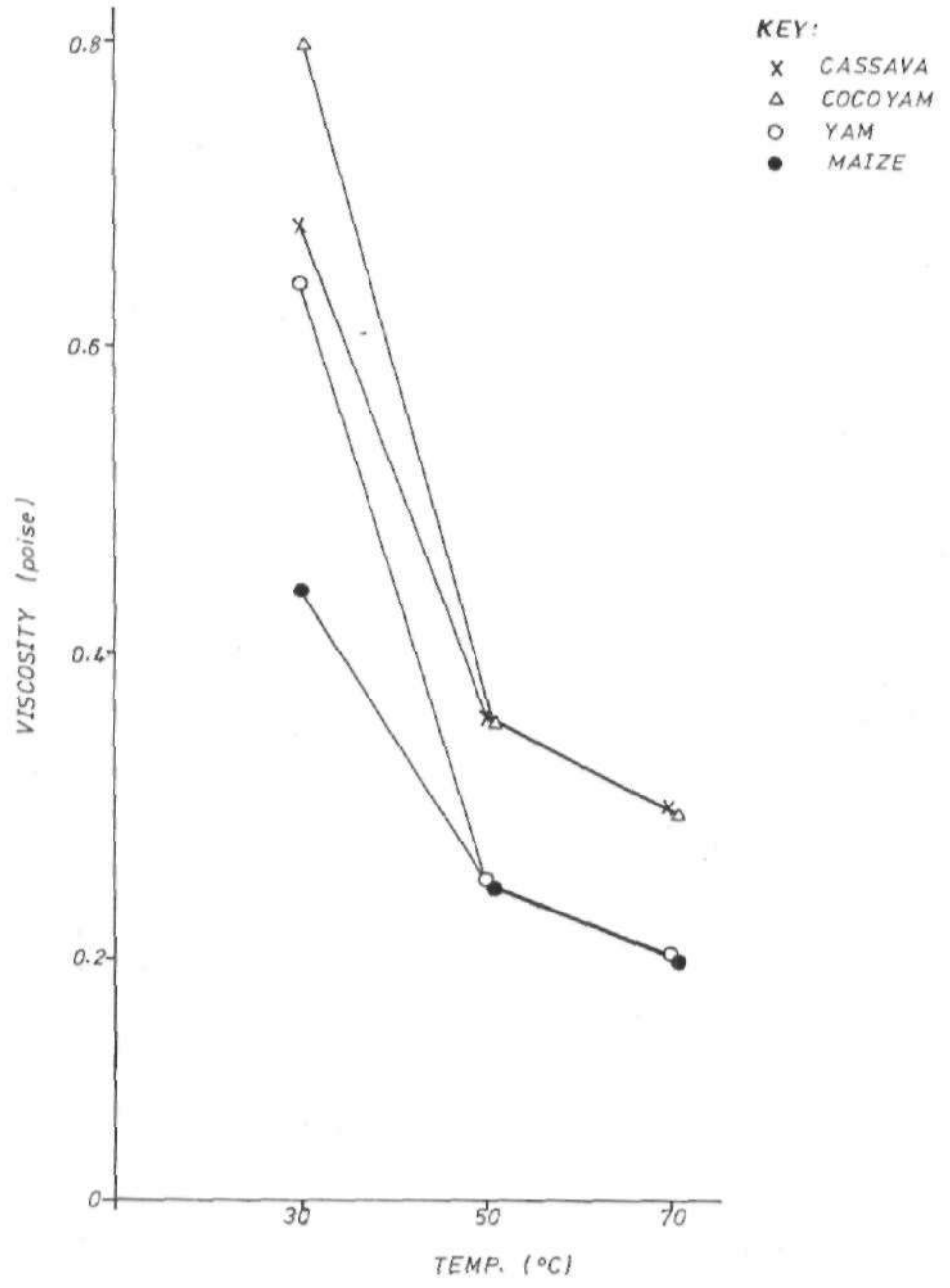
FLOW CURVES FOR 7.5 % W/W STARCH MUCILAGES.

APPENDIX 6c



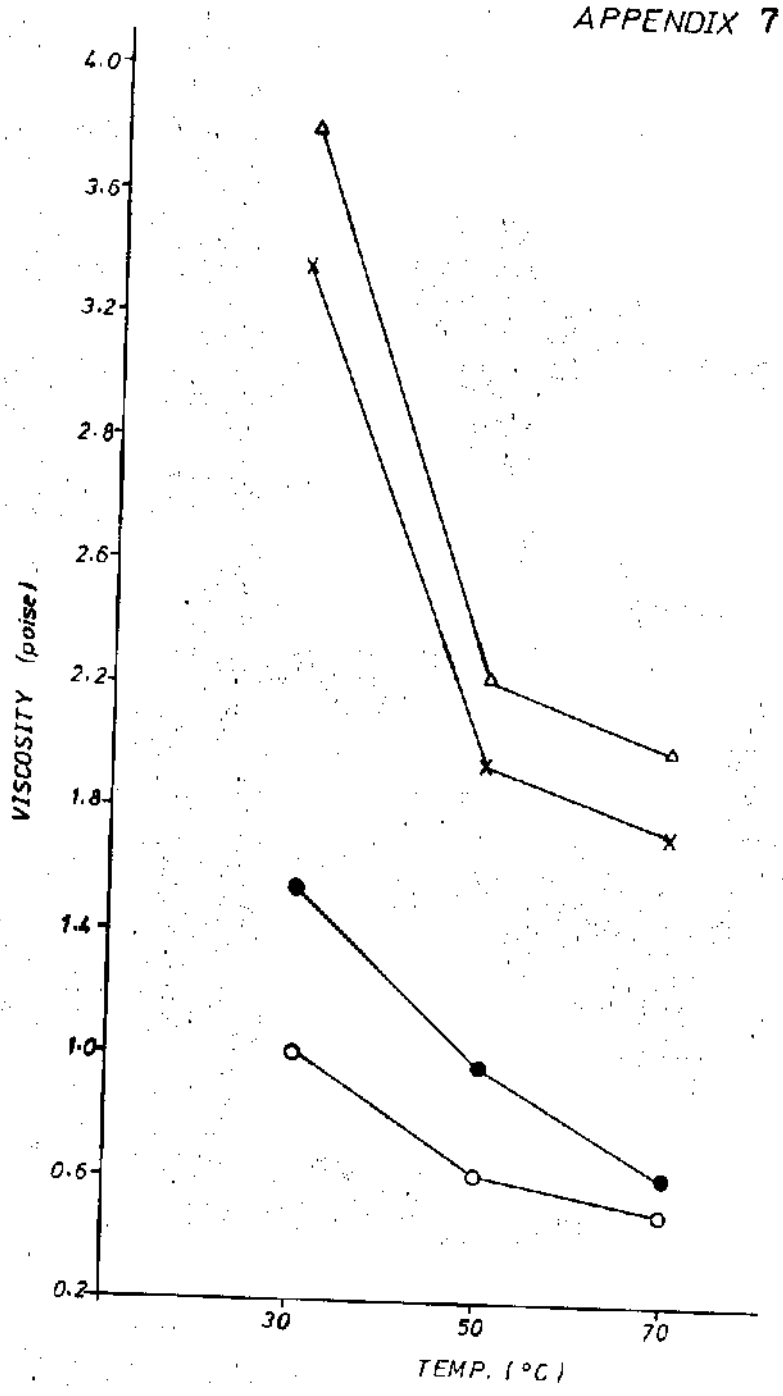
FLOW CURVES FOR 10 % W/W STARCH MUCILAGES.

APPENDIX 7a



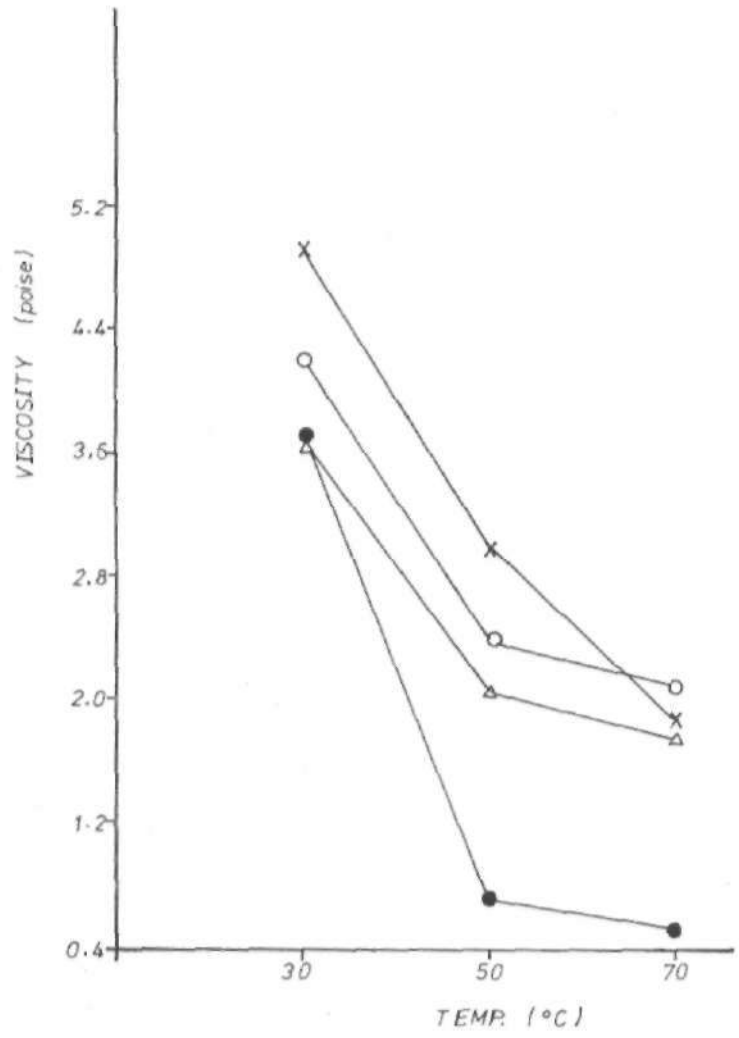
EFFECT OF TEMPERATURE ON VISCOSITY OF 5% STARCH MUCILAGES.

APPENDIX 7 b



EFFECT OF TEMPERATURE ON VISCOSITY OF 7.5% STARCH MUCILAGES.

APPENDIX 7c



EFFECT OF TEMPERATURE ON VISCOSITY OF 10% STARCH MUCILAGE.

APPENDIX 8a

Effect of binder type and concentration on the disintegration time of Promethazine tablets.

BINDER CONC.	5%w/w	7.5%w/w	10%w/w
a	35.8s	59.5s	72.83s
b	56.75s	72.5s	78.75s
c	22.33s	32s	42.67s
d	22s	27.5s	28.5s

APPENDIX 8b

Effect of disintegration type and concentration on the disintegration time of Promethazine tablets.

DISINTEGRANT CONC.	2.5%w/w	5%w/w	10%w/w
a	59.5s	43.83s	32s
b	72.5s	67s	49.66s
c	32s	29.6s	27.75s
d	27.5s	27.5s	25s

a - Cassava Starch
b - Cocoyam "
c - Yam "
d - Maize