TABLETING PROPERTIES OF *Detarium microcarpum* SEED MUCILAGE

BY

JOSIAH CHINYELU **OZUMBA**

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PHARMACEUTICAL MICROBIOLOGY
FACULTY OF PHARMACEUTICAL SCIENCES
AHMADU BELLO UNIVERSITY
ZARIA

OCTOBER, 1991

DECLARATION

I hereby declare that this thesis written by me is a record of my research work; done under the supervision of Dr. A.B. Bangudu. It has not been presented in any previous application for a higher degree.

All sources of information have been duely acknowledged by means of references.

Josiah Chinyelu Ozumba

October, 1991

CERTIFICATION

This thesis entitled "TABLETING PROPERTIES of *Detarium microcarpum* SEED MUCILAGE" by OZUMBA JOSIAH CHINYELU 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.

C Igwilo — Date: 20th feb 1992

External Examiner

Dr. (Mrs) C.I. IGWILO B. Pharm., M.Sc., Ph.D. MPSN

Date: 20th Feb. 1992

Internal Examiner

Dr. A.B. Bangudu, B.Sc. (Pharm.), M.Sc., Ph.D, MPSN

Date: _____

Internal Examiner

Dr. P.F. Olurinola, Ph.C., B.Sc. (Pharm.), Ph.D., MPSN

Date: _____

Head of Department

Dr. A.B. Bangudu, B.Sc. (Pharm.), M.Sc., Ph.D. MPSN

Date: 22/1/93

Dean, Post-graduate School

Prof. E.G. Kolawole , B.Sc, M.Sc., Ph.D

DEDICATION

To my late mother, Olianu, who for the future of her children, gave all.

To my late uncle, Umeadi, who taught me the joy of hardwork and the benefit of perseverance.

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I wish to express my gratitude first to the Almighty God for giving me the will to start this work, guiding every of my footsteps while at it, and seeing me through up to the point of its completion.

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ABSTRACT

The defatted powders and extracted mucilages prepared from pre-soaked and pre-boiled seeds of Detarium microcarpum, a savannah tree that grows abundantly in Nigeria were investigated for their binding and disintegrant properties in chloroquine phosphate tablet formulations. The potentials of the defatted powders as direct compression excipients were also studied.

Infra-red studies have suggested that Detarium oil extract is a non-aromatic open-chain or cyclic compound while paper chromatography suggested the presence of Xylose and Glucose as the polysaccharide building units. Rheological studies have shown that aqueous solutions of the test materials exhibited pseudoplastic flow with viscosity values that varied considerably with concentration. The defatted powders and extracted mucilages were shown to be capable of absorbing, at high humidity level 56.4 - 62.6%of their own weight of water over a period of 13 days. Results have shown that the mucilage extracted from the pre-soaked seeds of Detarium microcarpum performed well and can be employed in concentration range of 1-2% w/v as a binding agent in chloroquine phosphate tablet formulations. It compared favourably with 10-15% w/v maize starch and 5-15% w/v gelatin.

The defatted powders and extracted mucilages progressively prolonged the disintegration time of the tablets with increase in their concentration and cannot be used as disintegrants within the range of concentrations in the finished tablets of 2.5-10%

w/w investigated. The defatted powders possess poor direct compression properties.

1-2% w/v aqueous colloidal solution of mucilage extracted from pre-soaked seeds of Detarium microcarpum is therefore recommended in tableting as an alternative granulating fluid to maize starch paste and gelatin solution. The poor disintegrant property of the defatted powders and extracted mucilages can possibly be utilised in the formulation of sustained-release tablets.

TABLE OF CONTENTS

		Page
Title page		i
Declaration		ii
Certification		iii
Dedication		iv
Acknowledgements		v
Abstract		vii
Table of contents		ix
List of tables		xv
List of figures		xvi
List of appendices		xx
Abbreviations		
CHAPTER 1		
1.0	INTRODUTION AND LITERATURE REVIEW	1
1.1	TABLETS	1
1.1.1	Introduction	1
1.1.2	Tablet components	2
1.1.3	Binders and their importance in tableting	3
1.1.4	Disintegrants and their importance in tableting	6
1.1.5	Manufacture of compressed tablets	8
1.1.6	Interparticulate forces operating within tablets	11
1.1.7	Quality standards of tablets	12

		Page
1.2	GUMS AND MUCILAGES	19
1.2.1	Introduction	19
1.2.2	Classification	20
1.2.3	Structure	21
1.2.4	Properties	22
1.2.5	Applications	24
1.2.6	Gums and mucilages of pharmaceutical importance	26
1.2.7	Local substitutes from recent researches	29
1.3	FIXED OILS	31
1.3.1	Introduction	31
1.3.2	Properties of fixed oils	32
1.3.3	Applications	33
1.4	*DETERMINATION OF RHEOLOGICAL PROPERTIES*	34
1.4.1	Rheological properties of liquids	34
1.4.2	Classification	35
1.4.3	Viscosity measurement	40
1.4.4	The cone and plate viscometer	41
1.4.5	Importance of viscosity measurements	43
1.5	CHROMATOGRAPHY	44
1.5.1	Introduction	44
1.5.2	Paper chromatography	47
1.5.3	Pharmaceutical applications of chromatography	49

		Page
1.6	ULTRA VIOLET AND INFRA-RED SPECTROSCOPY IN ANALYTICAL WORK	50
1.6.1	Introduction	50
1.6.2	Ultra-violet spectrophotometry	51
1.6.3	Infra-red spectrophotometry	54
1.7	Detarium microcarpum PLANT (TALLOW TREE)	55
1.7.1	Introduction	55
1.7.2	Local Names	56
1.7.3	Applications	57
1.7.4	Detarium microcarpum seed	57
1.7.5	Traditional methods of processing	58
1.8	AIMS AND OBJECTIVES OF STUDY	58
1.8.1	Aims and objectives	58
1.8.2	Scope of work	59
CHAPTER 2		
2.0	MATERIALS AND EXPERIMENTAL METHODS	60
2.1	PRELIMINARY INVESTIGATION	60
2.1.1	Identification	60
2.1.2	Collection and processing of seed	60
2.1.3	Processing of the powders	61
2.1.4	Preparation of the mucilages	63
2.1.5	Analysis of the seed for its constituents	63

		Page
2.1.6	Chromatographic determination of polysaccharide building units	64
2.1.7	Other qualitative tests	65
2.1.8	Rheological properties	65
2.1.9	Water sorption studies	66
2.2	FORMULATION STUDIES	67
2.2.1	Materials	67
2.2.2	Methods	67
2.2.3	Analysis of granules	71
2.2.4	Compression of tablets	73
2.3	EVALUATION OF TABLETS	75
2.3.1	Uniformity of thickness and diameter	75
2.3.2	Uniformity of weight	75
2.3.3	Packing fraction	76
2.3.4	Tablet hardness	77
2.3.5	Tablet friability	77
2.3.6	Disintegration time	78
2.3.7	Dissolution rate	78

CHAPTER 3

3.0	RESULTS AND DISCUSSIONS I (PHYSICO-CHEMICAL PROPERTIES)	80
3.1	QUALITATIVE AND QUANTITATIVE ANALYSIS OF TEST MATERIALS	80

		Page
3.1.1	Analysis of Detarium seed	80
3.1.2	Seed processing	85
3.1.3	Rheological properties	86
3.1.4	Water sorption studies	89
3.2	SPECTROPHOTOMETRIC ASSAY OF CHLOROQUINE PHOSPHATE	95
3.2.1	Calibration curves	95
CHAPTER 4		
4.0	RESULTS AND DISCUSSIONS II (TABLETING PROPERTIES)	100
4.1	BINDING PROPERTY	100
4.1.1	General performance of the different binders	100
4.1.2	Effect of binder type and concentration on the hardness and friability of tablets	103
4.1.3	Effect of binder type and concentration on the disintegration and dissolution times of tablets	103
4.2	DISINTEGRANT PROPERTY	111
4.2.1	Effect of disintegrant type and concentration on the hardness and friability of tablets	111
4.2.2	Effect of disintegrant type and concentration on the disintegration and dissolution times of tablets	115

Page

4.2.3 Effect of pH of the dissolution medium on dissolution rate of tablets prepared with the test materials as disintegrants 119

4.3 DIRECT COMPRESSION PROPERTY 122

4.3.1 Effect of test materials on the hardness and friability of tablets 122

4.3.2 Effect of test materials on the disintegration time of tablets 127

CHAPTER 5

SUMMARY AND CONCLUSION 129

REFERENCES 133

APPENDICES 146

LIST OF TABLES

		PAGE
Table 1:	Formula for a batch of 100 chloroquine phosphate tablets	68
Table 2:	Formula for batches of 100 chloroquine phosphate tablets containing varying concentrations of binding agents	69
Table 3:	Formula for batches of 100 chloroquine phosphate tablets containing varying concentrations of disintegrants	70
Table 4:	Analytical report on the seed of the Detarium plant	81
Table 5:	Result of water sorption studies of the test materials and maize starch	92
Table 6:	Properties of granules and tablets prepared with varying concentrations of different forms of Detarium powder/mucilage in granulating fluid	101
Table 7:	Investigation of binding property - Result of Dissolution Test 1	108-9

Page

Table 8: Properties of tablets containing different concentrations of various forms of Detarium powder/mucilage as disintegrants 112

Table 9: Investigation of disintegrant property - Result of Dissolution Test II 117-8

Table 10: Mechanical strength and disintegration characteristics of tablets prepared from binary mixtures of the pre-boiled or pre-soaked Detarium powder added to Lactose, Avicel or Starch 1500. 123

LIST OF FIGURES

		Page
Figure 1:	Representative flow curves for various materials	37
Figure 2:	Schematic diagram of processes involved in preparation of samples for investigation	62
Figure 3:	Paper chromatography of hydrolysates compared with reference sugars	83
Figure 4:	Infra-red spectrum of Detarium oil	84
Figure 5:	The effect of varying the rate of shear on the viscosities of the binding agents	87
Figure 6:	Flow curves of different concentrations of Detarium mucilage	88
Figure 7:	Flow curves of 2% w/v solution of various forms of Detarium powder compared with 10% w/v gelatin solution and 10% w/v maize starch paste	90
Figure 8:	The effect of concentration on viscosity of Detarium mucilage at varying rates of shear	91

Page

Figure 9: Graph showing the rate and extent of water sorption and desorption by materials at different humidity levels 94

Figure 10: Ultra-violet spectrum of 160µg/ml standard solution of chloroquine phosphate 96

Figure 11(a): Calibration curve (The Beer-Lambert Plot) for absorbance of chloroquine phosphate at 241nm 97

Figure 11(b): Calibration curve (The Beer-Lambert Plot) for absorbance of chloroquine phosphate at 355nm 98

Figure 12(a): Graph of disintegration time of tablets against concentration of binder solution 104

Figure 12(b): Graph of disintegration time of tablets against concentration of maize starch and gelatin as binder 105

Figure 13: The effect of binder concentration on dissolution rate 107

Page

Figure 14: Dissolution rate profile for SM2 compared with those of MS 10, G10 and W 110

Figure 15: Models showing the effect of method of incorporating disintegrant on the mechanical strength of the tablets 114

Figure 16: Effects of nature and concentration of materials on the disintegration time of tablets 116

Figure 17: Dissolution rate profiles of SMD 10 and BCD 10 at pH 4.5 and pH 9.53 120

Figure 18: Effect of varying concentration of materials on hardness and friability of tablets 124

Figure 19: Effect of varying concentration of materials on direct compression property of Avicel 125

Figure 20: Effect of varying concentration of materials on direct compression property of Starch 1500 126

LIST OF APPENDICES

		Page
Appendix 1:	Shear stress values of various granulating fluids at varying rates of shear	146-148
Appendix 2:	Determination of True Densities of tablet components and oil extract	149
Appendix 3:	Particle size analysis of granules of chloroquine phosphate tablet formulations	150-152
Appendix 4(a):	Representative graph of cumulative % frequency undersize against particle size	153
Appendix 4(b):	Representative graph of cumulative % frequency undersize against log particle size	154

CHAPTER 1

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 TABLETS

1.1.1 Introduction

Tablets are defined as compact products containing medicaments in compressed or moulded form (BPC, 1973(i)). The British Patent No. 9977 entitled "Shaping pills, lozenges and black lead by pressure in dies" granted to Professor William Brockedon of England on the 8th of December 1843, in effect, constituted the invention of the tablet machine and the discovery and development of the compressed tablet (Miller, 1971). In the absence of any other suitable descriptive phase, the United States Registered Trade Marks Nos 1001 and 1002 of 13th March 1877 received by John Wyeth and his brother to protect and restrict the term "compressed tablet" was soon nullified with the declaration of the term as public property (Miller, 1971).

The basic procedure for the preparation of compressed tablets has not changed much from the early method. However, a lot of improvements in and modernisation of the processes involved as well as the introduction and use of new generation excipients have resulted from rapid technological developments. The various processes referred to include mixing, granulation, drying, comp-

ression and evaluation processes.

Tablets possess several advantages over other dosage forms. These include accuracy of dosage, elegance, patient acceptance, convenience of handling and administration and absence of alcohol during the process of manufacture thereby decreasing cost and increasing the range and scope of patients to whom it can be administered. Tablets are also amenable to rapid automatic production.

1.1.2 Tablet Components

Two basic groups of ingredients make up the compressed medicinal tablet. They are:

(a) the medicaments which are always present and

(b) the excipients which, in effect, refer to all materials other than the medicaments. An excipient is, therefore, an inert substance which is used for the purpose of confering on a preparation a suitable form or consistency. They include

(i) Diluents which give bulk to individual tablet to a practical and convenient workable size. An example is lactose.

(ii) Binders which are adhesive materials intended to hold powder particles together as granules and assist in ultimately holding the compressed tablet together.

Examples are water, starch paste, gelatin solution, natural and synthetic gums (King, 1970), alcohol, etc. Water and alcohol act by their solvent effect upon ingredients.

(iii) Disintegrants which induce the tablet to disintegrate after administration and release its active medicament(s).

The rate of disintegration and dissolution is affected by

1. Physical and chemical properties of the materials in the tablet formulation (Esezobo and Ambuiam, 1982; Zubair and Esezobo, 1988)
2. tablet hardness (Zubair and Esezobo, 1988) and
3. surface area.

Examples of disintegrants are maize starch, Avicel, etc.

(iv) Lubricants which improve flowability of granules, eliminate adhesion to the punch and die surfaces, and reduce die wall friction thus facilitating ejection of the finished tablet. Examples are magnessium stearate and Talc.

(v) Colorants used to impart colour to tablets when such is desired. Certified food and drug colour is normally used.

(vi) Flavouring agents which, as the name suggests, impart flavour to the tablet. They can also be used to mask unpleasant taste.

Examples are mannitol and chocolate.

1.1.3 Binders and their importance in tableting

Binders are substances included in granulating agents in solution to hold powder particles together and ultimately prevent

the production of friable granules that easily crumble to powder such as when water, alcohol or other simple solvent is used (Carter, 1972 (iv)). Granulation is a pharmaceutical manipulation tailored to improve flowability and compressibility of the tablet materials and the amount of binding that results depend on the nature and amount of the binder solution (Bangudu, 1982; Esezobo, 1986; Iwuagwu et al, 1986; Zubair and Esezobo, 1988).

Substances used as binders include starch mucilages, gums and mucilages in solution, gelatin and sucrose solutions. The addition of excess binder leads to the production of hard tablets that have prolonged distintegration time and also excessive wear of the punches and dies. Inadequate amount of binder will produce friable tablets. The concentration of binder used, therefore, has to be optimised and this varies depending on the nature of the binder and the tablet formulation. The same amount of the binder will be more effective if used in solution than in dry form moistened with the solvent. This is because incorporating in solution form facilitates wetting of each of the particles in the powder mass. The binders get forced into the interparticulate spaces thus increasing the area of contact between particles and resulting in the formation of solid bonds.

Increasing binder concentration leads to considerable influence on the chraracteristics of the resultant granules and the finished tablets. These include:

(a) Increasing percentage of large granules and decreasing percentage of fines are produced as a result of increased formation of bonds between the drug particles and other adjuvants (Iwuagwu et al, 1986).

(b) friability decreases since it is consequent upon interparticulate bonding in tablets (Esezobo and Ambujam, 1982; Iwuagwu et al. 1986).

(c) disintegration and dissolution times increase owing to increasing binding force of granules in the compact mass. This may also be attributed to the formation of thin film of mucilaginous viscous barrier between the tablet and water or between the break-up fragments and water (Esezobo, 1986).

(d) hardness increases (Esezobo and Ambujam, 1982). This is because the combined effect of high pressure and considerable friction at the particles' asperities lead to local melting during the compression stage. This is followed by cooling, solidification and formation of strong bonds on removal of pressure (York and Pilpel, 1972). Impervious tablets may thus result if excess binder is used (Zubair and Esezobo, 1988).

A number of subtances of plant origin have been identified from local researches in recent times as good substitutes for conventional binders. These include plantain starch (Esezobo and Ambujam, 1982), sorghum starch (Deshpande and Panya, 1985), mucuna gum (Udeala and Chukwu, 1985(ii)), Khaya gum (Boyinbode and Iranloye, 1986), sweet potato starch (Esezobo, 1986), and yam starches (Iwuagwu et al, 1986).

1.1.4 Disintegrants and their importance in tableting

In oral dosage forms in which the drug is present as a solid e.g tablets, the dissolution rate in the gastro-intestinal fluids is often the rate-determining step in the release of the drug as a solute in aqueous solution. Incorporation of disintegrants is one of the pharmaceutical manipulations designed to increase the rate of drug dissolution and hence its absorption through the gastro-intestinal tract. Disintegrants disrupt the tablet when in contact with water to produce suspension of smaller particles of the drug in the stomach. This decrease in particle size of the drug leads to increase in surface area and an increase in the rate at which the drug goes into solution. This is particularly important in tablet formulations where the drug is slowly soluble.

Several theories have been advanced to explain the mechanism of action of disintegrants. These include capillary action (Curlin, 1955), swelling (Patel and Hoppenon, 1966), heat of wetting and annihilation of cohesive forces between particles in the presence of water followed by particle-particle repulsion (Ringard and Guyot - Herman, 1988). It is possible that several mechanisms are involved but by whichever mechanisms the disintegration process occurs. the first step must be water uptake (Van Kamp et al, 1986). There is the need for fast water penetration and the maintainance of a continous hydrophilic network (Ringard and Guyot-Herman, 1988). Disintegrant efficiency depend on such factors as

(i) capacity for water uptake by disintegrant,

(ii) disintegrant concentration

(iii) wettability of other components of the tablet

(iv) porosity of the system and

(v) size of disintegrant particles in relation to other tablet components (Ringard and Guyot-Herman, 1988).

There are three types of disintegrants (Carter, 1972 (iv)) viz:

1. substances that swell up in contact with moisture e.g starches and gums

2. Substances that react with effervescence on contact with moisture e.g tartaric acid and sodium bicarbonate each added to half the material, separately granulated and dried before mixing and compression.

(3) substances that melt at body temperature. An example of this is cocoa butter which melts below body temperature and is used in the form of a solution in ether.

The first type is commonly used in conventional compressed tablets, the second type is used in effervescent tablets while the third type is used in the formulation of suppositories.

The best method of incorporating disintegrants in tablet material is still a controversial subject. While some believe that extragranular method is better (Shotton and Leonard, 1976), others prefer intragranular method of incorporation (Ho et al, 1977). A reason adduced by the first school of thought is that a

portion of an intragranularly incorporated disintegrant may act as an in situ binder (Iwuagwu et al. 1986) and prolong the disintegration time of tablets. At the concentration of gel barrier formation, penetration of water into the tablet matrix and outward movement of the drug in solution will be by diffusion process (Udeala and Chukwu, 1985) and the material thereafter prolongs rather than facilitate the release of drug. This provides the basis for the possible utilization of some such materials in certain prolonged-release dosage forms.

Recent researches have yielded some local raw materials found to possess good disintegrant property. They include plantain starch (Esezobo and Ambujam, 1982), sorghum starch (Deshpande and Panya, 1985), mucuna gum (Udeala and Chukwu, 1985(i)), sweet potato starch (Esezobo, 1986) and yam starches (Iwuagwu et al. 1986).

Local substitutes for some other components of tablet formulations have also been reported. These include among others Irvingia gabonensis as glidant (Obiorah, 1982), Nigerian chalk and clay as lubricants (Onyechi and Udeala, 1983) and plantain powder as glidant (Oladimeji et al. 1987).

1.1.5 The manufacture of compressed tablets

In the pharmaceutical industry, compressed tablets are prepared by either of three distinct methods. Viz:

(a) Direct compression which involves little or no preliminary treatment of materials before being fed into the tablet machine.

Materials amenable to direct compression are usually granular, have marked ionic properties, possess crystalline structures with good planes of slippage, and are comparatively soft materials. Example of such materials are Ammonium chloride, Sodium chloride, Acetylsalicylic acid crystals, etc.

Direct compression excipients are substances added to impart cohesive strength to particles of a powder mix intended to be compressed by a direct process that bye-passes the granulation stage. They are important in the sense that they permit production of tablets by direct compression method thereby avoiding two possible sources of decomposition - heat and moisture - and also minimises loss of volatile matter where present (Carter, 1972 (iv)). A good direct compression excipient such as Avicel gives firm tablets with no tendency to cap (Bangudu, 1982). In addition to Avicel, a few substances known to possess direct compression property include Fast-flo lactose, Starch 1500 and Emcompress. Rencently, local research has yielded results that indicate that the chemically modified form of mucuna gum can be successfully used as a good direct compression excipient (Udeala and Chukwu, 1985; Chukwu and Udeala, 1986).

(b) Wet granulation is a process of specially treating fine powders for conversion into the granular form. It involves the moistening of a uniform mixture of the powdered medicaments and the diluent until the consistency of a crumbling mass is

attained. This is followed by wet screening and drying. The quantity of the binder used and the uniformity of its distribution in the powder mix are important factors that determine how well the binder performs. Insufficiency leads to poor adhesion, soft tablets and "capping" while excessiveness yields tablets with greater hardness and longer disintegration time in addition to difficulty of wet screening.

(c) Dry granulation involves the preliminary compression of finely divided powders into large tablets called slugs, size reduction of the slugs to granular form followed by the usual method of lubrication and subsequent compression.
Direct compression excipients such as Avicel, Starch 1500, etc may be incorporated prior to compression to improve the binding qualities of the powder mixture. This method of production is very ideal for heat or moisture sensitive drugs and encourages rapid tablet disintegration since a binder solution is not used. Finely divided acetylsalicylic acid and dried starch mixture can be compressed by this method.

The other method of dry granulation is the roller compaction in which materials are fed into high pressure rollers, emerge from the latter as sheets which are ultimately broken down into granules. The rollers occassionally have serrated edges which break down the emergent mass into regular size granules.

Irrespective of the method of production, the tableting process is characterised by the following distinct stages in that sequence:

1. The flow of correct amount of granules into the die cavity
2. Application of pressure
3. Reduction of voids and rearrangement
4. Bond formation
5. Removal of pressure and
6. Ejection of tablet.

1.1.6 Interparticulate forces operating within tablets

During the compression stage in tableting, the pressure applied on the powder particles within the die cavity gets transmitted to only a few points of contact on the rough powder surfaces known as asperities. Under the influence of the extremely high pressure, melting point of the material is lowered and considerable frictional heat is generated. This, in low melting point materials, leads to substantial local melting at these asperities. Removal of pressure is followed by cooling of the material and this, coupled with plastic and elastic deformation of the particles, leads to bond formation (York and Pilpel, 1972). Bond formation can also result from oxidation-reduction reaction or by way of hydrogen bonding.

Increasing binder concentration has been shown to be an important factor in the production of welded bonds and, there-

fore, strong and impervious tablets (Esezobo and Ambujam, 1982; Esezobo, 1986; Iwuagwu et al., 1986). This is attributed to the fact that the binder is forced into the interparticular spaces thereby increasing the area of contact between particles and subsequent formation of additional solid bonds (Zubair and Esezobo, 1988).

Dissolved substances may, in crystallizing out during drying, form strong solid bonds. Presence of moisture in granules of which the following states - pendular, funicullar, capillary and droplet states (in increasing order of moisture content) - have been identified can contribute to bonding between particles in the tablet. Bond formation can also result from interplay of molecular forces. Notable in this respect are the temporary dipole-dipole interaction between particles otherwise known as Van der Waals forces and valency forces due to unsaturated bonds. Electrostatic forces resulting from imbalance of electrons due to friction could be in form of attraction or repulsion. Mechanical interlocking can take place especially with fibrous materials, bulky particles and rough surfaces.

1.1.7 Quality standards of tablets

Pharmaceutically acceptable tablets should have the following essential qualities:

(i) Weight uniformity: The weights of a given batch of tablets should be uniform. Slight variation in weight is inevitable and acceptable as long as it is within the limits of deviation that is specified in the compendia.

(ii) Uniformity of active ingredient: A tablet should contain the stated dose of the drug. This property is necessary for a number of reasons which include compliance with regulations, confidence and acceptance by the health personnel and the patient. Even where repeated handling results in wears, abrasion, chipping and fracturing, dose of the active ingredients has a direct relationship with the progressive reduction in tablet weight.

(iii) Freedom from incompatibilities: Physical incompatibilities such as liquefaction of solid ingredients are those in which the physical properties of the ingredients produce a mixture unacceptable in appearance or in accuracy of dosage while chemical incompatibilities such as oxidation, reduction and cementation are those in which the ingredients interact or decompose to give new compounds (Dale and Booth, 1971). Freedom from these assures both the labelled potency for the maximum shelf life and the desired therapeutic effect. Mild incompatibilities may manifest in visible or odoriferous changes on ageing.

(iv) Stability and hardness: Tablets must be stable enough to withstand the physical factors to which they are subjected - atmospheric oxygen, high humidity, light and microorganisms. They are also expected to be robust enough to maintain their shape during the expected life of the tablet. The mechanical strength should be enough to enable them withstand rough handling right from packaging through transportation and up to administration to the patient. They should be compact without chipping or breaking apart when subjected to stress.

(v) Ease of disintegration: Tablets must of necessity readily disintegrate in the stomach so as to release the active ingredients in good time and enable the latter to exert the desired therapeutic effects. This relates to dissolution and may constitute the rate-limiting step.

(vi) Reasonable size and shape for administration: The tablet must necessarily possess such size and shape that are consistent with the patient's ability to accept the tablet by the prescribed route or method of administration.

(vii) Aesthetic appearance: To ensure acceptability and compliance by the patient, the tablet must pleasantly appeal to, or be totally devoid of the ability to offend the senses of vision, smell, taste and feel.

To ensure that tablets in any given batch possess these essential qualities, certain stringent tests are prescribed in the official compendia (British Pharmacopoeia, 1980). The first recorded official standards for tablets was in the British Pharmacopoeia 1932. Addendum VII 1945 (Carter, 1972 (i)). There are yet other tests which, though not official, are even more stringent. Many manufacturers subject their products to these unofficial tests in addition to the official ones. This is designed to ensure that they excel in quality and handling properties of their products.

The official tests include the following. Viz:

(a) Uniformity of Diameter:

This is supposed to act as a guide for the dimension of the compressed official tablet formulation. Different diameters with maximum permissible deviations are prescribed for different formulations. For instance, Chloroquine phosphate tablet containing 250mg of the active ingredient is expected to have a diameter of 9.5mm. The maximum permissible deviation allowed for this product is ± 5%.

(b) Content of active ingredients:

This test is usually carried out with 20 tablets or, where not feasible, a minimum of 5 tablets. The tablets are crushed

together and subjected to any suitable method of assay for the active ingredient. The percentage of medicament is often, but not always so, expected to lie between 90 and 110%. These limits are widened if less than 20 tablets are used.

Some variation is inevitable and this may be as a result of

1. Variation between samples taken from the bulk of powders. This affects the powder mix even if perfectly random. Subsequently, the granules made from this powder and the tablets resulting from the compression of these granules are similarly affected.

2. Variation in tablets weight. This is especially of great significance in high-dose tablets. Sources of error include the limitation of accuracy of the assay method and permitted variation in the purity of the drug. The absolute reliability of this test is put to question by the fact that gross deficiency in some tablets may be offset by a large excess in others so that the bulk sample of 20 tablets still comply (Train, 1960). To eliminate this source of error, a more objective approach in which the tablets are individually assayed needs to be adopted especially nowadays that automatic analysers are available.

(c) Uniformity of weight:

Acceptable limits of weight deviation for uncoated tablets are specified in the official compendia. This is because small variations are acceptable since they cannot be completely avoi-

ded. The permissible percentage deviation depends on the size of the tablet and the number taken for the test. The percentage deviation quoted below are acceptable following the standard test in which 20 tablets are used (British Pharmacopoeia, 1980).

Average weight of tablet	Permissible percentage deviation
Not more than 80mg	10
More than 80mg but less than 250mg	7.5
Not less than 250mg	5

The 20 tablets are selected at random and their mean weight determined. The result is satisfactory if not more than two individual tablets deviate from the average weight by more than the stated percentage deviation and none at all deviates by more than twice that value.

(d) Disintegration test:

This test is designed to ensure that the need for the tablet to readily disintegrate in the stomach or intestine and release its medicament to exert its desired therapeutic effect is met. A tablet that passes through the gastro-intestinal tract and is eventually recovered intact from the patient's stool is, at best, useless and, at the other extreme, dangerous especially if the active ingredient were a life-saving drug.

The British Pharmacopoeia (British Pharmacopoeia, 1980) specifies a maximum period of 15 minutes within which time the uncoated tablets must disintegrate. A batch of tablets is deemed to have passed the test if all the six tablets disintegrate and pass through the sieve within 15 minutes.

(e) Dissolution rate:

For a tablet to elicit the desired systemic therapeutic response, the medicament it contains must first go into solution as a preliminary step to absorption and subsequent distribution. The dissolution test is considered to be of greater importance than the disintegration test. This is because it is possible for tablets to disintegrate and yet not readily release their medicaments into solution. The British Pharmacopoeia (British Pharmacopeia. 1980) stipulates that after 45 minutes run, the filterate must contain not less than 70% of the stated amount of medicament.

The unofficial tests are designed mainly to assess the mechanical strength of tablets. Manufacturers, as a matter of necessity, subject their tablets to these tests to ensure that the tablets would be able to withstand the normal risks associated with handling and transportation. They are:

(a) Hardness test:

This is carried out with hardness testers of which there are various types. The pressure sufficient to break the tablet is noted and the mean of several determinations taken as the hardness value for a given batch of tablets.

(b) Friability test:

This test involves the subjection of the tablets to controlled series of falling shocks in a device known as the friabilator. It assesses the relative extent to which the tablets will suffer abrasion when subjected to tumbling effects. A design in common use is the Roche friabilator. Tablets are put into the rotating drum furnished with a baffle which is then operated to rotate at a constant rate (usually 25 rpm) and for a specified period of time (usually 4 minutes). After this period of time, the tablets are removed from the drum, carefully dusted and weighed and the percentage loss due to abrasion is then calculated and recorded as the friability of the tablets.

1.2 GUMS AND MUCILAGES

1.2.1 Introduction

"Gums" and "mucilages" are terms oftentimes used interchangeably. Although they are both carbohydrate polymers of high molecular weight obtained from plants, plant gums are

polysaccharide - containing exudations which form after injury to certain trees and fruits. These injuries are often mechanically produced and an attack by organisms at the site of the wound causes formation of the gum in a process known as gummosis (Lowson, 1946). Plant mucilages, on the other hand, generally occur naturally in various parts of the plants and act as food reserves or as a means of storing water (Coutts and Smail, 1966). In other words, plant mucilages are not extra-cellular in origin but are obtained by extraction with either hot or cold water from seeds, roots or other parts of plants. While gums form tachy or sticky solutions, mucilages give slippery or mucilaginous solutions. Examples are those from guar bean, linseed and other leguminous plant seeds (Dutton et al. 1966).

1.2.2 Classification

For classification purposes, there is no clear distinction between gums and mucilages. They are best classified according to their chemical composition. Although classification based on their monosaccharide building units have been reported by various authors (Aspinal. 1969; Finar, 1975 (i)), the simplest and most widely used method is that based on whether or not they contain acidic components. Acid gums and mucilages are, therefore, those that contain acidic components such as D-glucuronic acid (or its 4-o-methyl derivative), D-galacturonic or D-mannuronic acids and

neutral components which are pentoses and/or hexoses.

On the other hand, neutral gums and mucilages, as the name implies, are devoid of acidic components. Rather, they are simply composed of pentoses such as L-arabinose and D-xylose and/or hexoses such as D-glucose, D- or L-galactose, and D-mannose (Dutton et al, 1966).

1.2.3 Structure

Gums and mucilages are macromolecules with structural similarities. They are composed of acidic and/or neutral monosaccharide building units joined by glycosidic bonds. The acid group may be - COOH or - SO_3H and is usually present as calcium, potassium, sodium or magnesium salts. Methyl or acetyl substituent group may also be present. It is, in fact, the complexity of their structures that inform their classification on the basis of sugar residues that comprise the interior chains of the molecular structure. Several gums and mucilages are even known to contain more than one polysaccharide component. Examples are found in gum tragacanth and Khaya senegalensis gum where two structurally different polysaccharide types exist. Others are some seed mucilages such as linseed and cress seeds (Aspinal, 1969). The exudates, generally, are structurally more complicated than the intracellular mucilages, their central core often composed of D-glucuronic acid and D-galactose units joined

by glycosidic bonds which are relatively stable to acid hydrolysis. The neutral gums and mucilages have relatively simple structures. The galactomannans, for example, are usually composed of a backbone of linear chains of D-mannose units joined by 1,6-glycosidic bonds and having galactose residues as side chains. The glucomannans also show the same structural simplicity being essentially linear polymers joined by 1.4 linkages (Dutton et al, 1966). Structural investigation of mucilages is often difficult and the precise structure is often inconclusive. However, controlled cleavage of glycosidic bonds had been most useful in leading scientists to propose structures.

1.2.4 Properties

Gums and mucilages are macromolecules in that they are carbohydrate polymers of high molecular weight. An example is Gum arabic which has a molecular weight of 250,000-300,000 (Dutton et al, 1966).

They are hydrocolloids and as such form viscous colloidal solutions when dispersed in water. These solutions which are, with very few exceptions, hazy to opaque in appearance are now recognised as true monophasic, thermodynamically stable system in contrast to the old system of considering them as heterogeneous dispersions (Takruri and Ecanow, 1971). Those that possess

relatively more linear molecules such as gum tragacanth form more viscous solutions than their more spherically shaped counterparts such as gum arabic at the same concentration. Also, owing to their elongated molecular shape, the seed mucilages give solutions whose viscosity vary considerably with concentration. In other words, they exhibit structure viscosity. The viscosities of solutions given by exudates, on the other hand, do not depend so much on concentration (Dutton et al, 1966). Hence, the viscosity is considered as an important criterion for evaluation of mucilages as it helps in the detection of adulteration (Karawya et al, 1971).

The viscosity of aqueous dispersions may be influenced by such factors as temperature, pH, presence of salts, enzyme action on standing, and microbial attack. For example, tragacanth shows maximum viscosity at pH 5. The viscosity drops sharply at pH values less than 4.5 or higher than 6. Acacia, on the other hand, is tolerant to a wide variation in pH (Pernarowski, 1970; King and Baker, 1971).

Very often when added to water they form large aggregates (clumps) whose dissolution rate is very low. The reason adduced for this phenomenon is that on coming into contact with a number of small particles, water hydrates their surfaces and form a very viscous film that envelopes the particles inside thus preventing or delaying further contact with water. A way out to rapidly put them into solution is by wetting them with a non-solvent such as

alcohol or glycerin prior to addition of water with rapid trituration (Dale and Booth, 1971; Takruri and Ecanow, 1971).

They adsorb on surfaces and can form mono- or polymolecular films. This in conjuction with their high viscosity, provide a basis for their use as colloid, suspension, emulsion and foam stabilizers. These films impart the properties of hydrophillic macromolecules to hydrophobic particles, thereby increasing the resistance of these particles to destabilizing factors (Takruri and Ecanow, 1971).

Some group of polysaccharides from plant seeds to which the term "amyloids" has been ascribed give characteristic blue stain when reacted with iodine solution (Aspinal, 1969).

Many gums and mucilages are surface active. They may therefore also be utilised as emulsifying agents. As a result of their surface tension lowering effect, preparations containing them may foam when shaken (Schwarz, 1971). Being carbohydrates, they are susceptible to microbial decomposition (Schwarz, 1971). They are precipitated from their aqueous dispersions by the addition of alcohol or acetone.

1.2.5 Applications

Gums and mucilages have a very wide industrial and pharmaceutical applications (Dutton et al, 1966). They are used as adhesives to increase the strength of starch pastes. Gum tra-

gacanth is used in toothpastes, for coating soap chips to prevent dusting and lumping and also in hairwaving preparations. Their high viscosity, adsorption and surface active properties qualify them for use as emulsion stabilizers. The seaweed gums such as carrageenin and seed mucilages such as guar gum are used as stabilizers in dairy products like ice-cream and cheese. They are used in confectionery, in jam and jelly making, in stabilizing salad dressings and as a fixative for 2,3-butenedione in the baking industry. The textile industry uses them in spinning and printing. An example is gum tragacanth which is used in calico-printing. They are used as excellent beeter additives to increase paper strength. They possess good binding properties and this is the basis for their use in welding rods and in explosives used under water. By virtue of their protective effect, they have found use in the refining of certain kinds of ores where they coat impurities and thus facilitate their separation. Psyllium and Karaya gums by virtue of their swelling to a hydrogel in the intestine on absorption of water are used as bulk laxatives (Pernarowski, 1970).

1.2.6 Gums and mucilages of pharmaceutical importance

Acacia (Gum arabic):

Acacia is the air-dried gummy exudation from the stem and branches of Acacia senegal or other species of Acacia (Fam. Legu-

minosae). It is used chiefly for oral preparations as a suspending agent, emulsifying agent, and binding agent in lozenges and pastilles (Dale and Booth, 1971; King and Baker, 1971; Schwarz, 1971; BPC, 1973 (iii)).

Sterculia (Karaya gum; Indian Tragacanth)

Sterculia is the gum obtained from Sterculia urens and other species of sterculia (Fam. Sterculiaceae). It is used as a substitute for tragacanth in lozenges, pastes and denture-fixative powders (BPC, 1973 (v)).

Tragacanth

Tragacanth is the dried gummy exudation from Astragalus gummifer and some other species of Astragalus (Fam. Leguminosae). It is composed of two fractions - tragacanthin which is water soluble and bassorin which, though insoluble, swells in water. It is used as a suspending agent and emulsion stabilizer, in medicated and toilet creams and jellies containing glycerol, as excipient for pills, tablets and lozenges, in obstetric creams and as the basis of lubricants for catheters and surgical instruments. The powder is used as an adhesive for dentures (Dale and Booth, 1971; King and Baker, 1971; Schwarz, 1971; BPC, 1973 (vi)).

Guar gum

Guar gum is the refined endosperm of the guar seed. The gum is chemically a non-ionic polysaccharide, which consists mainly of galactose and mannose units. It is used as a suspension stabilizer (Schwarz, 1971).

Gum myrrh

Myrrh is an oleo-gum-resin obtained from the stem of Commiphora molmol. It contains 25-40% resin, 57-61% gum, 7-17% volatile oil and 3-4% impurities. It is used as perfume, and in form of tincture as mouth-washes and gargles for application to ulcers in the mouth and pharynx because of its astringent action on the mucous membrane (Coutts and Smail, 1966; BPC, 1973 (iv)).

Carrageenin

Carrageenin is the calcium salt of a sulphonate polysaccharide and the active principle obtained by aqueous extraction from the dried bleached plant of Chondrus crispus or Girgatina mamillosa. It is used as a suspension and an emulsion stabilizer (King and Baker, 1971; Schwarz, 1971).

Algins

The terms "algins" and "alginates" designate various derivatives of alginic acid, which are obtained from several species of Kelp, a common seaweed. Chemically, alginic acid is a

linear polymer of β-D-mannuronic acid. Sodium alginate is official. It is the sodium salt of alginic acid. There are varying grades depending on the viscosities of the solutions they give. It is used for the preparation of gels, pastes, and creams; for the thickening and stabilizing of emulsions; and for its haemostatic properties as a surgical dressing. It is also used as a suspending agent and as a tablet disintegrant (Dale and Booth, 1971, King and Baker, 1971; Schwarz, 1971).

Agar

Agar is a gel-forming polysaccharide from various species of Gelidium, a marine algae. It is a negatively charged colloid. It is used in the preparation of culture media (Dale and Booth, 1971; King and Baker, 1971).

Pectin

Pectin is the mucilaginous carbohydrate contained in the cellular tissues of citrus fruits, apples and many other fruits. It makes possible the preparation of jellies from fruit juices. The molecule consists chiefly of polygalacturonic acids which are partially in the form of methyl esters. It is used in making jellies and pharmaceutical pastes (Dale and Booth, 1971; King and Baker, 1971).

1.2.7 Local substitutes from recent researches

It was not until the post-independence era that local drug production in Nigeria started. Since then tremendous improvement has been made as evidenced by the growing number of production units springing up in different localities. It has, however, been observed that the key elements to improvement in drug manufacture are the provision of technology, raw materials and market and that as long as materials, manufacturing technology and additional finished drugs still have to be imported, overseas influence can manipulate and frustrate the local industry and negate any advantages of local production (Adenika, 1986). Unfortunately, Nigeria still imports the bulk of the raw materials she needs for her pharmaceutical industry. The themes of the seminars and annual national conferences of the Pharmaceutical Society of Nigeria held in the last decade are testimonies to the realisation of the need to reorder our priorities and look inwards with a view to finding ways of sourcing our raw materials locally. Nigeria is endowed with enormous natural resources waiting to be tapped.

However, it is gratifying to note that several research findings have been made and other researches are still underway all in a bid to put Nigeria on the road to self-sufficiency in pharmaceutical production. These include medicinal plants with

proven active principles and pharmaceutical aids from plant and mineral sources. Some of these findings have been documented (Olaniyi, 1985). Included in these are gums and mucilages from various plant species which have been found to variously substitute for the official excipients used in pharmaceutical production. Examples are those from

(a) Mucuna flagillepes found to possess suspending (Udeala and Uwaga, 1981), disintegrant (Udeala and Chukwu, 1985 (i)) and binding (Udeala and Chukwu, 1985 (ii)) properties.

(b) Khaya grandifolia found to possess binding property (Boyinbode and Iranloye, 1986).

and (c) Zanthoxylum tessmani found to be a good emulsifying agent (Orafidiya and Oyedele, 1985).

The good potential of Mucuna flagillepes as a source of direct compression exipient has also been reported (Udeala and Chukwu, 1985 (ii); Chukwu and Udeala, 1986).

Further investigations of the potential pharmaceutical uses of gums and mucilages are still in progress. Some researchers have, for example, reported the potential use of gums and

mucilages as sustained-release excipients (Huber and Christensen, 1966; Baveja et al, 1989).

1.3 FIXED OILS

1.3.1 Introduction

Fixed oils share structural similarity with fats. They are both lipids and belong to the group often referred to as "simple" lipids. They are all made up of glycerol and fatty acids i.e. they are glyceryl esters or glycerides. The fatty acids they contain are almost exclusively straight-chain acids that contain even number of carbon atoms. The distinguishing factor, however, is the degree of saturation of their fatty acid content and the state in which they exist at ordinary temperatures. While fats contain mainly saturated acids and exist in the solid state at room temperature, oils which are liquids at similar temperature conditions have a larger proportion of unsaturated acids. The main saturated acids are lauric, myristic, palmitic and stearic acids while oleic, linoleic and linolenic acids in their cis - forms constitute the chief unsaturated acids. The acid residue occupies a position that is dependent upon the chain length of the unsaturated acids and the degree of their unsaturation. In vegetable oils the 1- and 3-positions are mainly occupied by the saturated acids and the 2-position the unsaturated acids (Finar, 1973 (iii)).

Fats and oils are found in greatest quantity in storage regions of plants and particularly in seeds (Hill et al. 1967). Oil glands are generally lysigenous cavities i.e. they arise from the disruption of cell-walls. Some, however, are schizo-lysigenous, i.e. they are initiated schizogenously from a group of cells whose walls subsequently break down (Mangham and Hockley, 1951).

1.3.2 Properties of fixed oils

Oils possess hydrophobic structures and are therefore insoluble in water, but easily soluble in organic solvents such as ether and chloroform. They are less dense than water having a specific gravity range of 0.875 - 0.970 (Hill et al, 1967). They leave transluscent mark on paper and this does not disappear on heating in an oven. They form glycerol and soap when subjected to treatment with either sodium hydroxide or potassium hydroxide. The process is known as saponification. They are liquids at ordinary temperatures and may undergo decomposition by a process known as autoxidation and become rancid. This is a chain reaction that involves abstraction of free hydrogen radicals activated by the presence of unsaturated C=C linkages, or initiated from effects of heat, light or ionising radiation on some ingredients of an oil e.g. dissociation of a peroxide or photo-oxidation of a ketone (Carter, 1972(iii)).

Rancid oils have objectionable odours and tastes. Contact with metals in the dark can also cause rancidity (Dale and Booth, 1971).

1.3.3 Applications

Vegetable oils, if edible, are used for cooking and in this way provide an important source of calories for the energy requirements of the body. For the industrial preparation of glycerol, oils are hydrolysed in water under pressure and at elevated temperature of 220°C. The glycerol is recovered from the aqueous solution. The free fatty acids liberated during the hydrolysis are used in the manufacture of candles (Finar, 1973 (iii). Soft soaps are obtained as product of saponification. Some of the unsaturated acids of edible oils can be saturated by a process of hydrogenation under pressure and at a temperature of 150-200°C in the presence of finely divided nickel catalyst to give edible fats known as margarine.

Fixed oils are extensively used in pharmacy. Examples are olive oil, corn oil, almond oil and peanut oil which are variously used as demulcents, laxatives, for preparation of emollient applications and as vehicles for oily injections. Others include coconut oil used as ointment bases, anise oil used as carminative and expectorant and castor oil used as purgative, vehicle for soothing oily applications for the eyes and emollient preparations for the skin.

1.4 DETERMINATION OF RHEOLOGICAL PROPERTIES

1.4.1 Rheological properties of liquids

Rheology is the science associated with the deformation of matter under the influence of stresses (Cater, 1972 (ii)). A shearing stress is one applied tangentially to the surface and, in the case of fluids (i.e liquid or gas), result in permanent or irreversible deformations referred to as flow. This is because fluid cannot support a strain for very long periods of time. The deformation may be considered to involve a shearing action between infinitely thin layers or laminae within the fluid. The shear stress that causes a particular rate of shear is obtained by dividing the shearing force by the area of the surface to which the shearing force is tangentially applied. The ratio of the applied shear stress to the rate of shear is known as the coefficient of viscosity or simply viscosity.

Viscosity has been defined as the resistance to flow due to the internal friction in a liquid and is believed to depend on such factors as the size and shape of the molecules, the Van der Waals forces between them, and the temperature (Finar, 1975(iii)) as well as pH (King and Baker, 1971). The rheological properties of liquids are usually expressed in the form of flow diagrams, which consist of graphs showing the variation of shear rate with shear stress.

1.4.2 Classification

Liquids are classified on the basis of the effect of rate of shear on the viscosity. The flow properties of Newtonian systems (which include water, simple organic liquids, true solutions, dilute suspensions and emulsions) are governed by the Newtonian law which can be expressed as:

$$S = n\frac{du}{dx} \quad \text{..... Equation 1}$$

where S = shear stress

n = coefficient of viscosity or simply viscosity and

du/dx = rate of shear

The flow diagram of such a system is linear and the viscosity, n, is constant irrespective of the value of the shear rate.

Liquids that do not obey Newton's law of flow are referred to as non-Newtonian. The value of viscosity for a non-Newtonian fluid varies with the rate of shear and the above equation does not apply. The usual practice is to consider the apparent viscosities at particular rates of shear. Thus,

$$n_{app} = \frac{\text{Shear stress}}{\text{shear rate}} = \frac{S}{du/dx} \quad \text{..... Equation 2}$$

where n_{app} = apparent viscosity.

The three common types of non-Newtonian flow are plastic, pseudoplastic and dilatant flow. Since the apparent viscosity varies with rate of shear, a single determination of it from the shear stress at any given shear rate would therefore be of little use and the necessity arises of determining the whole flow diagram in order to characterise these systems. Typical flow curves for the Newtonian and the various types of non-Newtonian systems are shown in Figure 1.

Plastic flow is described by a curve that does not pass through the origin but which arises on some point on the shear stress axis. This indicates that a certain shearing stress must be exerted before flow commences. This stress is termed the yield value. Below the yield value, the system exhibits elastic deformations that are reversible on removal of the small stresses and above the yield value, a plastic system resembles a Newtonian system. Materials that exhibit plastic flow are also termed Bingham bodies and their quantitative behaviour expressed by the Bingham equation:

$$n_{pl} = \frac{S - f_B}{du/dx} \qquad \text{Equation 3}$$

where f_B = Bingham yield value

n_{pl} = plastic viscosity

S = Shear stress

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. The yield value is due to

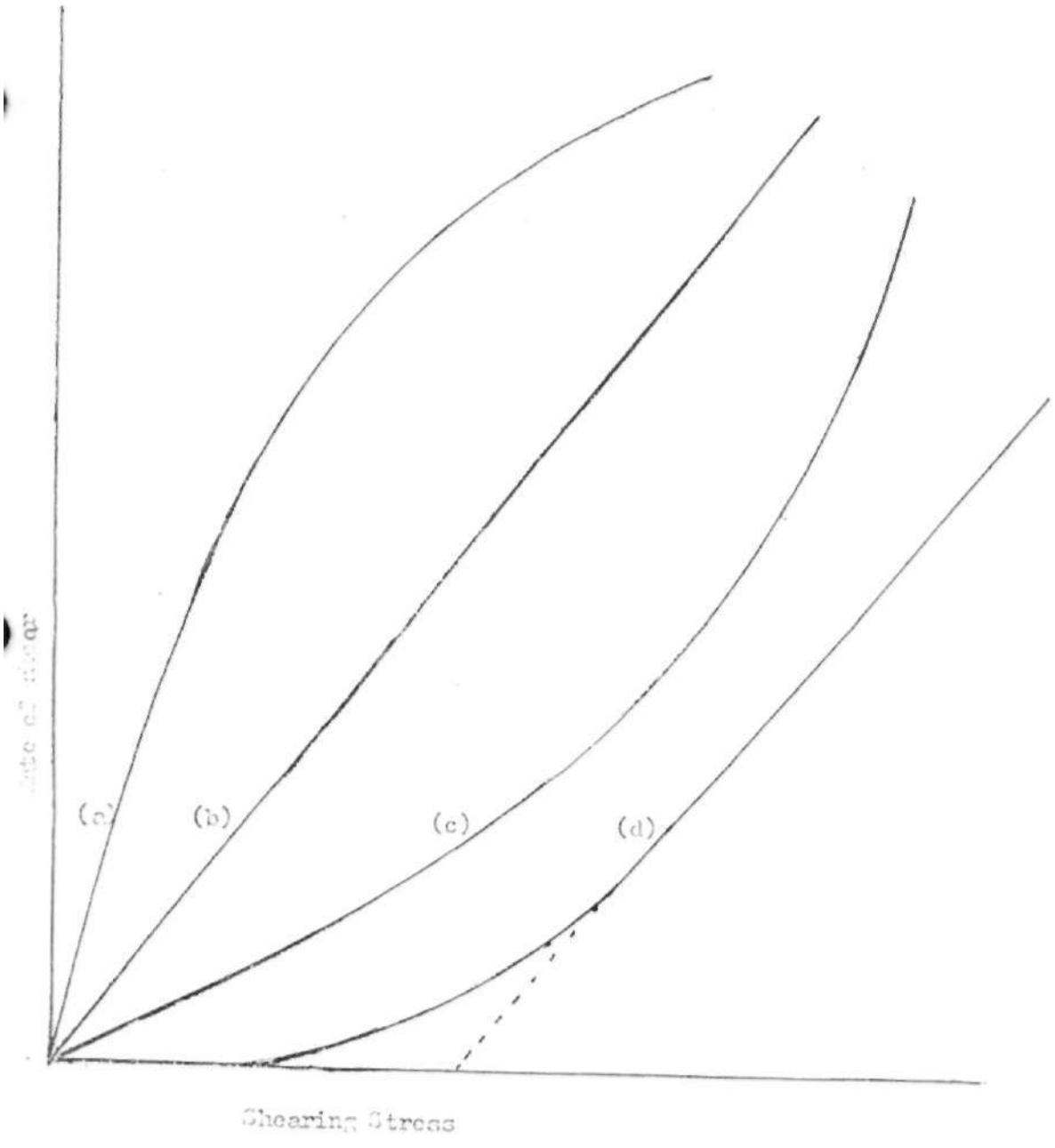


Figure 1: Representative flow curves for various materials

(a) = DILATANT
(b) = NEWTONIAN
(c) = PSEUDOPLASTIC
(d) = PLASTIC

the contacts between adjacent molecules which have to be broken down before flow can occur and also frictional forces between moving particles which have to be overcome (Martin et al, 1969 (ii)).

Pseudoplastic flow is exhibited by materials in which flow starts immediately shearing stress is aplied and whose rheogram is a curve starting from the origin (i.e devoid of yield value) and the gradient progressively increase until a maximum value is reached. Increasing gradient means decreasing apparent viscosity. An empirical equation that is often used is:

$$S^N = n' \frac{du}{dx} \quad \text{..... Equation 4}$$

where N = a constant for the particular system and is greater than unity.

n' = a viscosity coefficient.

The greater the value of N, the more pseudoplastic the flow is.

Written in logarithm form, the equation becomes:

$$N \log S = \log n' + \log du/dx \quad \text{..... Equation 5}$$

i.e $\log du/dx = N \log S - \log n'$

A graph of log du/dx against log S will give a straight line where the slope will be equal to N and the intercept on the log S

axis equivalent to log n'. Several of the more important pseudoplastic suspending agents do not conform to this equation (Martin et al, 1969 (ii)). Breakdown of structures (e.g aggregates of dispersed particles) in the system has been advanced as the reason behind decrease in apparent viscosity of pseudoplastic and plastic systems under the influence of increasing shear stress. The extent of breakdown increases with increasing shear rates up till a point where no more breakdown of structures is possible. The structures in these systems may, on removal or reduction of shear stress, immediately reform such that flow curve obtained as shear stress is reduced becomes identical to and superimposable on that obtained as shear stress is increased. On the other hand, the reformation process may be markedly time-dependent resulting in downward curve that is not superimposable on the upward curve but in which the two curves describe a loop known as the hysteresis loop. This phenomenon is known as thixotropy and is defined as "an isothermal and comparatively slow recovery, on standing of a material, of a consistency lost through shearing" (Reiner and Scott-Blair, 1967). The area of the hysteresis loop gives an indication of the relative extent of structural breakdown that has taken place in the system. Polymers (such as natural and synthetic gums) in solution generally exhibit pseudoplastic flow (Martin et al, 1969 (ii)) and they are most satisfactorily represented by a graphical plot of the entire consistency curve.

Dilatant flow is the reverse of pseudoplastic flow. Dilatant systems actually increase in volume when sheared. Dilatancy is exhibited by suspensions containing a high concentration (> 50%) of small deflocculated particles. The hitherto closely-packed particles with minimum void spaces assume, on being sheared, an open-packed structure with increased interparticulate void spaces which at a point is no longer sufficiently filled by the vehicle. Consequently, resistance to flow increases. The rheogram, therefore, is a curve whose slope gradually decreases to a constant value. Conversely, the apparent viscosity increases up to a maximum value with increase in shear rate. The behaviour of dilatant systems can also be described by the equation used for pseudoplastic flow. In this case, the value of N is less than unity and decreases as the dilatancy increases.

1.4.3 Viscosity measurement

Viscosity is measured by means of instruments known as viscometers. Various types are in use. These include:

(a) Capillary viscometers which are used for Newtonian liquids and which measure the rate of flow of liquids through capillary tubes,

(b) The falling sphere viscometer which is based on the Stoke's law and in which a glass or steel sphere of known diameter and density and whose temperature is in equilibrium with that of the liquid under test is made to fall in a tube containing the liquid

and the time taken for the sphere to move between two marks, A and B, accurately measured, and

(c) The rotational viscometers in which the material under test is placed between two components which are then relatively rotated about the same axis of symmetry.

All viscometers can be used to determine the viscosity of Newtonian systems but only the rotational viscometers with variable shear stress controls can be used for non-Newtonian materials.

1.4.4 The cone and plate viscometer

This is an example of the rotational viscometer. The liquid sample being tested is placed on a plate which is then gently raised to make contact with the apex of a slightly conical disc. The latter is then rotated at a fixed speed, the material is sheared in the narrow gap between the rotating cone and the stationary plate, and the torque (shearing stress) transmitted through the sample to the cone at each rate of shear is measured. A graph of shear rate (in r.p.m) can then be plotted against shearing stress. The equation for calculating the viscosity as given in the operating manual of the Ferranti-Shirley viscometer is:

$$n = \frac{3\omega}{2\pi R^3} \times \frac{G}{\Omega} \qquad \text{..... Equation 6}$$

where ω = cone angle

Ω = Angular velocity

R = Radius of cone

G = Torque on the cone

The cone and plate viscometer possesses several advantages over other viscometers. These include:

(a) Water from a thermostatted bath is circulated through the rigid plate thereby allowing for temperature stabilization of the sample during a run.

(b) The shear rate is equal to the ratio of the linear velocity to the gap width.

i.e shear rate = $\Omega r/c$. ..... Equation 7

where Ωr = linear velocity

and c = gap width

The shear rate is therefore constant throughout the entire sample under test since both the linear velocity and the gap width are proportional to the radius, r.

(c) Only a small sample volume of 0.1 to 0.2ml is required.

(d) Ease of clearing off sample allows for wastage of less time between discontinuing one measurement and initiating another.

(e) Being a rotational viscometer, it can be used for both Newtonian and non-Newtonian systems.

(f) Ease of increasing or decreasing the rate of shear in a pre-determined reproducible manner.

(g) The possibility of connecting the viscometer to an x-y recorder which automatically plots the shear stress as a function of the rate of shear.

1.4.5 Importance of viscosity measurements

The result of viscosity determinations provide valuable information for use in formulating pharmaceutical products (Martin et al, 1969(iii)). An example of such useful information is the suspending property of a material. A non-Newtonian dispersion medium that exhibits plastic or pseudoplastic behaviour will retard the sedimentation of small particles since its apparent viscosity will be high at the small stresses associated with sedimentation. In addition, pourability and redispersion are facilitated by the decrease in apparent viscosity that occurs at the higher shear rates involved in these processes (Finar, 1975 (iii)). Rheological properties can provide information as to the chemical structure of pure liquids. For example, in a homologous series, viscosity increases with molecular weight, n - compounds exhibit higher viscosities than their isomers with branched carbon chains, and trans-compounds show higher viscosities than their corresponding cis-isomers (Finar, 1975 (iii)). Viscosity values can be used to determine the degree of association in liquids since associated liquids show abnormal viscosities (Finar, 1975 (iii)). More energy is required to break bonds and permit flow in liquids composed of

molecules which are associated through hydrogen bonds (Martin et al, 1969 (ii)). The molecular weights of macromolecules (e.g polysaccharides) in solution can be determined from viscosity measurements (Carter, 1972(ii); Finar, 1975 (iii)). An equation used for this purpose is

$$[n] = KM^{a} \quad \ldots\ldots\ldots \text{ Equation 8.}$$

where $[n]$ = intrinsic viscosity

M = molecular weight

K and a = empirical constants which depend on the nature of the solvent, the macromolecule, and the temperature, and which have to be obtained by separate experiments at fixed temperature with a given polymer-solvent system.

1.5 CHROMATOGRAPHY

1.5.1 Introduction

Chromatography provides a useful means of separating two or more substances by distributing them between two phases, one stationary and the other mobile. There are various forms available which may be used for separation, isolation, purification and identification of components in a mixture. The name ascribed to each type is determined by the nature of the two phases used.

Adsorption chromatography employs a solid (the adsorbent) as the stationary phase and a liquid as the mobile phase. Passage of a solution of the mixture down the adsorbent column results in the components being adsorbed on different parts of the column and the separation is made more efficient by the subsequent passage of a suitable solvent, the eluent, down the column. The components which have now been separated into distinct zones are extracted individually or eluted from the column in a continous process.

Thin-layer chromatography (TLC) is a special case of adsorption chromatography in which a chromoplate replaces the column. Development of the chromatogram after application with a micropipette of an aqueous solution of the mixture and drying occurs by capillary movement of the solvent up the adsorbent layer.

Partition chromatography is the method in which a liquid (usually water) strongly adsorbed on a solid column represents the stationary phase while a solution of the mixture in a suitable solvent (immiscible with the adsorbed liquid) serves as the mobile phase. The mobile phase and the pure solvent are successively made to slowly pass down the column. The solutes are thus distributed between the stationary and mobile phases. Owing to their different partition coefficients, the components are separated by elution.

Paper chromatography is a special case of partition chromatography where the adsorbent column is replaced by a strip or sheet of paper and the mobile phase is an organic solvent or mixture of solvents.

Other methods include:

Zone electrophoresis which is based upon the principle that ions in a dispersion medium migrate at different rates under the influence of a potential difference applied between two electrodes.

Ion-exchange chromatography in which the solid phase is a synthetic resin. The two types of exchange resins in use are the cation and anion exchangers. Mixtures of bases or acids may thus be separated and the column eluted with buffer solutions of different pH values.

Gas chromatography in which the mobile phase is a mixture of gases and the stationary phase solid (gas-solid chromatography, GSC) or solid coated with a suitable non-volatile liquid (gas-liquid chromatography, GLC). A 'carrier' gas such as nitrogen or hydrogen replaces the solvent in column chromatography and the technique is suitable for volatile substances that do not decompose at temperatures up to 300°C.

High performance liquid chromatography, HPLC, which closely resembles Gas chromatography, GC, and is capable of separating non-readily volatilised substances. It is particularly suitable for separation of compounds possessing one or more of the following characteristics. Viz:

(a) high polarity

(b) high molecular weight

(c) thermal instability and

(d) a tendency to ionise in solution.

It combines the advantages of high pressure pumps, specially designed injectors, high sensitivity detectors and gradient elution devices. Thus the sample for analysis is small and is injected directly onto the column. HPLC mainly differs from GC on account of the use of liquid in place of a gaseous eluent (Simpson, 1978; Knox, 1978).

1.5.2 Paper chromatography

In paper chromatography a suitable filter paper such as Watman No 1 filter paper is used as a support for the stationary liquid phase. An aqueous solution of the mixture is applied with a micropipette near the middle of one edge of the paper and dried. The dried sheet of paper is then placed in a suitable glass vessel containing the organic solvent which has been previously saturated with water such that the solvent makes contact with it but the level still remains below the spot. The chromatogram is developed by either of three techniques - ascending, descending or radial - depending on the direction of movement of the mobile phase.

If the components of the mixture are coloured, detection would pose no problem as their different positions on the developed chromatogram would be quite visible to the naked eye.

However, as is often the case, the solutes are colourless and this necessitates that a reagent that gives colours with the various components be used to spray the chromatogram. Examples of such reagents are ammoniacal silver nitrate solution and N,N-dimethylaniline hydrochloride which give black and coloured spots respectively with reducing sugars. Also ninhydrin gives colour reactions with hexosamines (Partridge, 1948). The resultant coloured spots reveal the position of each component of the mixture on the chromatogram. The ratio of the distance moved by a component to the distance moved by the solvent front is known as the Rf number and is characteristic of each component and dependent on experimental conditions. It is, therefore, very helpful for detection purposes if the process is carried out simultaneously with the mixture and reference samples.

A technique sometimes used for better separation is the two-dimensional chromatography. In this, the aqueous solution of the mixture is applied with a micropipette near one corner of the chromatographic paper and the chromatogram is developed in the usual manner. The components occupy different positions near and parallel to the edge. The chromatogram is dried, turned through 90° and the edge dipped into the solvent for another development. The paper is then dried, sprayed and re-dried. The product is a two-dimensional chromatogram with each component having two Rf numbers.

Paper chromatography is official for detecting the presence of and distinguishing between isoprenaline, orciprenaline and salbutamol in aerosol inhalations. Its use in detecting the presence of the active ingredients in Physostigmine and Pilocarpine eye drops and in Brilliant Green and Crystal Violet Paint are also official (BPC, 1973 (ii)).

1.5.3 Pharmaceutical Applications of Chromatography

Chromatography is used for the resolution of solute mixtures by the exploitation of differences between the solutes of adsorptive power, partition coefficient and affinity for ion-exchangers. Chromatography can also be employed in qualitative analysis for the identification of substances such as reducing sugars, amino acids, alkaloids, etc. This can be done, for example, through colour reactions given by the resolved components when interacted with spray reagents or by Rf numbers. The components of a mixture can also be isolated and quantitatively assayed by chromatographic methods. Limit tests for impurities can also be carried out in this manner (BPC, 1973 (ii)). Purification exercise can also be carried out by chromatographic means. For instance, it has been reported that linseed mucilage can best be deproteinised non-destructively on a carboxymethylcellulose column. Ion-exchange column chromatography

was also found to be effective in purification of the mucilage from mineral components (Kalac et al, 1968).

1.6 ULTRA-VIOLET AND INFRA-RED SPECTROSCOPY IN ANALYTICAL WORK

1.6.1 Introduction

When electromagnetic waves including visible light is absorbed by a molecule, transition to a state of higher energy is undergone by the molecule. Energy changes in a molecule result from four types of motion. The energies of all these motions are quantised and possess only certain discreet values. These motions are electronic transition between atomic orbitals, translational, rotational and vibrational motions (Martins et al, 1969(i)). If the molecule is monoatomic, the absorbed energy only raises the energy levels of electrons thus leading to electronic transition of bonding σ or π electron to antibonding σ or π orbitals. Lone pair, non-bonding electron (n) can also be excited to antibonding σ or π orbitals (Finar, 1973 (ii); Finar 1975 (ii)). These transitions and their general order of energy difference are as given below:

$$\sigma \longrightarrow \sigma^* > n \longrightarrow \sigma^* > \pi \longrightarrow \pi^* > n \longrightarrow \pi^*$$

While electronic transitions give absorption or emission in the ultra-violet and visible part of the electro-magnetic spectrum, the rotational and vibrational changes give absorption or

emission in the far and near infra-red (Martin et al, 1969 (i); Finar, 1975 (ii)). Change in translational energy of molecule brings with it alteration in temperature since the latter is directly proportional to kinetic enery (Martin et al, 1969(i)).

It is possible to calculate the wavelengths of the spectra resulting from energy changes by means of Plank's law.

$$E = h.c/\lambda \quad \ldots\ldots\ldots \text{Equation 9.}$$

where E = Quantum energy

h = Plank's constant

c = Velocity of light

λ = Wavelength of the radiation

$c/\lambda = V$ = frequency of radiation

The frequency of absorption is affected by such factors as masses of the bonded atoms, naiure of neighbouring atoms and steric effect. Thus a particular group is associated with a region of absorption rather than a fixed maximum absorption wavelength. The rest of the molecule determine the actual position of the maximum absorption (Finar, 1975 (ii)).

1.6.2 Ultra-violet spectrophotometry

The wavelength of absorption in the Ultra-violet region range from 200 to 400nm. Exposure of molecules of a liquid or solution to continous radiation in this or the visible region (400-750nm) of the electromagnetic spectrum leads to absorption

of light of various frequencies or wavelengths. The transitional energy accompanying the absorption determine the frequency or wavelength (Martin et al, 1969(i)). Any structural feature that produces light absorption in the ultra-violet region or colour in the visible region is referred to as a chromophore (Martin et al, 1969(i); Finar, 1973 (ii)).

An ultra-violet spectrophotometer is an instrument used for the quantitative measurement of light absorption in the ultra-violet region (Martin et al, 1969 (i)). In its simplest form, a beam of monochromatic light is focussed on a prism where it gets reflected and pass through the test solution or a blank solution contained in a cell. The emergent beam strikes a photocell and current, which is proportional to the intensity of the radiation, is consequently released. The current is read on a galvanometer. By varying the position of the prism, the measurement can be carried out at various wavelengths. If I_o is the intensity of an incident beam of monochromatic light, and I that of the emergent beam which has passed through the cell b cm thick containing the test solution whose concentration is c g/litre, then the extent of absorption can be calculated from the Beer law.

$$A = \log \frac{I_o}{I} = abc \quad \ldots\ldots \text{Equation 10}$$

where A = Absorbance (or Optical density)

a = proportionality constant known as absorptivity

(extinction or absorption coefficient)

The wavelength, nature of solvent and the temperature at which the analysis is carried out all affect the value of a. By varying the wavelength, different values of absorbance are obtained for the same solution. The absorbance when plotted as a function of the wavelength gives the ultra-violet spectrum for that material.

For quantitative analysis, the absorbance given by different concentrations of the test material in solution is measured at any suitable wavelength (usually the wavelength of maximum absorbance). The absorbance is then plotted against the concentration to give a linear graph popularly known as the Beer-Lambert plot. To obey the Beer law, it is important that the solutions be sufficiently dilute. The unknown concentration of a given solution can be easily determined using the Beer-Lambert plot once its absorbance at the specified wavelength is known.

Apart from its use in quantitative determination of known molecules in solution, ultra-violet spectrophotometry can also be used qualitatively in the detection and elucidation of nature of conjugated systems including aromatics and in detection of a few functional groups since wavelength of maximum absorbance is characteristic for different chromophores (Martin et al, 1969 (i); Finar, 1975 (ii)). The effect of different solvents on the spectrum of the solute can be of some significance in elucidating molecular structure and interactions (Martin et al, 1969(i)).

1.6.3 Infra-red spectrophotometry

The frequency of absorption in the infra-red region falls between 4000 and 650 cm^{-1}. Absorption in this region is attributed to changes in vibrational energy (Martin et al. 1969(i); Finar, 1975 (ii)) and this absorption is possible as long as the vibration in the molecule of a substance produces unsymmetrical charge distribution. It is therefore not necessary for a molecule to possess a permanent dipole moment (Finar, 1975 (ii)). There are two possible vibrational modes. These are stretching and bending of interatomic bonds (Martin et al. 1969(i)). The stretching mode can be a symmetrical or asymmetrical vibration along the bonds while the bending mode or deformation is displacement perpendicular to the bonds and this could be in-plane deformation (scissoring or rocking) or out-of-plane deformation (wagging or twisting) (Finar, 1975 (ii)). The stretching regions have higher frequencies or lower wavelengths and the absorptions are of much greater intensity than the bending regions. Of very great importance is the finger-print region (1400-650 cm^{-1}) which is associated with vibrational and rotational energy changes of the molecular skeleton and so is characteristic of the molecule and therefore invaluable for identification.

Infra-red spectrophotometers are used for the measurement of absorptions in the infra-red region of the electromagnetic spectrum. An example is the Perkin-Elmer IR spectrophotometer 7108 and the basic features are essentially same as for UV

spectrophotometers. Absorption bands are characteristic for the individual groups contained within a molecule. Infra-red spectroscopy, therefore, is invaluable in qualitative analysis for identifying materials and elucidating the structure of unknown compounds (Martin et al, 1969(i)). It can also be used to distinguish between geometric isomers, ascertain the existence of tautomerism, evaluate dipole moments, ascertain the presence of hydrogen bonding and differentiate between intra- and inter-molecular hydrogen bonding (Finar, 1975 (ii)). By virtue of the fact that the height of an absorption band is theoretically directly proportional to the concentration of a particular group present, it is also useful in the quantitative determination of compounds (Martin et al, 1969(i)). The number of hydroxyl groups present in a molecule of known molecular formula can, for instance, be ascertained by measuring the intensity of free hydroxyl bands. Presence of different conformations can similarly be identified and quantified (Finar, 1975 (ii)).

1.7 Detarium microcarpum PLANT (TALLOW TREE)

1.7.1 Introduction

Detarium microcarpum Guill and Perr. (Fam. Caesalpiniaceae) is a savannah tree with reddish-brown scaly bark and which produces sweet edible fruits with fibrous exocarp and bony endocarp. It grows up to a height of about 30ft. The other two known species of the Detarium plant, namely D. senegalenses and

D. macrocarpum are forest trees that grow to a height of 30-120ft and 180ft, respectively. Detarium microcarpum has been documented in the literature by several authors (Hutchinson and Dalziel, 1958; Oliver, 1960; Hutchinson, 1964; Keay et al, 1964) but these are mainly botanical descriptions.

1.7.2 Local Names

Detarium microcarpum grows wildly in the drier savannah areas, widespread from Senegal to Sudan and Nigeria (Keay et al, 1964). It is not suprising, therefore, that most tribes in Nigeria have local names by which the plant is known. These tribes and the corresponding local names of the plant are given below. Viz:

Tribe	Local Name
Igbo	"ofo"
Yoruba	"ogbogbo"
Hausa	"taura"
Tiv	"agashidam"
Fulani	"konkehi"
Etsako	"aikpelarimi"
Nupe	"gungorochi"
Kanuri	"gatapo"

1.7.3 Applications

Perhaps various tribes in Nigeria use the plant for different purposes. The bark is reported to yield gum-resin, and that, as well as the leaves, are said to be used in wound dressing and in dysentery. This gum-resin is also believed to have antibiotic action against venereal diseases (Oliver, 1960). The fruit, as previously mentioned, is sweet and edible. The seed cotyledons are used as thickening agent in soup making in some parts of Igbo land.

Also in the same region, there are some localities that regard the tree as sacred. The twigs provide staffs of authority that can be found in many a pagan homestead often smeared with several layers of encrusted animal blood and sporting the plumage and hairs of many animals sacrificed to idols. To them, it is the symbol of uprightness and is believed to be capable of vindicating the just and metting out severe punishment to oppressors and the wicked.

1.7.4 Detarium microcarpum seed

The seed is enclosed in a hard disc-shaped wrinkled stone (the endocarp). Only one seed is contained in each stone. The testa is dark brown in colour but the cotyledon is white. The cotyledons contain the seed mucilage which serves as a food and water reservoir and as a protective for the germinating seed. It

has the capacity to swell tremendously in water and the ground powder hydrates slowly in aqueous medium to form a very viscous colloidal dispersion.

1.7.5 Traditional methods of processing

There are three methods by which the seeds may be processed. These methods are designed to facilitate the removal of the testa since it is only the cotyledon that is of use as broth thickener. The seeds may be pre-soaked in water for two to three days or pre-boiled for about one hour or roasted over red-hot charcoal. After this pre-treatment, the testa is easily detached and the cotyledons ground on a stone slab or with the manually-operated grinding machine. It is then ready for immediate use. It can also, at this stage, be dried in open air and stored for future use.

1.8 AIMS AND OBJECTIVES OF STUDY

1.8.1 Aims and Objectives

This study aims at scientifically contributing to knowledge of the potentials of our flora as regards its benefits to the pharmaceutical industry. It aims at finding local substitutes for hitherto imported pharmaceutical raw materials thus disengaging the country from over-dependence on importation.

It is hoped that utilization of the findings derived from this work will go a long way towards conserving Nigeria's scarce foreign reserves.

1.8.2 Scope of work

The work covers such investigations as

(i) Qualitative analysis of Detarium microcarpum seed and its oil constituent.

(ii) Comparative study of two different traditional methods of processing the seed.

(iii) Rheological properties of aqueous dispersions of the powdered pre-treated seed and seed mucilage.

(iv) Water sorption studies of the powdered pre-treated seed.

(v) The binding, disintegrant and direct compression properties of various forms of the material in tableting and

(vi) Evaluation of the properties of the tablets formulated with the test materials.

CHAPTER 2

2.0 MATERIALS AND EXPERIMENTAL METHODS

2.1 PRELIMINARY INVESTIGATION

2.1.1 Identification

The seeds, leaves and twigs of the plant were identified at the Department of Biological Sciences, Ahmadu Bello University, Zaria as belonging to the plant Detarium microcarpum.

2.1.2 Collection and processing of seed

Some dry fruits from the previous year's harvest were collected from Nimo in Njikoka Local Government Area of Anambra State. The seed was enclosed in a hard disc-shaped wrinkled stone that had to be cracked before extraction. Some of the seeds were bought from the Sabon-gari market in Zaria.

Some of the seeds were soaked in water for three days while some others were boiled in water for one and a half hours. The objective was to facilitate the easy removal of the dark-brown testa prior to grinding. The latter process was carried out by means of a kitchen blender (Moulinex Standard blender-mill 2, Moulinex, France).

2.1.3 Processing of the powders

The ground mass derived from the two methods of seed processing (i.e pre-soaking and pre-boiling) were separately subjected to the following sequential treatment.

(i) Drying in an oven (Gallenkamp oven BS size 3) at a temperature of 80°C for three hours.

(ii) Defattening in a Soxhlet extractor using Petroleum ether 60°-80°C (BDH Chemicals, England) as the solvent.

(iii) Separation of the oil extract from petroleum ether by means of a distillation apparatus (Rotavapor R 110, Switzerland) connected to a vacuum pump.

(iv) Heating the oil on a water bath to remove residual traces of petroleum ether.

(v) Air-drying the defatted powder. The resultant powder was labelled "SS" for that got from the pre-soaked seeds and "BS" for that got from the pre-boiled seeds.

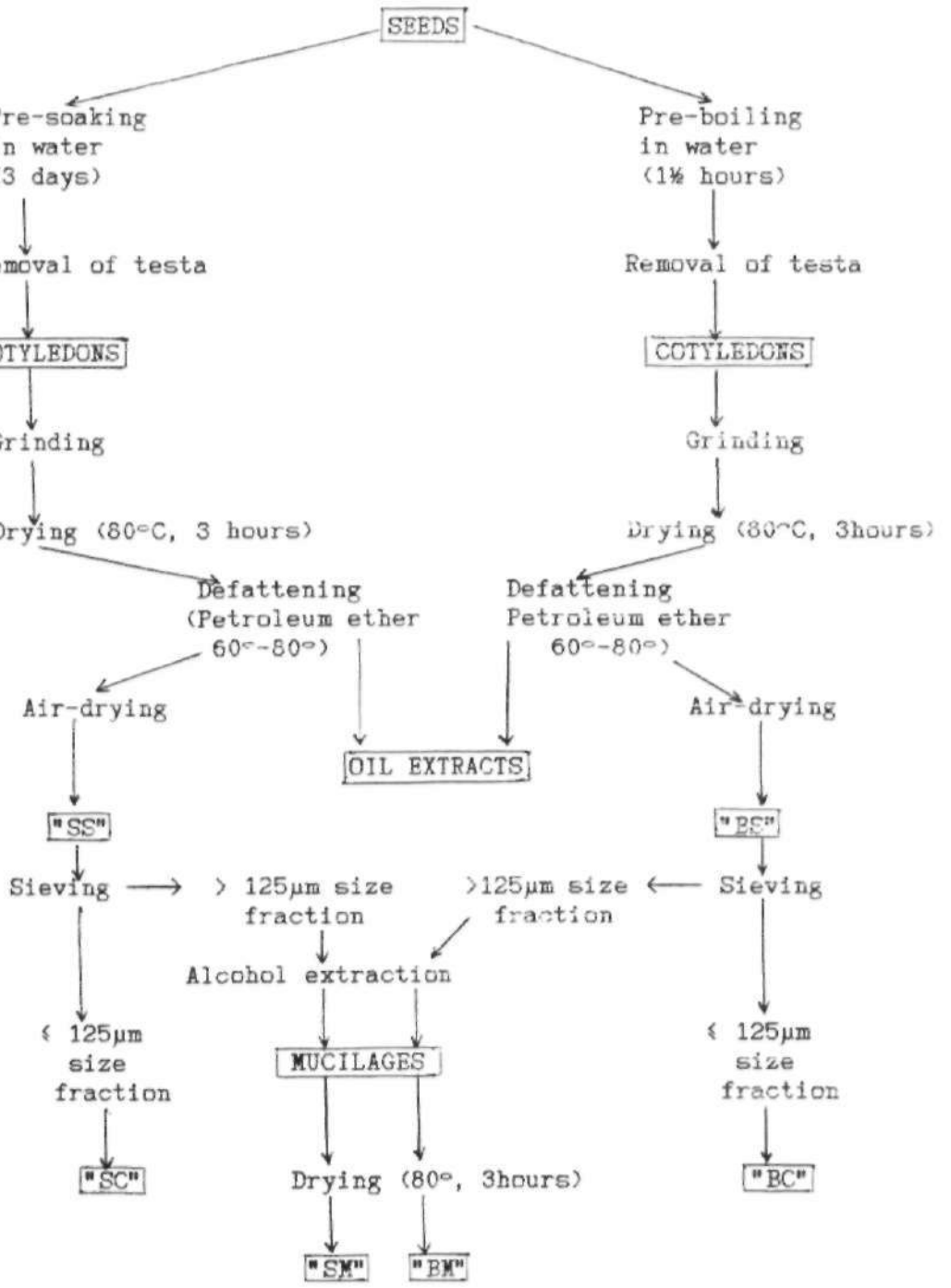
and (vi) Sieving each of the powder samples with a 125µm sieve with a view to separating them into two size fractions. Viz.

(a) Powder of particle size ‹ 125µm meant to be used in its crude form. This was labelled "SC" if it originated from the pre-soaked seed and "BC" if the source was the pre-boiled seed.

and (b) powder of particle size › 125µm meant to be subjected to further treatment.

A diagramatic representation of these processes is shown in Figure 2.

Figure 2....:
Schematic diagram of processes involved in preparation of samples for investigation



2.1.4 Preparation of the mucilages

The powder fraction of particle size > 125µm was soaked in water and allowed to hydrate overnight. The viscous dispersion that resulted was passed through a 500µm sieve to break up any lumps that could have been formed. Sufficient quantity of absolute alcohol was added with stirring to precipitate the mucilage in the sample. The mucilage was then washed with acetone and dried in an oven (Gallenkamp oven BS size 3) at a temperature of 80°C for three hours. The dried mucilage was comminuted with a kitchen blender (Moulinex Standard blender-mill 2, Moulinex, France) and sieved with a 125µm sieve. The fraction with particle size ⩽ 125µm was packaged and labelled "SM" (if derived from the pre-soaked seeds) and "BM" (if derived from the pre-boiled seeds)

2.1.5 Analysis of seed for its constituents

A sample of ground undefatted pure pre-soaked cotyledons labelled "SAMPLE A" and another of ground unprocessed dry seeds labelled "SAMPLE B" were submitted to the Analysis Laboratory of the National Animal Production Research Institute (NAPRI) of the Ahmadu Bello University for analysis of its constituents.

A sample of the oil extract was used to run an Infra-red spectrum in a Perkin-Elmer IR spectrophotometer 7108 at the Chemistry Department of the Ahmadu Bello University.

2.1.6 Chromatographic determination of polysaccharide building units

0.5g "SM" was refluxed in 50ml 4% sulphuric acid for 20 hours on a water bath to hydrolyse it. Sufficient quantity of barium carbonate (BDH Chemicals, England) was added to neutralise the excess acid in the hydrolysate and the contents of the flask filtered to yield a clear brown filterate which was then labelled "MUCILAGE HYDROLYSATE". The same process was carried out with 0.5g SC and the resultant filterate in this case labelled "CRUDE HYDROLYSATE". The hydrolysate, in each case, was concentrated by partial evaporation on a water bath.

5% w/v aqueous solution each of xylose, galactose, galacturonic acid, glucose, arabinose and fructose (all from BDH Chemicals, England) were prepared and, along with the hydrolysates, applied with fine capillary tubes on Whatman No 1 chromatographic paper. The chromatogram was developed in a chromatographic tank (PANGLAS T.L.C Chromatank, Shandon Unikit, England) by the ascending technique until the solvent front has moved a distance of approximately 15cm. The solvent system was n-butanol-pyridine-water in the ratio of 6:4:3. The chromatogram was then dried in air and sprayed with freshly prepared ammoniacal silver nitrate solution. The positions of the reducing sugars as revealed by darkened spots were marked with pencil.

2.1.7 Other qualitative tests

The following tests were also carried out on the crude powder, SC.

(i) A little quantity of the powder was placed on a slide, irrigated with iodine solution and examined under the microscope.

(ii) 5ml of 1% w/v aqueous colloidal solution of the material was measured into a test tube and heated following treatment with a mixture of Fehling's solutions A and B.

(iii) 5ml of 1% w/v aqueous colloidal solution of the material was heated with dilute hydrochloric acid in a test tube. This was followed by treatment with Fehling's solutions A and B and raising the temperature to boiling.

(iv) 5ml of 1% w/v aqueous colloidal solution of the material was tested with a universal indicator.

(v) A sample of the powder was observed for colour and tested for feel, taste and smell.

2.1.8 Rheological properties

Aqueous dispersions of SC (4,2,1 and 0.5% w/v), BC (4,2,1 and 0.5% w/v), SM (4, 2, 1 and 0.5% w/v) and BM (4, 2, 1 and 0.5% w/v) were prepared. Maize starch paste (15, 10 and 5% w/v) and gelatin solution (15, 10 and 5% w/v) were also prepared in water. A drop of these preparations were separately fed into the Ferranti-Shirley viscometer (Ferranti Ltd., England) and sheared at different speeds starting with zero, increasing step-wise to

100 r.p.m. and thereafter decreasing in the reverse order to zero. The instrument reading (i.e the shear stress) at each rate of shear was recorded. The apparent viscosities at shear rates ranging from zero to 100 r.p.m were calculated using the formula provided in the operating manual of the viscometer.

$$\text{Viscosity} = \frac{\text{Cone constant} \times \text{Instrument Reading} \times \text{range}}{\text{Speed}}$$

..... Equation 11

Graphs of shear stress against shear rate and those of viscosity against shear rate were plotted.

2.1.9 Water sorption studies

SC (2.0g), BC (2.0g), SM (1.0g), BM (2.0g) and maize starch, MS (2.0g) were each accurately weighed into an evaporating dish and the final weight of both the dish and material noted. The dishes were then stored in a desiccator first over a saturated solution of potassium chloride for 7 days, then over water for 5 days and lastly, over a desiccant (anhydrous calcium sulphate) for the next 4 days. The dishes and their contents were weighed on daily basis and the water content calculated.

2.2 FORMULATION STUDIES

2.2.1 Materials

Powdered samples of SM, SC, BM and BC prepared as previously described, Maize starch (May and Baker, England), Gelatin powder (BDH Chemicals Ltd. England), Chloroquine phosphate , Magesium stearate (Hopkin and Williams Ltd., Switzerland), Talc, Lactose (May and Baker, England), Avicel and Starch 1500.

2.2.2 METHODS OF PREPARATION OF GRANULES AND TABLETS

A 1% w/v colloidal solution of SM in water was prepared for the test run. The calculated quantities of the chloroquine phosphate and maize starch were mixed. Aliquots of the binder solution were added into the powder mix with trituration in a mortar until a desirable consistency was obtained. The volume of binder used was calculated from the difference in volumes of the binder solution before and after its addition to the powder mass. The wet mass was passed through a 1 mm sieve to produce the wet granules which were then dried in oven (Gallenkamp oven BS size 3) at a temperature of 80°C for 3 hours. Magnesium stearate and Talc were then added as lubricants before tableting. The formula

for a batch of 100 tablets containing 150mg chloroquine phosphate per tablet is given in Table 1.

Table 1: Formula for a batch of 100 chloroquine phosphate tablets

Chloroquine phosphate powder (active ingredient)	-	15.00g ≡ 92.3% w/w
Maize starch (disintegrant)	-	1.00g ≡ 6.2% w/w
SM in 1% w/v solution (binding agent)	-	0.05g ≡ 0.3% w/w
Magnesium stearate (lubricant)	-	0.10g ≡ 0.6% w/w
Talc (lubricant)	-	0.10g ≡ 0.6% w/w
		16.25g

Batches of granules for a hundred tablets per batch were prepared using 4% w/v, 2% w/v, 1% w/v and 0.5% w/v of BM, SM, BC and SC solutions as binding agents. Other batches were prepared with 15% w/v, 10% w/v and 5% w/v of maize starch (MS) paste and gelatin (G) solution. One batch was prepared in which only water was used as the granulating fluid. 2.5ml of the granulating fluid was used in each case. The formula for the different batches of tablets containing varying amounts of binders is shown in Table 2.

Table 2. Formula for batches of 100 chloroquine phosphate tablets containing varying concentrations of binding agents.

Chloroquine phosphate powder	-	15.0g
Maize starch	-	1.0g
Binder solution	-	q.s.
Magnesium stearate	-	0.1g
Talc	-	0.1g

40ml of 2% w/v SM solution was used to granulate 240g of chloroquine phosphate and the resultant granules coded SM2 (II).. Wet massing operation as previously described was also used. 1.6g each of magnesium stearate and talc were added as the lubricants. After "bolting the granules" with the lubricants, 0.31g, 0.803g or 1.694g of SM, SC, BM, BC and maize starch (MS) were added to 15.25g portions of the lubricated granules to ultimately make 2.5, 5.0 and 10.0 % w/w of the finished tablet. One batch containing no disintegrant was also produced. The formula for a 100 tablets of the different batches of chloroquine phosphate tablets containing varying concentrations of disintegrants is shown in Table 3.

Table 3: Formula for batches of 100 chloroquine phosphate tablets containing varying concentrations of disintegrants

Chloroquine phosphate powder	-	15.0g
SM in 2% w/v solution	-	0.05g
Disintegrant	-	q.s.
Magnesium stearate	-	0.1g
Talc	-	0.1g

For the investigation of direct compression properties, binary mixtures in proportions of 0:100, 25:75, 50:50, 75:25 and 100:0 comprising SC and lactose (coded SC-L) and others comprising BC and lactose (coded BC-L) were prepared. Similar concentrations of Avicel - lactose and starch 1500-lactose binary mixtures were prepared for comparison and coded Av-L and St-L, respectively. Similar proportions of SC-Avicel (coded SC-Av), BC-Avicel (coded BC-Av), SC- Starch 1500 (coded SC-St) and BC-Starch 1500 (coded BC-St) binary mixtures were also prepared.

2.2.3 Analysis of granules

Each batch of granules prepared for the purpose of investigating the binding properties of the test materials and the bulk granules prepared for investigating the disintegrant properties of the test materials were analysed for the following physico-mechanical properties. Viz:

(i) Particle size analysis:

This was by sieving method. A stack of sieves were arranged in a sieve shaker (Endecott test sieve shaker, E.F.L.I. MK II, Endecotts Ltd., England) in the order of decreasing aperture size from top to bottom and ending up with the pan. The sieve shaker which operated at a frequency of 50 cycles per minute was set to operate for 30 minutes after which the granules retained on each sieve was weighed on Mettler P 163 balance.

(ii) Bulk density:

This was carried out by simply measuring the volume occupied by a known weight of the granules as it is poured into a dry 100ml glass cylinder. The bulk density was calculated from the formula

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Volume of granules}} \text{ g/cm}^3 \quad \text{.... Equation 12}$$

(iii) Tapped density:

A known weight of the granules was poured into a dry 100ml glass cylinder and the latter tapped 90 times on a flat laboratory bench after which there ceased to be any further decrease in volume. The final volume was recorded and the tapped density calculated from the formula

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules}}\ g/cm^3 \quad \text{..... Equation 13}$$

(iv) Percentage compressibility:

This was simply calculated from the formula

$$\%\ \text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100\% \quad \text{..... Equation 14}$$

(v) Angle of repose:

A plastic funnel was clamped on a retort stand such that it hanged over a sheet of paper spread on a flat laboratory bench. The granules were gently poured through the funnel onto the sheet of paper on which they ultimately rested in a conical heap. The height of the funnel was kept at 3.2cm in the case of granules prepared with different granulating fluids and 6.5cm in the case of the bulk granules prior to extra-granular incorporation of disintegrants such that its tip was close to but not touching the tip of the cone. The height and diameter of the cone were measured. The angle of repose, ø, which is the angle made by the edge of the cone with the horizontal, was calculated from the relationship

$$\tan \phi = \frac{\text{height of cone}}{\text{radius of cone}} \quad \ldots\ldots\ldots \text{Equation 15}$$

where ϕ = Angle of repose

and $\tan \phi$ = Coefficient of friction, μ.

The granules were also tested for flowability. 52.377g of the granules (enough to just fill the funnel of the flowability apparatus Type GDT Erweka-Apparatebau, W. Germany) was poured into the funnel of the flowability apparatus and the time it took the granules to completely leave the cone of the funnel was recorded.

2.2.4 Compression of tablets

The various formulations and binary mixtures were compressed into tablets in a single punch tableting machine (Korsch-Berlin Type EKO coupled to Erweka AR 400 motor) fitted with 8mm flat-faced punches. For the investigation of each tableting property, a constant compression pressure setting was used. They were 6 units for the formulations and binary mixtures used for the evaluation of the binding and direct compression properties and 5 units for the formulations used for the evaluation of the disintegrant properties.

The batches of compressed tablets formulated with different types and concentrations of binder solutions were coded SM 4, SM 2, SM 1, SM 0.5; SC 4, SC 2, SC 1, SC 0.5; BM 4, BM 2, BM 1, BM 0.5; BC 4, BC 2, BC 1, BC 0.5; MS 15, MS 10, MS 5; G 15, G 10, and G 5, the figures denoting the concentration in per cent weight-in-volume of the binder solution. The tablet batch for which only water was used as the granulating fluid was coded W. The batches formulated with different forms and concentrations of disintegrants were coded SMD 2.5, SMD 5, SMD 10; SCD 2.5, SCD 5, SCD 10, BMD 2.5, BMD 5, BMD 10; BCD 2.5, BCD 5, BCD 10; MSD 2.5, MSD 5 and MSD 10. The batch formulated without any disintegrant was coded D0. The binary mixtures were coded in accordance with their constituents and the concentration in per cent by weight in which these were present. Thus AV-L 25:75 represents a batch of tablets obtained from compressing 25% w/w of Avicel and 75% w/w of lactose. Other codes and proportions of the mixture constituents are as explained in section 2.2.2 of this chapter. All the tablet batches were separately stored in air-tight containers for 24 hours to allow for elastic recovery and hardening before they were tested.

Evaluation of the binding properties of the various granulating fluids in the finished tablets was based on such parameters as hardness, friability, packing fraction, disintegration time, and for those batches that did not cap and which

passed the friability test, dissolution rate. Batch W was also subjected to the dissolution test. The disintegrant properties were also similarly evaluated the only differences being that all the tablet batches were subjected to the dissolution test and two of them namely SMD 10 and BCD 10 had their dissolution tests carried out in both acid (pH 4.50) and alkaline (pH 9.53) media. The hardness, friability, packing fraction and disintegration time of tablets produced by direct compression were also determined.

2.3 EVALUATION OF TABLETS

2.3.1 Uniformity of thickness and diameter

The thickness and diameter of the tablets were measured with vernier calipers. The mean value of six determinations was recorded in each case.

2.3.2 Uniformity of weight

Twenty tablets were randomly selected from each batch. They were first weighed together and then individually on Mettler P 163 balance (Mettler Instrumente AG, Switzerland). The mean weight for each batch of tablets was then calculated and the standard deviation determined.

2.3.3 Packing fraction

The true density of the mixture of tablet components under investigation was calulated from the formula

$$\frac{1}{\rho_{AB}} = \frac{W_A}{\rho_A} + \frac{W_B}{\rho_B} \quad \text{..... Equation 16}$$

where ρ_{AB} = True density of mixture with components A and B

W_A = Weight fraction of component A

W_B = Weight fraction of component B

ρ_A and ρ_B = True densities of substances A and B, respectively.

The densities of the tablet components were determined by specific gravity bottle method. The bulk density was also calculated from the formula

$$\text{Bulk density} = \frac{\text{Weight of tablet}}{\text{Volume of tablet}} \quad \text{..... Equation 17}$$

$$\text{Thus, Bulk density} = \frac{4W}{\pi d^2 h} \quad \text{..... Equation 18}$$

where W = weight of tablet

d = diameter of tablet

h = Thickness of tablet

Since the mean values of weight, diameter and thickness of each tablet batch were known from the previously described methods of

determination, the packing fraction was then calculated from the formula

$$\text{Packing fraction} = \frac{\text{Bulk density}}{\text{True density}} \quad \text{..... Equation 19}$$

2.3.4 Tablet hardness

Six tablets were randomly selected from each batch. Each of these was in turn placed between the anvil and the spindle of the Monsanto hardness tester (Monsanto Chemical Co. Ltd.) and subjected to increasing pressures by turning the knurled knob in a clock-wise direction and in as uniform a manner as possible until the tablet was crushed. The unit on the scale where the pointer rested and which corresponded with the pressure required to break the tablet was noted and the mean of six determinations was taken for each batch.

2.3.5 Tablet friability

The Erweka friabilator Type TA 3R (Erweka-Apparatebau, W. Germany) was used. Ten tablets were selected from each batch of tablets at random, weighed on Mettler P163 balance (Mettler Instrumente AG, Switzerland) and placed in the drum of the friabilator. The machine was set such that the drum rotated at a constant rate of 25 r.p.m. and for a period of 4 minutes. There-

after, the intact tablets were removed from the drum, dusted and weighed. The percentage loss of weight was calculated and recorded as the friability value for that batch.

2.3.6 Disintegration time

This was done using the BP (1980) method. The Erweka Tablet Disintegration Test Apparatus Type ZT3 (Erweka Apparatebau, W. Germany) was used. Six tablets were randomly selected from each batch and placed in the rack of six glass cylinders such that each cylinder contained only one tablet. The rack of cylinders containing the tablets was raised and lowered at a constant rate in water contained in the glass jar suspended in water bath whose temperature was thermostatically maintained at 37 ± 0.5°C. The apparatus was operated for a maximum period of 1 hour and the time taken for the tablets to completely disintegrate such that no visible speck of tablet matrix remained in the cylinders was recorded as the disintegration time for the batch of tablets under investigation.

2.3.7 Dissolution rate

The British Pharmacopoeia (1980) rotating basket method was used. For each of the batches of chloroquine phosphate tablets tested, one tablet was randomly selected, placed in the basket of the dissolution rate apparatus which was then immersed in 1 litre of the dissolution medium (0.1N Hydrochloric acid, pH

4.50) and made to rotate at a constant speed of 100 r.p.m. The temperature of the dissolution medium was maintained at 37 ± 2°C. 2ml aliquots were withdrawn from the dissolution medium at intervals of 2 minutes for the first 10 minutes, then at 5 minutes interval for the next 50 minutes and lastly at 15 minutes interval for the next 1 hour. Each withdrawal was followed by replacement with an equal volume of 0.1N HCl and dilution of the aliquot with 2ml of 0.1N HCl. The withdrawal, in each case, was effected by a syringe and rubber tubing assembly modified to contain within the tubing a plug of cotton wool so that the solution withdrawn was simultaneously filtered.

The UV absorbances of the diluted aliquots were measured at pre-determined wavelengths of 241nm in the SP 8-100 Pye-Unicam UV spectrophotometer or at 355nm in the Syva S-111 UV spectrophotometer. Absorbances of standard solutions of chloroquine phosphate whose concentrations ranged from 2.5 to 120µg/ml were also measured at 241nm and at 355nm in the corresponding UV spectrophotometers and the values obtained used to plot graphs of absorbances against concentrations otherwise known as Beer-Lambert plots and to calculate their regression equations. Values of percentage of drug dissolved were calculated from the regression equations and graphs of percentage dissolution were plotted against time to obtain the dissolution rate profiles. Dissolution test for SMD 10 and BCD 10 were also carried out in alkaline medium (0.1N NaOH, pH 9.53) for comparative work.

CHAPTER 3

3.0 RESULTS AND DISCUSSIONS I

(PHYSICO-CHEMICAL PROPERTIES)

3.1 QUALITATIVE AND QUANTITATIVE ANALYSIS OF TEST MATERIALS

3.1.1 Analysis of Detarium seed

Table 4 shows the analytical report on the Detarium seed (Lawal, 1990). It could be seen that the various constituents in %w/w that make up the cotyledons are oil (7.82), crude fibre (1.16), crude protein (12.88), mineral matter (3.97) and carbohydrates (74.17). In the whole seed, higher values in % w/w of crude fibre (3.32) and protein (15.44) suggest that the testa must be rich in these constituents and the lower values in %w/w of mineral matter (2.96) and carbohydrates (70.39) suggest that the testa contain little or no amount of these substances. This is so because the only differences between the two samples are the presence of testa and the absence of pre-treatment in sample B.

With iodine solution, SC gave few blue stains that were without sharp distinct boundaries, hilum or striations and this suggests either that starch was present or more probably that the seed polysaccharide may be classified as an "amyloid". Similar result was reported as having been given by a group of substances

TABLE 4: ANALYTICAL REPORT ON THE SEED OF THE DETARIUM PLANT

CONSTITUENTS	SAMPLE A (Ground non-defatted pure pre-soaked cotyledons)	SAMPLE B (Ground unprocessed dry seeds)
Nitrogen	2.06	2.47
Ether extract	7.82	7.89
Crude fibre	1.16	3.32
Crude protein	12.88	15.44
Ash	3.97	2.96
Nitrogen-free extract	74.17	70.39

from plant seeds such as the seeds of Tamarindus indica and to which the term "amyloid" has been applied (Aspinal, 1969). Aqueous dispersion of SC which was found to be neutral to universal indicator gave a brown precipitate with a mixture of Fehling's solutions A and B only after partial hydrolysis with dilute hydrochloric acid. These indicate that the cotyledon was devoid of a reducing sugar but composed of neutral polysaccharide(s). Physical examination showed SC to be buff, almost white in colour, brittle to touch and tasteless substance with an agreeable odour.

Paper chromatography yielded the developed chromatogram shown in Figure 3. It is, from this, evident that the hydrolysates resolved into two sugars labelled "a" and "b" with Rf numbers 0.38 and 0.49, respectively, whose positions were revealed by darkened spots (although faint in the case of the mucilage hydrolysate) and whose ascent on the chromatogram relative to the solvent system corresponded with those of glucose (Rf number 0.38) and xylose (Rf number 0.50). The value of Rf number depends on experimental conditions and is characteristic of each component (Finar, 1975(iv)). It therefore follows that the Detarium seed polysaccharide falls within the class of xyloglucans.

Figure 4 shows the infra-red spectrum of the Detarium oil. The absorption bands at various frequencies and the individual

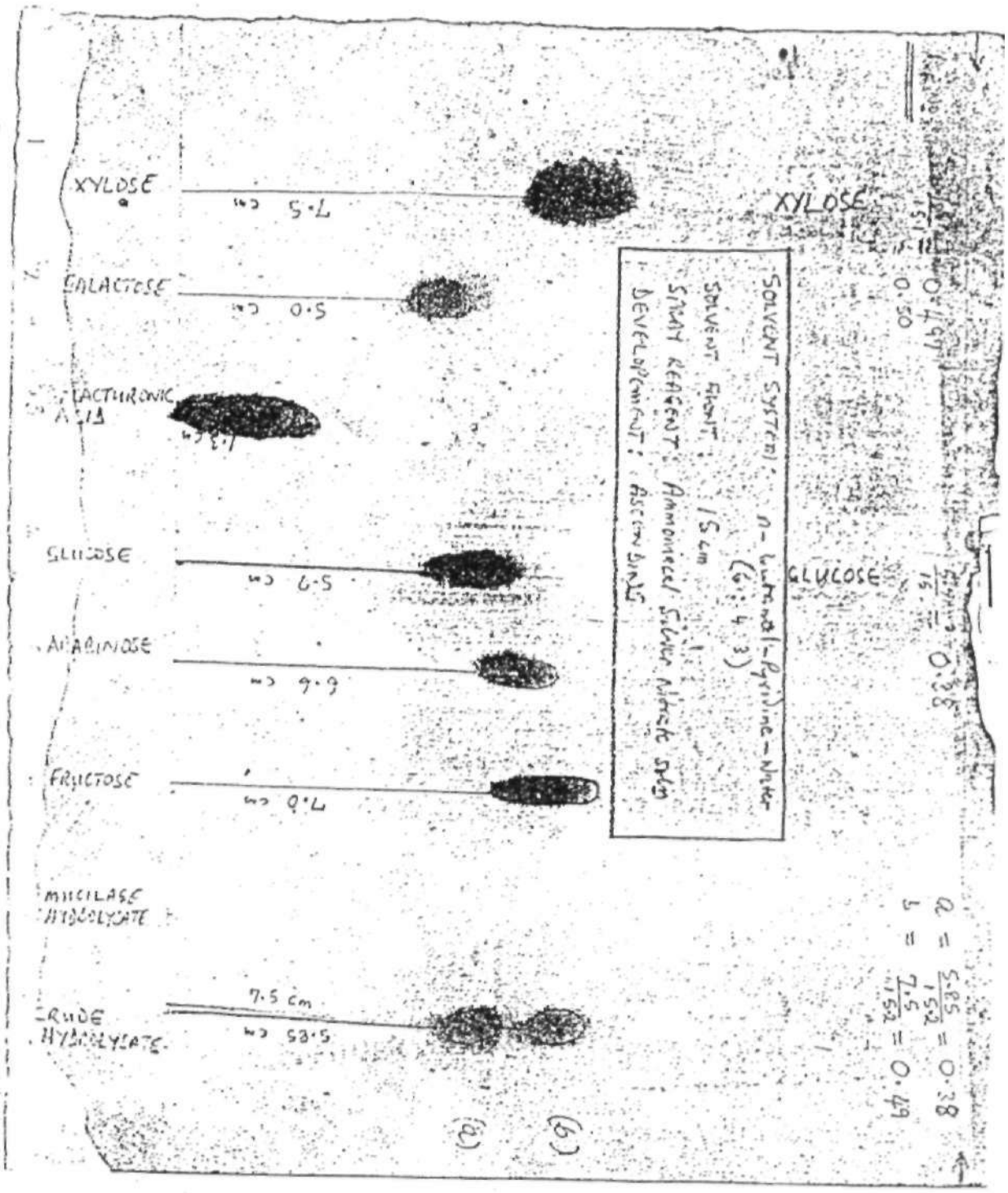


Figure 3: Paper Chromatogram of Hydrolysates Compared with Reference sugars.

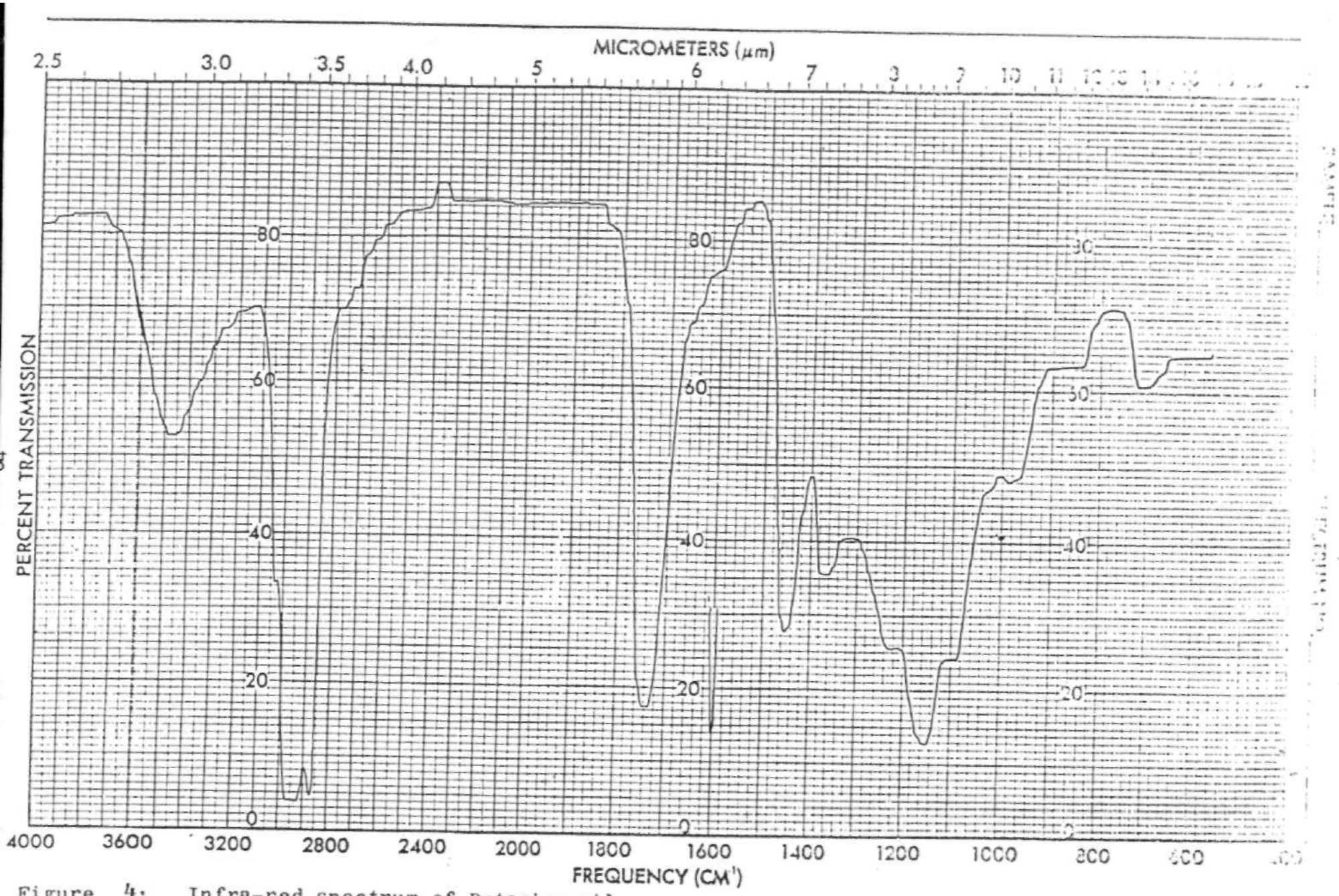


Figure 4: Infra-red spectrum of Detarium oil.

groups to which they are characteristic are as follows: 3500cm^{-1} (OH group), 2900cm^{-1} (C-H stretching), 1740cm^{-1} (>C=O group of acid or ester), 1450cm^{-1} (-C-H bending) and 1150cm^{-1} (-C-OH group). Absorptions in the infra-red region of the electromagnetic spectrum are known to be due to vibrational energy changes of which there are two modes - stretching or bending of inter-atomic bonds (Martin et al. 1969(i); Finar, 1975 (ii)). The absorptions at the observed frequencies suggest an open chain or cyclic compound that is certainly non-aromatic. However, in view of the fact that the material is a fixed oil and that fixed oils are glyceryl esters i.e. compounds of glycerol and fatty acids, the >C=O group giving the absorption at 1740cm^{-1} should be that of an ester and the compound is certainly acyclic. The specific gravity of the oil was found to be 0.897. This is within the specific gravity range of 0.875-0.970 expected of fixed oils. That the material is a fixed oil is also substantiated by the fact that it made a translucent patch when dropped on filter paper and the translucency did not disappear after heating the filter paper in an oven.

3.1.2 Seed processing

The nature of the pre-treatment given to the seed to facilitate removal of the testa was found to have some effect on the characteristics of the resultant powder and mucilage. Pre-soaking yielded whiter powder (SC) than pre-boiling. This can be

attributed to a substantial amount of the dark-brown colour of the testa that got imparted to the seed during boiling. Also, as can be seen from Figure 5, SM, the mucilage originating from the pre-soaked seeds gave more viscous aqueous dispersions than the corresponding concentrations of the mucilage extracted from the pre-boiled seeds. A reason for this observation is that heat treatment to which the pre-boiled seeds were subjected may have led to partial fragmentation of the seed polysaccharide. The same reason may have accounted for the observed insignificant difference between the viscosities of aqueous dispersions of BM and BC. SC, however, gave aqueous dispersions with lower viscosities than the corresponding concentrations of BM and BC. Structural breakdown due possibly to enzyme or microbial action when the seeds were soaked in water may be responsible for that since those factors, where present, are known to influence the viscosity of aqueous dispersions of gums and mucilages (Pernarowski, 1970; King and Baker, 1971).

3.1.3 Rheological properties

Figure 6 shows the rheograms of different concentrations of SM in water. It can be seen that the material exhibits pseudoplastic flow with no significant thixotrophy and that the shear stress at any given rate of shear increases with concentration. The pseudoplastic behaviour diminishes with decrease in concentration. Figure 7 also shows pseudoplastic

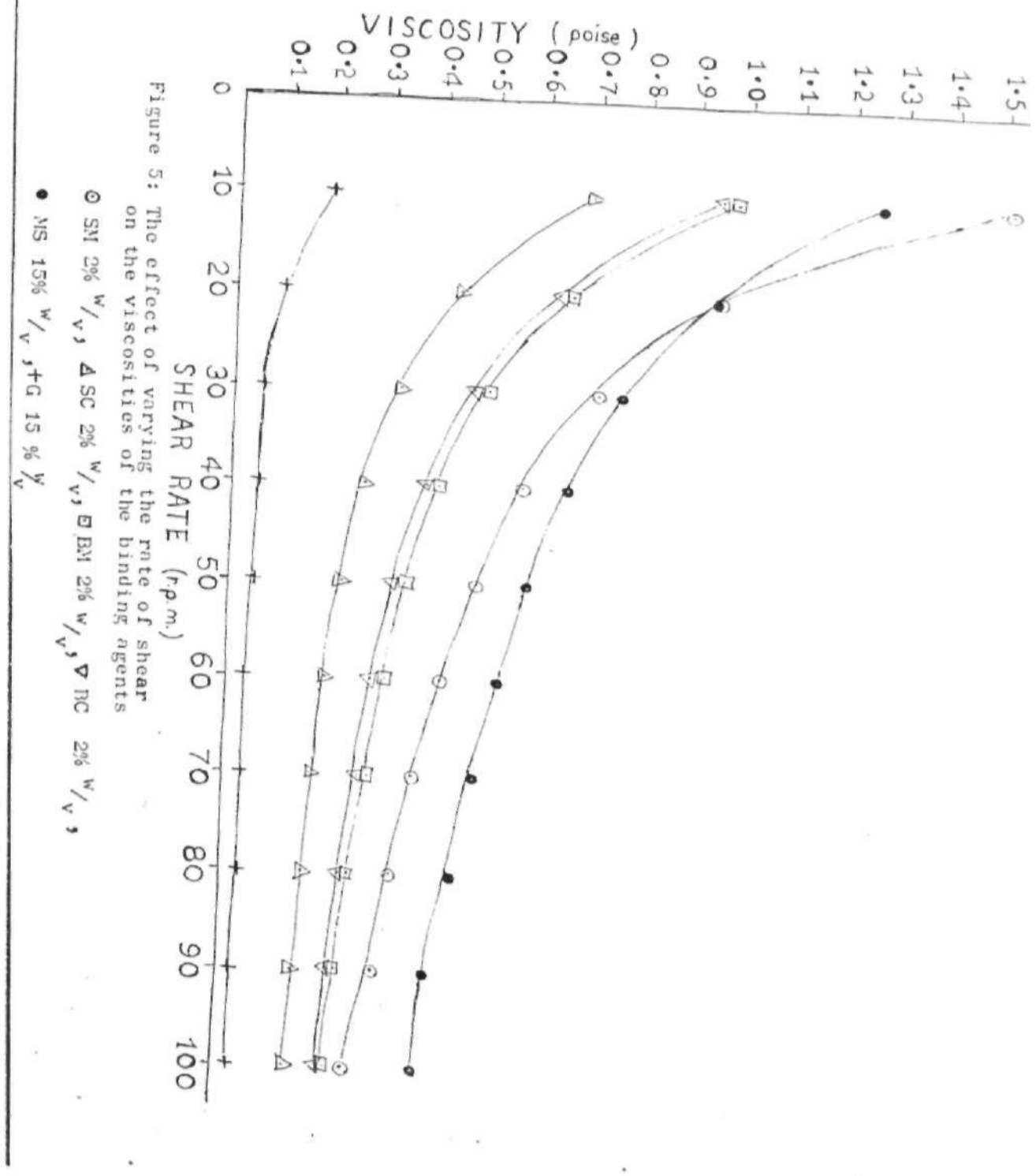


Figure 5: The effect of varying the rate of shear on the viscosities of the binding agents

⊙ SM 2% $^{w}/_{v}$, Δ SC 2% $^{w}/_{v}$, ⊡ BM 2% $^{w}/_{v}$, ∇ NC 2% $^{w}/_{v}$,

• MS 15% $^{w}/_{v}$, +G 15 % $^{w}/_{v}$

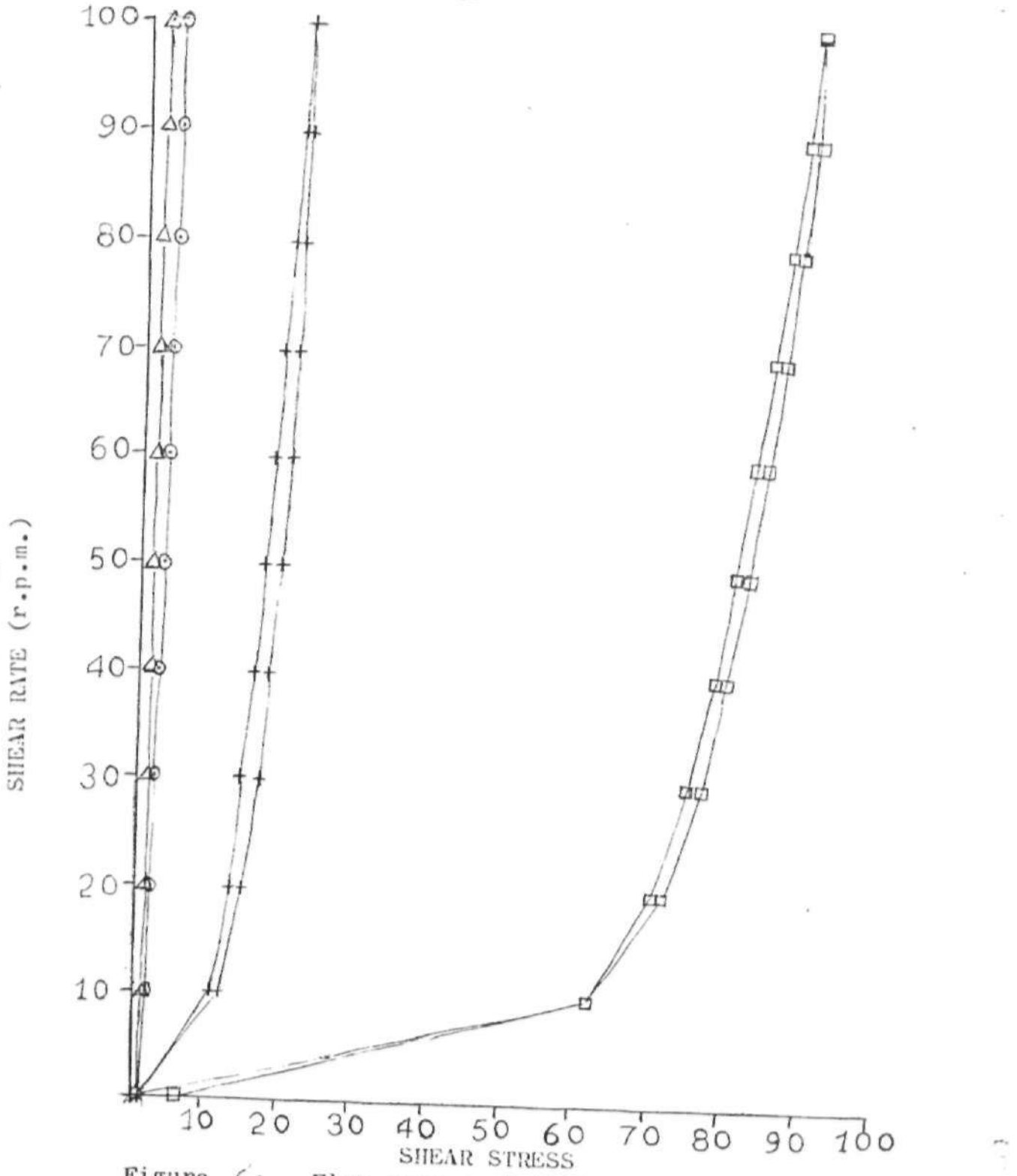


Figure 6: Flow curves of different concentrations of Detarium mucilage.

□ SM 4% $^{w}/_{v}$, + SM 2% $^{w}/_{v}$, ⊙ SM 1% $^{w}/_{v}$, Δ SM0.5% $^{w}/_{v}$

behaviour of the aqueous dispersions of all the materials investigated other than gelatin. It can be seen that the shear stress in decreasing order at any given rate of shear above 20 r.p.m. is MS > SM > BM > BC > SC > G. Figure 5 shows that the viscosity of each of the materials decreases with increase in shear rate - typical of pseudoplastic systems. When some aqueous dispersions of polymers are sheared, there is usually a structural breakdown of aggregates of the dispersed particles and subsequent decrease in the internal friction which accounts for the resistance to flow in the body of the liquid (Martin et al, 1969 (ii)). Again, pseudoplastic behaviour is generally exhibited by polymers in solution (Martin et al, 1969 (ii)).

The viscosity of aqueous dispersions of the Detarium mucilage at any given rate of shear was found to significantly increase with increase in concentration as shown in Figure 8. This is expected since mucilages are known to possess relatively linear molecules and form aqueous solutions whose viscosities vary widely with concentration contrary to the behaviour of the more spherically-shaped exhudate gums which give aqueous solutions with viscosities that do not depend so much on concentration (Dutton et al, 1966).

3.1.4 Water sorption studies

Table 5 shows the result of the water sorption studies carried out on the test materials and maize starch. The rate and

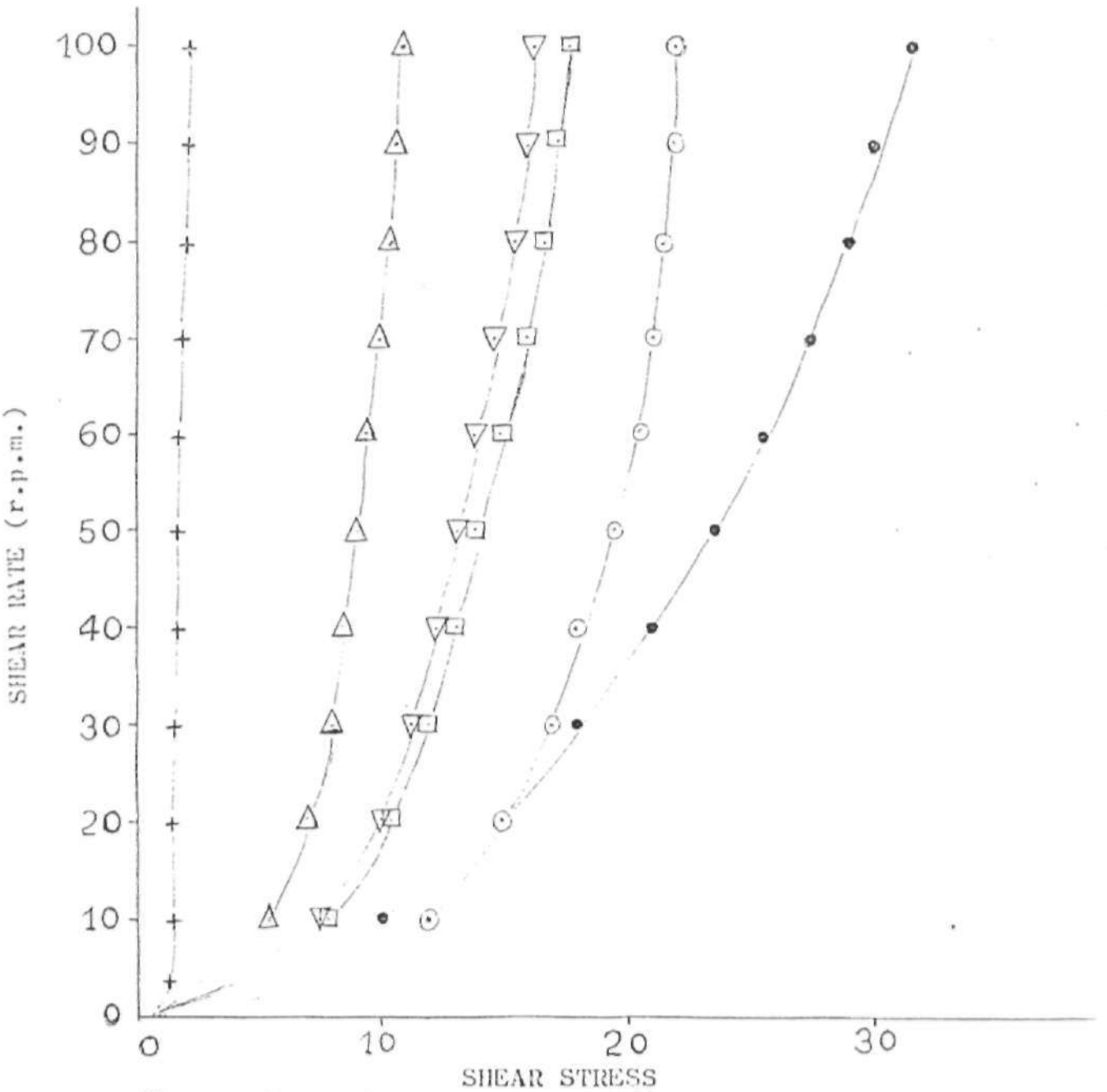


Figure 7: Flow curves of 2% $^{w}/_{v}$ solutions of various forms of Detarium powder compared with 10% $^{w}/_{v}$ gelatin solution and 10% $^{w}/_{v}$ maize starch paste

SM 2% $^{w}/_{v}$ SC 2% $^{w}/_{v}$ BM 2% $^{w}/_{v}$ BC 2% $^{w}/_{v}$

G 10% $^{w}/_{v}$ MS 10% $^{w}/_{v}$

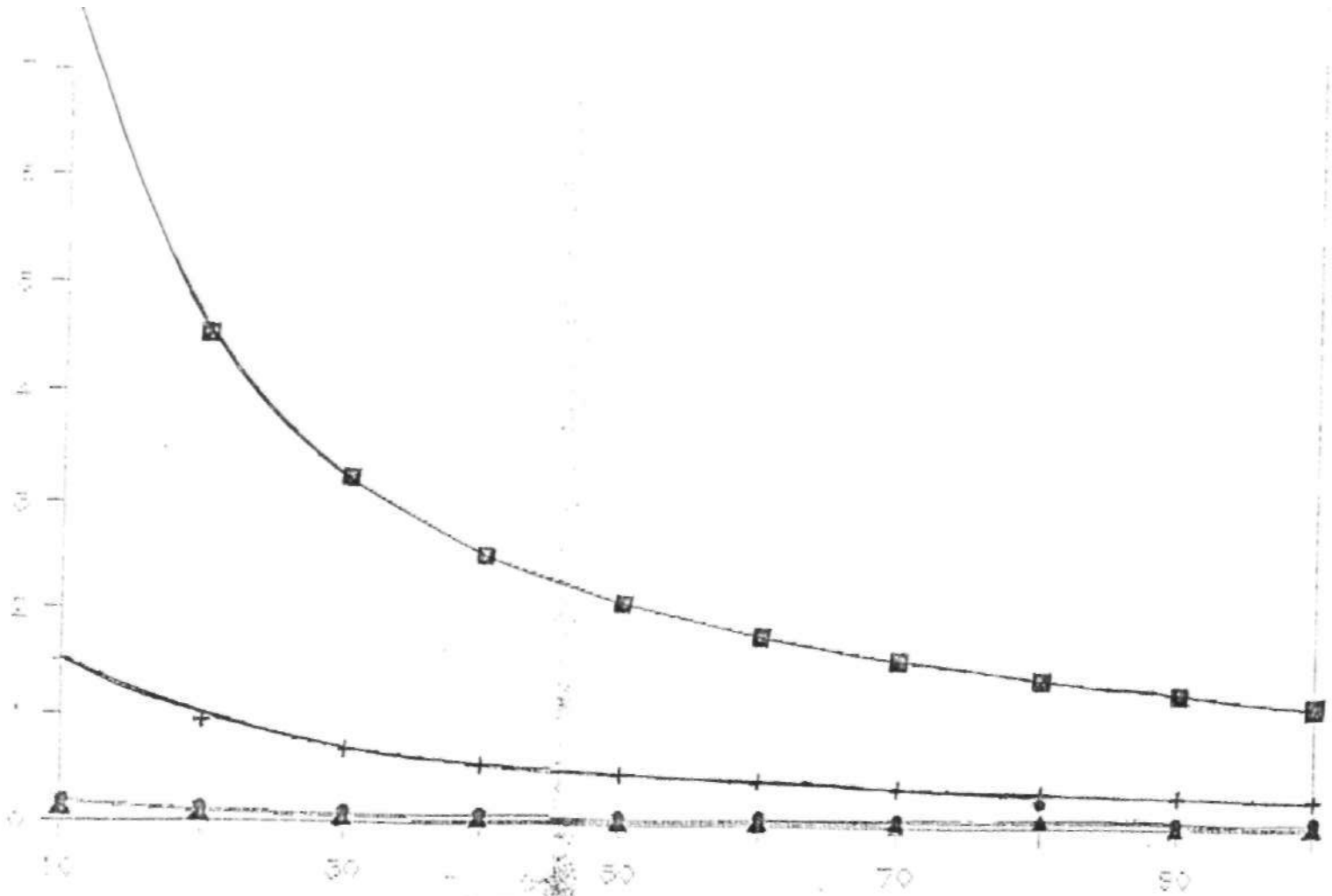


Figure 8: The effect of concentration on viscosity of Detarium mucilage at Varying rates of shear.

■ SM 4%^{w}/v; + SM 2% ^{w}/v; ● SM 1% ^{w}/v; ▲SM 0.5% ^{w}/v

TABLE 5: RESULT OF WATER SORPTION STUDIES OF THE TEST MATERIALS AND MAIZE STARCH

CONDITION OF STORAGE AND DURATION (DAYS		WEIGHT OF WATER TAKEN UP (g)					PERCENTAGE MOISTURE CONTENT (% w/w)				
		SC	BC	SM	BM	MS	SC	BC	SM	BM	MS
	0	0.000	0.000	0.000	.0000	0.000	0.0	0.0	0.0	0.0	0.0
	1	0.208	0.194	0.085	0.293	0.102	10.4	9.7	8.5	14.7	5.1
	2	0.231	0.221	0.109	0.329	0.122	11.6	11.1	10.9	16.5	6.1
(a)	3	0.235	0.224	0.106	0.322	0.124	11.8	11.2	10.6	16.1	6.2
	4	0.238	0.220	0.109	0.322	0.124	11.9	11.0	10.9	16.1	6.2
	5	-	-	-	-	-	-	-	-	-	-
	6	0.239	0.221	0.105	0.325	0.123	12.0	11.1	10.5	16.3	6.2
	7	0.238	0.221	0.110	0.329	0.123	11.9	11.1	11.0	16.5	6.2
	8	0.650	0.612	0.340	0.754	0.343	32.5	30.6	34.0	37.7	17.2
	9	0.786	0.763	0.412	0.907	0.373	39.3	38.2	41.2	45.4	18.7
(b)	10	0.937	0.876	0.477	1.051	0.404	46.9	43.8	47.7	52.6	20.2
	11	1.006	0.967	0.523	1.145	0.403	50.3	48.4	52.3	57.3	20.2
	12	-	-	-	-	-	-	-	-	-	-
	13	1.233	1.127	0.574	1.251	0.449	61.7	56.4	57.4	62.6	22.5
	14	0.028	0.028	0.015	0.127	0.119	1.4	1.4	1.5	6.4	6.0
	15	0.005	0.004	0.002	0.099	0.002	0.3	0.2	0.2	5.0	0.1
(c)	16	0.004	0.006	0.001	0.095	0.010	0.2	0.3	0.1	4.8	0.5
	17	-.001	0.003	0.000	0.095	0.001	-0.05	0.15	0.00	4.75	0.05
Initial weight of material (g)		2.0	2.0	1.0	2.0	2.0					

a = storage over saturated KCl solution (R.H. ≈ 85%)

b = " " water (R.H. ≈ 90%)

c = " " desiccant (R.H. ≈ 0%)

extent to which water was taken up or released in environments of different humidity levels by these materials are graphically shown in Figure 9.

The saturated solution of potassium chloride in environment (a) would, at 20°C, give a relative humidity (R.H) of 85% (Winston and Bates, 1960). However, no attempt at temperature control was made in this study and so a lower R.H. prevailed in this environment since the average room temperature is considered to be not less than 25°C. Environment (b) is expected to give the maximum R.H. of about 90%. Both environments yielded curves analogous to the normal Langmuir isotherms, the so-called L-curves, which is suggestive of unimolecular adsorbed layer (Albert, 1973). The decreasing gradients from left to right of the curves indicate that the more water is taken up, the more difficult it becomes for additional amounts to become fixed. At the lower humidity level, maximum water uptake was, for most part, achieved within 3 days of storage. On being transferred to the higher humidity environment, water uptake continued at a faster rate and the maximum was not attained even by the 6th day of storage. Of all the test materials, BM recorded the highest water uptake - 16.5% w/w and 62.6% w/w at the lower and higher R.H. values, respectively. At the other extreme, maize starch which served as the control, had the lowest water uptake whose maximum values were 6.2% w/w and 22.5% w/w at the lower and higher R.H. values, respectively. Intermediate between these two

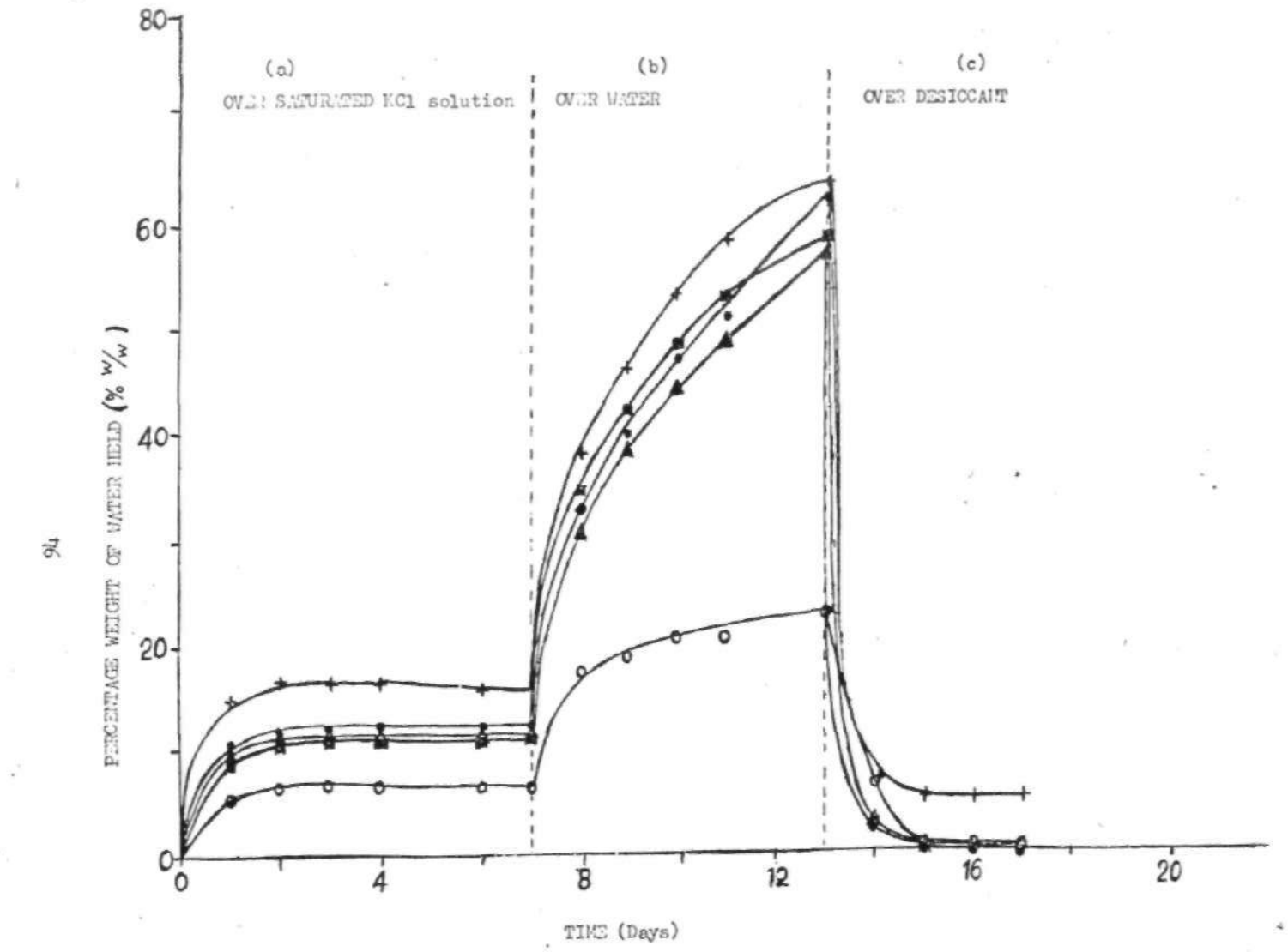


Figure 9: Graph showing the rate and the extent of water sorption and desorption by materials at different humidity levels.

● SC ; ▲BC ; ■SM ; +BM ; oMS

substances are to be found SC, BC and SM with no significant difference between them. On transferring the materials to the dry environment (c) provided by anhydrous calcium sulphate, however, they rapidly lost the amount of water previously taken up. This shows that water uptake by the materials is a reversible process. The picture presented is suggestive of an adsorption process.

It is, therefore, suggested that tablets formulated with Detarium mucilage should be stored in containers in which a suitable non-toxic desiccant such as dried silicol gel enclosed in a small porous bag is also included. The label "Protect from moisture" or "Keep tightly closed" should also be used.

3.2 SPECTROPHOTOMETRIC ASSAY OF CHLOROQUINE PHOSPHATE

3.2.1 Calibration curves

Figure 10 is the Ultra-violet spectrum of 160µg/ml standard solution of chloroquine phosphate with peak absorbances at wavelengths of 241, 320, and 350nm considered necessary for the selection of convenient wavelength for the spectrophotometric assay of aliquots taken during dissolution tests. Absorbances at 241nm and 355nm of varying concentrations of chloroquine phosphate yielded the calibration curves shown in Figures 11(a) and 11(b), respectively. The corresponding correlation coeffici-

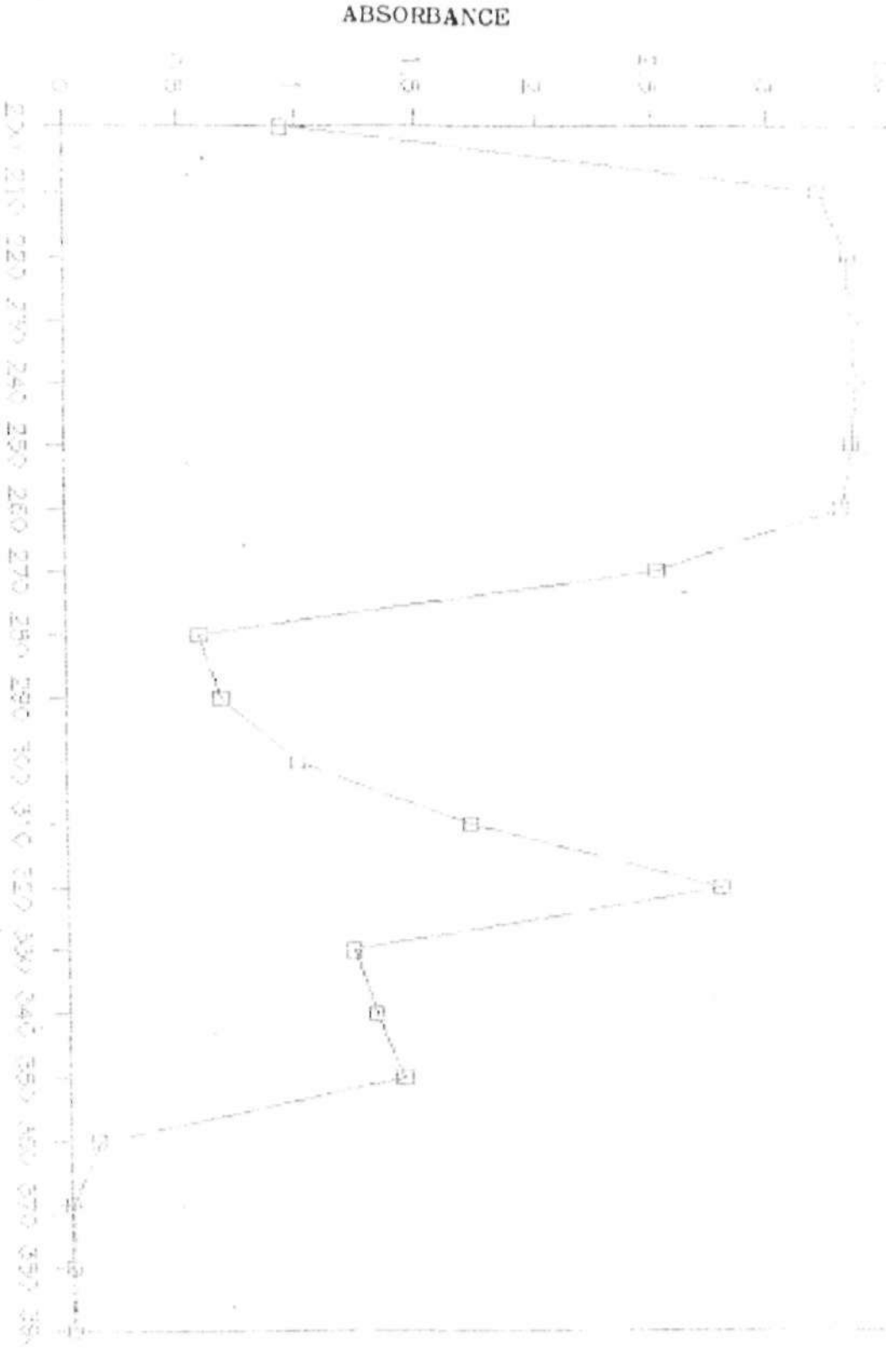


Figure 10 Ultra-violet Spectrum of 160 ug/ml standard solution of Chloroquine phosphate.

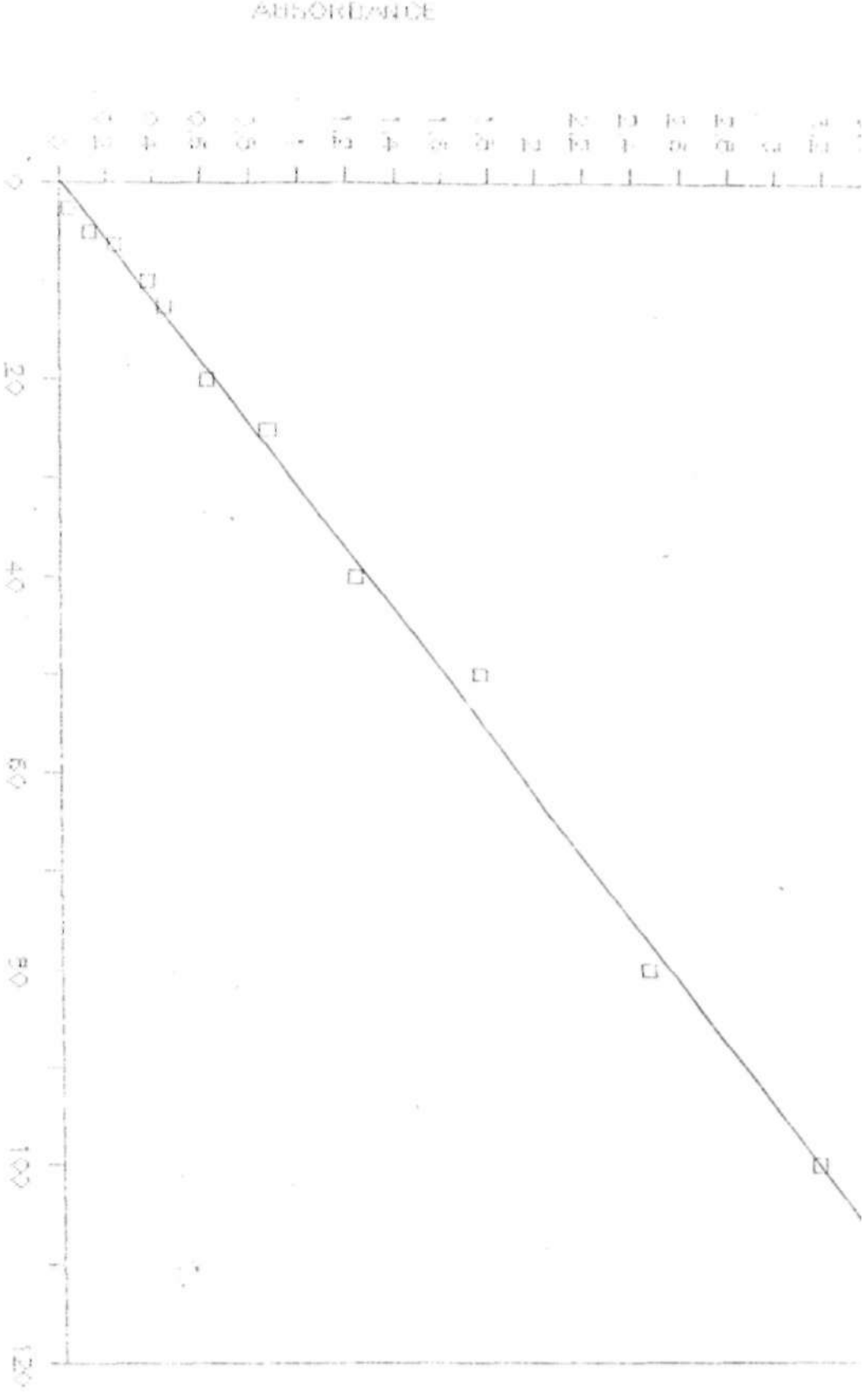


Figure 11(a) Calibration curve (The Beer -Lambert Plot)
For Absorbance of Chloroquine Phosphate at
241nm.

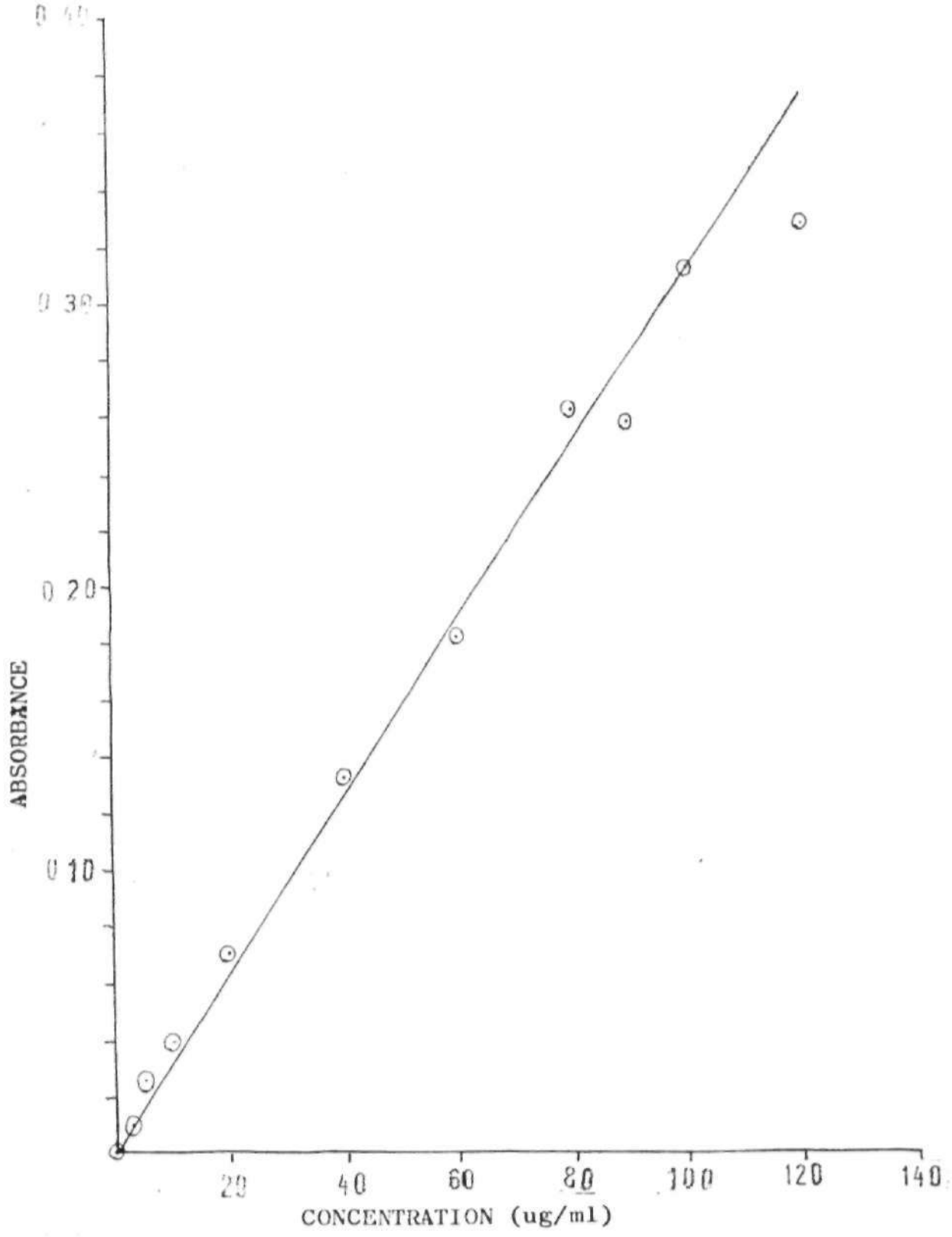


Figure 11(b) Calibration curve (The Beer-Lambert Plot) For Absorbance of Chloroquine Phosphate at 355nm.

ents were 0.995 and 0.994, respectively, and the regression equations y = 0.03x + 0.06 and y = 0.003x + 0.005, respectively. 241nm was the most convenient wavelength for the assay using the SP8-100 Pye Unicam UV spectrophotometer. Assay at 355nm using the Syva S-111 UV spectrophotometer was later resorted to on account of the breakdown of the former machine and the inability of the latter to measure at 241nm.

CHAPTER 4

4.0 RESULTS AND DISCUSSIONS II

(TABLETING PROPERTIES)

4.1 BINDING PROPERTY

4.1.1 General performance of the different binders

The relative binding efficiencies of the different forms of Detarium powder and mucilage, maize starch and gelatin are shown in Table 6. The mean particle size of granules ranged from 709μm to 887μm. There was no significant difference in the angles of repose of the granules whose values were between 35° and 40°. Most pharmaceutical powders are known to have angles of repose that lie within the range of 35° and 45° and angle of repose exceeding 50° is known to be characteristic of materials with unsatisfactory flow due to high cohesive and other forces (Carter, 1972 (i)).

SM in concentration range of 1-4% w/v yielded pharmaceutically acceptable tablets but at 0.5% w/v the tablets capped due to inadequate binding. SC and BC performed satisfactorily only at a concentration of 4% w/v. All tablets formulated with lower concentrations of these materials capped. Tablets formulated with BM 0.5-4% also capped. At 4% w/v concen-

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Table 6: PROPERTIES OF GRANULES AND TABLETS PREPARED WITH VARYING CONCENTRATIONS OF DIFFERENT FORMS OF DETARIUM POWDER/MUCILAGE IN GRANULATING FLUID

BATCH	GRANULES			TABLETS									
	a	b	c	d	e	f	g	h	i	j	k	l	*
SM 4	732	16.7	38	6.1	0.84	0.6	13.0	94.3	15	25	2.60	164.4	
2	857	12.1	36	6.7	0.87	0.2	9.3	99.5	15	20	2.50	164.4	
1	870	16.4	39	6.3	0.86	0.6	7.8	101 9	20	25	2.50	162.7	
0.5	834	9.9	35	5.7	0.84	1.9	6.7	-	-	-	2.60	164.1	**
SC 4	828	12.5	36	7.0	0.84	0.5	10.5	99.6	20	20	2.60	164.1	
2	771	10.8	37	7.3	0.89	1.9	7.3	-	-	-	2.45	163.9	*
1	859	9.7	38	6.8	0.90	1.6	6.5	-	-	-	2.40	163.6	*
0.5	882	14.1	36	6.4	0.84	2.0	6.8	-	-	-	2.60	164.5	**
BM 4	714	22.5	36	6.0	0.82	0.7	10.0	-	-	-	2.65	164.8	*
2	709	17.7	38	5.4	0.82	2.3	9.8	-	-	-	2.65	163.9	*
1	861	9.1	40	6.0	0.88	0.7	7.3	-	-	-	2.45	163.3	*
0.5	772	20.7	38	5.4	0.85	6.7	6.5	-	-	-	2.50	161.0	**
BC 4	887	4.2	38	7.0	0.86	0.5	12.0	93.88	25	25	2.50	163.1	
2	844	12.3	36	6.7	0.89	3.8	8.3	-	-	-	2.45	163.9	*
1	844	11.5	37	5.8	0.86	0.6	9.0	-	-	-	2.50	162.8	*
0.5	825	11.1	36	5.4	0.83	2.0	6.0	-	-	-	2.60	163.1	**
MS 15	718	21.6	39	7.5	0.82	0.4	11.0	95.84	30	40	2.70	167.3	
10	740	17.6	38	9.1	0.80	0.4	9.3	101.6	25	25	2.85	172.6	
5	785	22.9	35	8.0	0.78	0.6	7.0	-	-	-	2.80	165.2	*
G 15	830	23.0	39	8.7	0.84	0.4	8.4	96.96	8	15	2.65	167.0	
10	883	20.6	38	9.0	0.84	0.7	8.4	97.94	8	15	2.65	167.3	
5	860	22.2	38	8.9	0.87	0.4	8.8	96.69	8	10	2.50	163.9	
W	832	22.6	37	5.6	-	0.7	5.8	101.2	6	8	-	163.0	*

Key:

a = Mean particle size (μm)
b = % compressibility
c = Angle of repose (°)
d = Hardness (Kgf)
e = Packing fraction
f = % friability
g = Disintegration time (mins)
h = Dissolution at 45mins (%)
i = t_{75} (mins)
j = t_{90} (mins)
k = Thickness weight (mg)
l = mean weight (mg
* = Tendency to cap

ABDULKADIR IBRAHIM MBA
AHMADU BELLO UNIVERSITY
ZARIA

tration, the four materials under investigation - SM, SC, BM and BC - gave very viscous solutions that were difficult to pour. This is an undesirable property. Lower concentrations that still retain good binding property are therefore preferred. Only SM satisfied this requirement since it gave firm tablets at 1-2% w/v concentration range. Comparatively, maize starch performed well in the concentration range of 10-15% w/v but gave capped tablets when used in concentration of 5% w/v. On the other hand, gelatin formed good tablets at all the concentrations investigated.

The observed differences in the binding efficiency of the test materials, maize starch and gelatin are reasonable because it is well known that the amount of binding that ultimately result depends on the nature and amount of the binder solution (Bangudu, 1982; Esezobo, 1986; Iwuagwu et al. 1986; Zubair and Esezobo, 1988). Of the two forms of Detarium mucilage used - SM and BM - heat treatment to which the latter was subjected during seed processing may have resulted in partial polysaccharide fragmentation and subsequent poor binding capacity of BM in relation to SM. There was no significant difference in the performance of the crude powders, SC and BC. 5% w/v of maize starch failed to produce intact tablets where as low as 1% w/v of SM did so.

4.1.2 Effect of binder type and concentration on the hardness and friability of tablets

It can be seen from Table 6 that the general trend was increase in hardness as concentration of binder solution increased up to 2% w/v and then a decrease. Also friability generally decreased with increasing concentration of binder solution. The slight decrease in the hardness of tablets formulated with 4% w/v SM or SC compared with those formulated with 2% w/v of the same materials and also of tablets formulated with 15% w/v of maize starch or gelatin compared with those formulated with lower concentration of 10% w/v can be attributed to an increased difficulty of thorough dispersion of the binder solution in the powder mix during the granulation stage due to high viscosity. The viscosity of liquids is known to influence their handling properties. Kunle (1988) obtained results which suggest that, up to a point, increasing concentration of maize starch led to increase in binding capacity. Other workers have obtained results which show that increase in binder concentration result in decreased friability (Esezobo and Ambujam, 1982; Iwuagwu et al, 1986) and increased hardness (Esezobo and Ambujam, 1982) due to increased degree and strength of interparticulate bonding.

4.1.3 Effect of binder type and concentration on the disintegration and dissolution times of tablets

Figures 12(a) and 12(b) show that disintegration times of tablets generally increased with the concentration of binders.

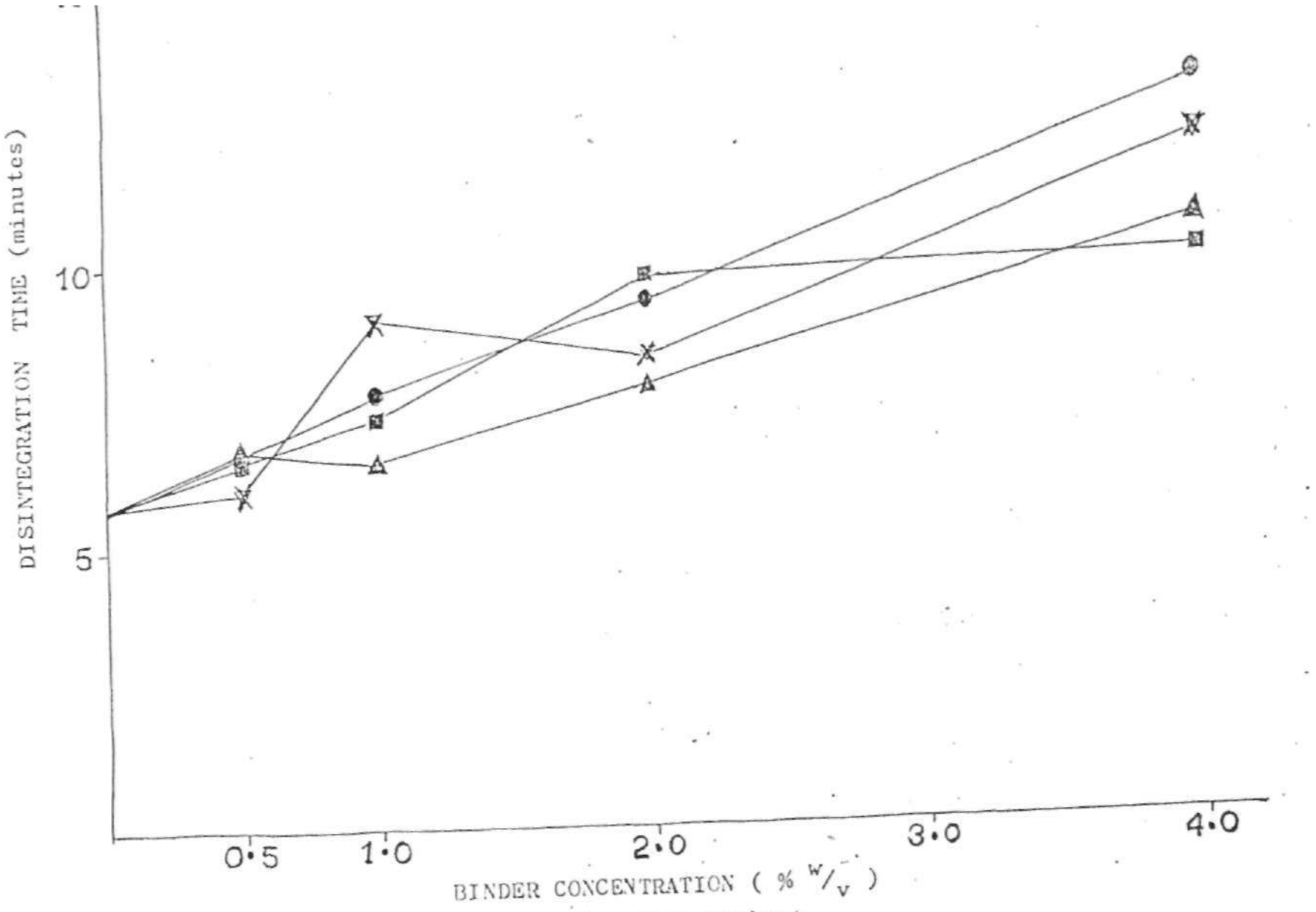


Figure 12(a) Graph of Disintegration time against concentration of Binder Solution.

● SM, ▲SC, ■BM, ✕BC .

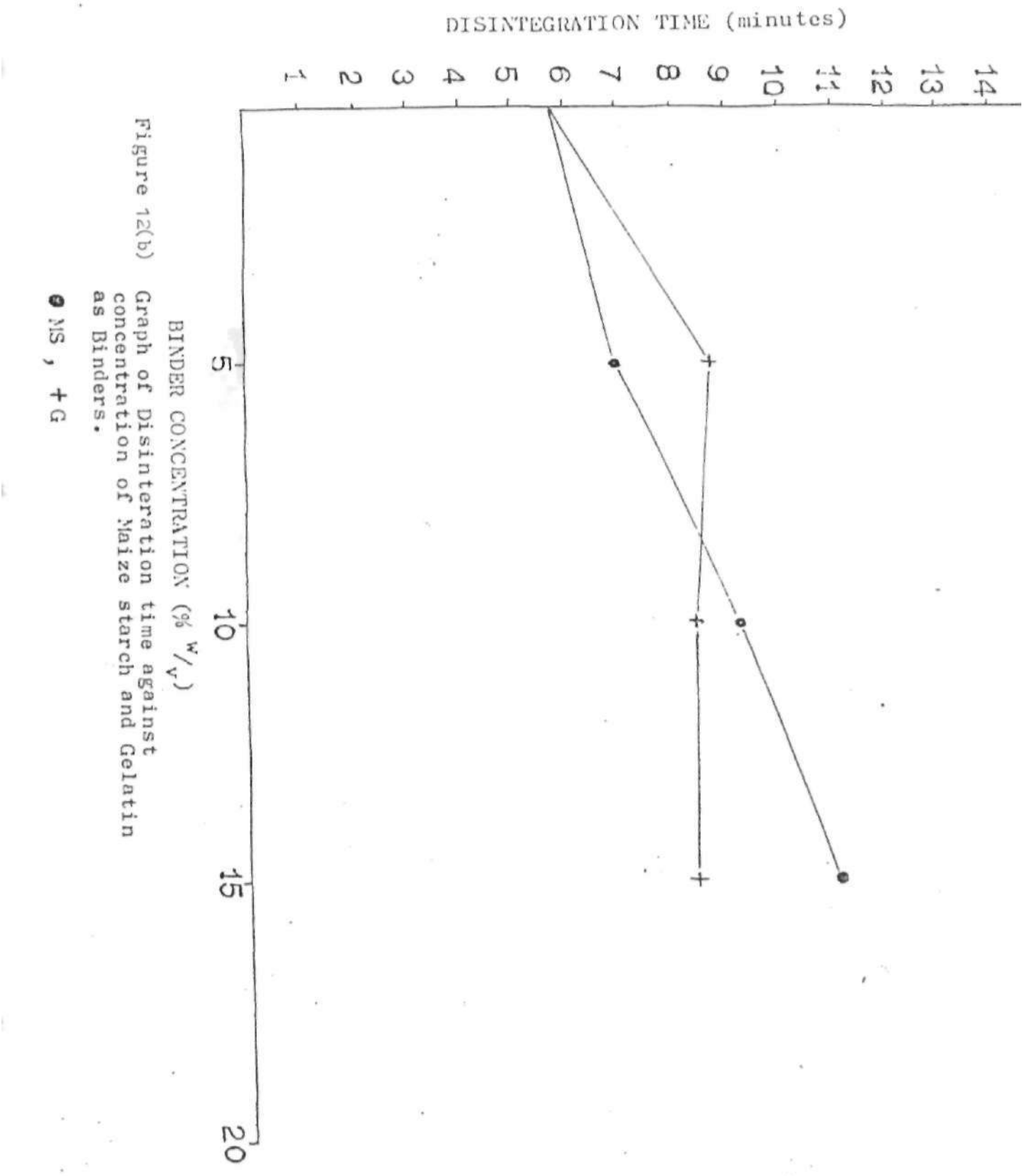


Figure 12(b) Graph of Disinteration time against concentration of Maize starch and Gelatin as Binders.

● MS , + G

It can be seen from Figure 13 that between 2-5 minutes of the dissolution test, the pattern of the rate of release of chloroquine phosphate in decreasing order was W> SM1 > SM2 > SM4 and that after the first half of an hour when maximum dissolution had practically been attained, extent of release of medicament followed the same trend. This shows that the rate of release of the medicament decreased with increasing concentration of the binder solution. It can also be seen that SM, in concentration of 1-4% w/v, yielded tablets that satisfied the official requirement of not less than 70% dissolution within 45 minutes (British Pharmacopoeia, 1980). In fact, as can also be verified from Table 7, this requirement was met within 15 minutes run of the dissolution test. Even 90% dissolution was attained by each of the batches within a maximum period of 25 minutes. Figure 14 shows the comparative dissolution rate profiles for SM2, MS10, G10 and W. It can be seen that SM2 compares favourably with MS10 and G10. The rate of release of medicament in decreasing order at least within the first half of an hour was W > G10 > SM2 > MS10. In other words, although there was no significant difference in the extent of dissolution ultimately reached as the graphs practically levelled after 30 minutes, the rate of dissolution of SM2 was intermediate between those of G10 and MS10.

The observed increase in disintegration and dissolution times with increasing binder concentration is consistent with the

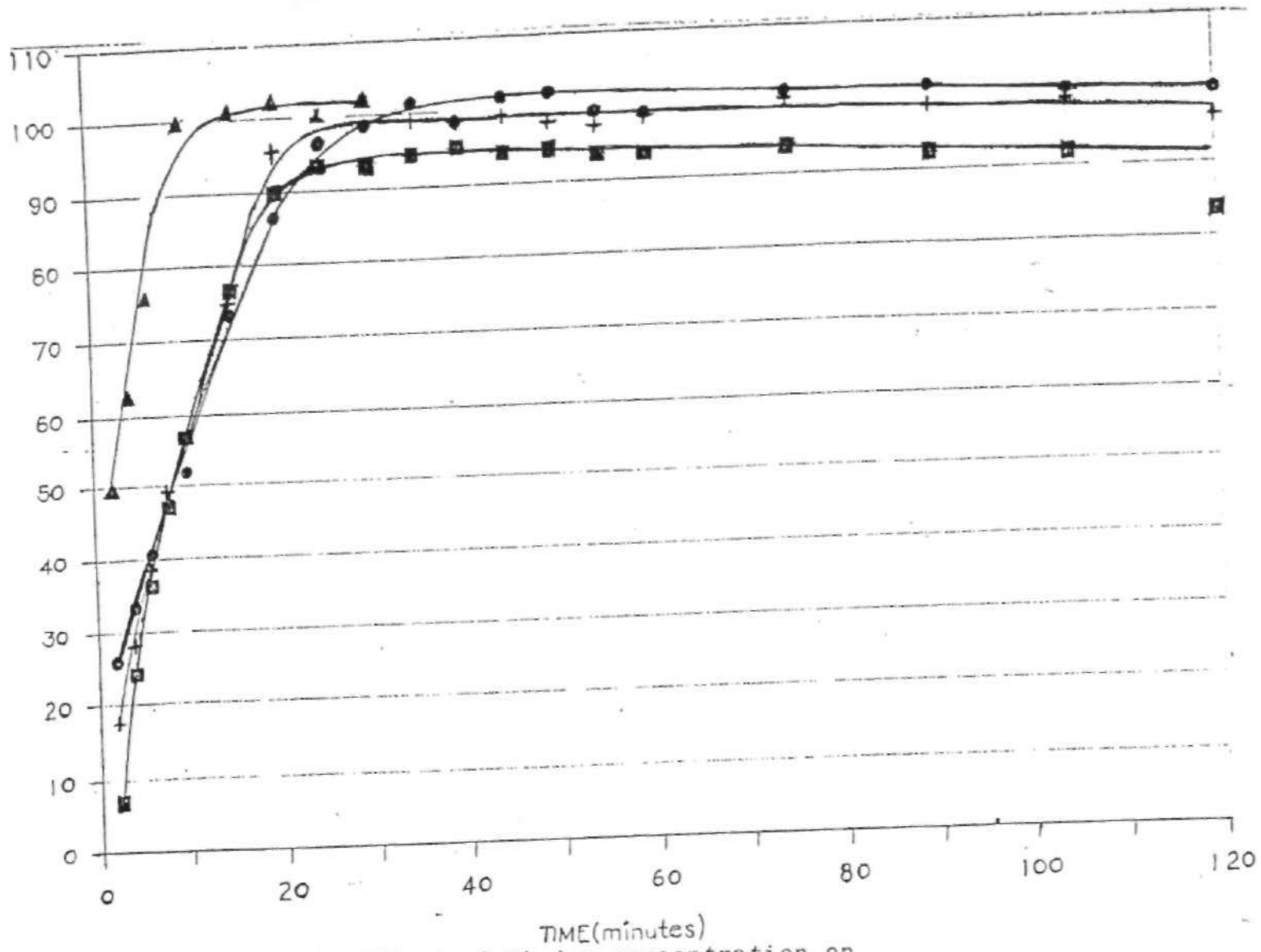


Figure 13 The Effect of Binder concentration on Dissolution Rate.

■ SM4 , + SM2 , ● SM1 , ▲ W

TABLE 7: Investigation of binding property - Result of Dissolution Test 1

(a) = Absorbance at 241nm

(b) = % w/w Dissolution

BATCH		TIME IN MINUTES									
		2	4	6	8	10	15	20	25	30	35
SM4	a	0.223	0.656	0.954	1.221	1.461	1.946	2.277	2.368	2.359	2.388
	b	6.61	24.17	36.25	47.08	56.81	76.48	89.90	93.59	93.23	94.40
SM2	a	0.492	0.753	1.009	1.282	1.405	1.915	2.415	2.514	2.494	2.513
	b	17.52	28.10	38.48	49.55	54.54	75.22	95.50	99.51	98.70	99.47
SM1	a	0.685	0.870	1.047	1.217	1.327	1.842	2.171	2.413	2.464	2.536
	b	25.61	33.19	40.44	47.41	51.92	73.02	86.50	96.41	98.50	101.45
SC4	a	0.658	0.793	1.013	1.350	1.604	2.105	2.357	2.532	2.506	2.522
	b	24.29	29.78	38.72	52.61	62.73	83.08	93.32	100.43	99.37	100.02
BC4	a	0.498	0.700	1.018	1.237	1.485	1.853	2.235	2.369	2.413	2.417
	b	17.91	26.17	39.17	48.12	58.26	73.31	88.93	94.41	96.21	96.37
MS15	a	0.576	0.622	0.763	0.910	1.009	1.221	1.493	1.799	2.064	2.283
	b	20.56	22.40	28.01	33.87	37.82	46.26	57.10	69.30	79.86	88.58
MS10	a	0.523	0.758	0.921	1.123	1.455	1.644	1.978	2.434	2.605	2.590
	b	17.88	26.96	33.26	41.06	53.88	61.18	74.08	91.70	98.30	97.72
G15	a	1.344	1.548	1.783	2.024	2.215	2.409	2.482	2.532	2.545	2.498
	b	51.27	59.42	68.80	78.43	86.05	93.80	96.72	98.71	99.23	97.35
G10	a	0.647	1.169	1.606	2.040	2.300	2.475	2.500	2.506	2.516	2.485
	b	23.40	44.21	62.82	78.92	89.29	96.26	97.26	97.50	97.90	96.66
G5	a	0.892	1.359	1.805	2.113	2.408	2.454	2.477	2.491	2.458	2.455
	b	33.84	52.84	70.98	83.51	95.51	97.38	98.31	98.88	97.54	97.42
W	a	1.274	1.589	1.914	2.332	2.507	2.541	2.567	2.520	2.561	-
	b	49.65	62.54	75.83	92.92	100.08	101.47	102.54	100.61	102.29	-

Table 7 continued:

BATCH		TIME IN MINUTES								
		40	45	50	55	60	75	90	105	120
SM4	a	2.407	2.386	2.387	2.365	2.367	2.376	2.335	2.333	2.123
	b	95.17	94.32	94.36	93.47	93.55	93.92	92.25	92.17	83.66
SM2	a	2.501	2.514	2.483	2.470	2.493	2.535	2.496	2.512	2.443
	b	98.99	99.51	98.26	97.73	98.66	100.36	98.78	99.43	96.63
SM1	a	2.460	2.547	2.551	2.488	2.471	2.529	2.535	2.505	2.508
	b	98.34	101.91	102.07	99.49	98.79	101.17	101.41	100.18	100.31
SC4	a	2.517	2.513	2.504	2.517	2.511	2.523	2.522	2.523	2.518
	b	99.82	99.61	99.29	99.82	99.57	100.06	100.02	100.06	99.86
BC4	a	2.408	2.356	2.400	2.382	2.378	2.386	2.416	2.414	2.354
	b	96.00	93.88	95.68	94.94	94.78	95.10	96.33	96.25	93.80
MS15	a	2.401	2.465	2.460	2.436	2.455	2.466	2.469	2.468	2.471
	b	93.29	95.84	95.64	94.68	95.44	95.88	96.00	95.96	96.07
MS10	a	2.606	2.665	2.618	2.668	2.587	2.667	2.657	2.602	2.663
	b	98.34	100.62	98.80	100.73	97.61	100.70	100.31	98.18	100.54
G15	a	2.501	2.488	2.485	2.463	2.504	2.485	2.509	2.503	2.472
	b	97.47	96.96	96.84	95.96	97.59	96.84	97.79	97.55	96.32
G10	a	2.500	2.517	2.470	2.492	2.503	2.451	2.475	2.456	2.446
	b	97.27	97.94	96.06	96.94	97.38	95.31	96.26	95.51	95.11
G5	a	2.432	2.437	2.430	2.423	2.431	2.438	2.426	2.424	2.448
	b	96.48	96.69	96.40	96.12	96.44	96.73	96.24	96.16	97.13
W	a	-	2.533	-	-	-	-	-	-	-
	b	-	101.15	-	-	-	-	-	-	-

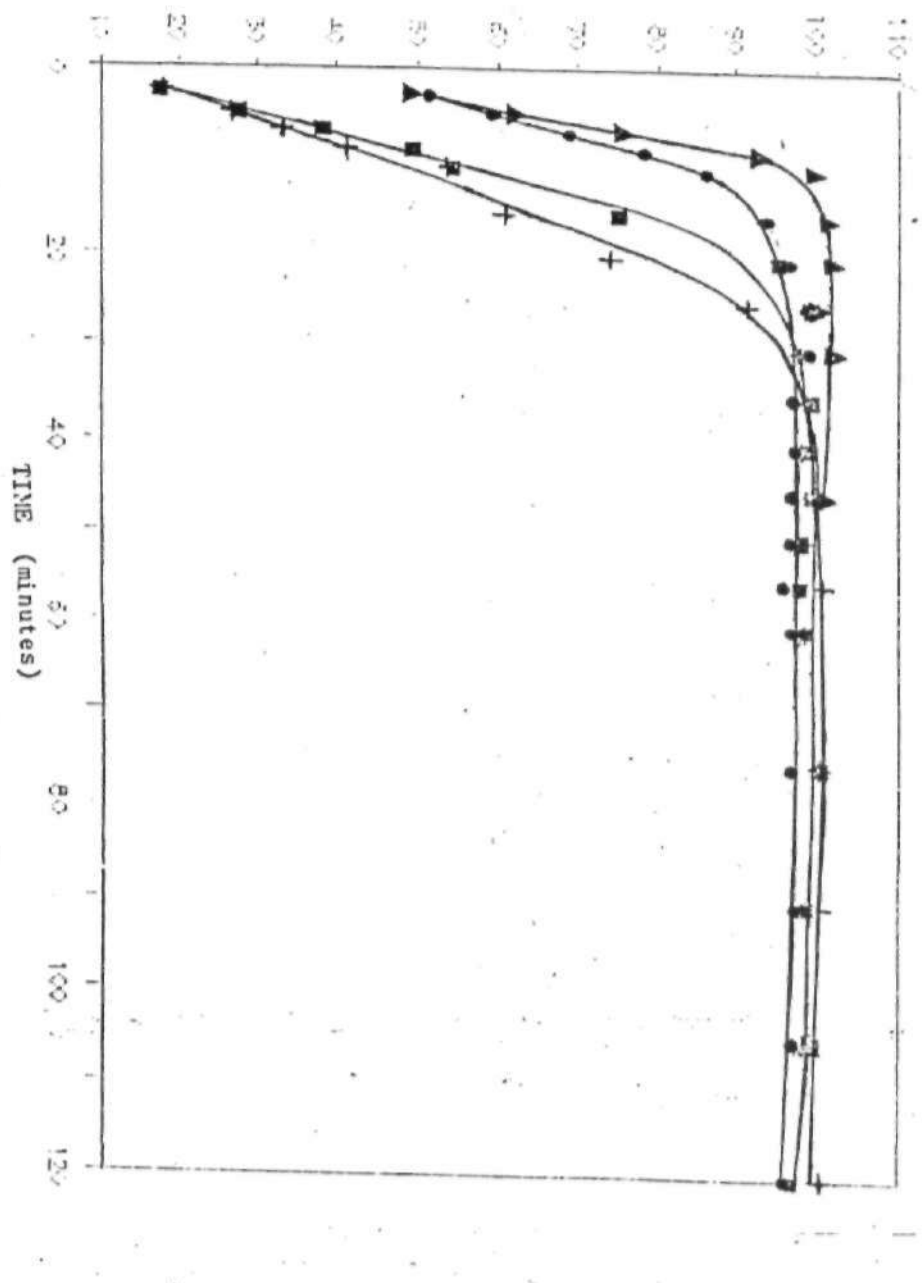


Figure 14 Dissolution Rate Profile for SM 2 compared with those of MS 10, G10 and W.

■ SM 2; + MS 10; ● G 10; ▲ W

results obtained by previous workers (Esezobo, 1986) and this phenomenon is ascribed to increasing binding force of the granules in the compact and/or formation of thin mucilaginous film that may constitute a viscous barrier between the tablet or its break-up fragments and water.

However, all the tablet batches passed the disintegration test. Again, all the batches of intact tablets i.e those that passed the friability test, passed the dissolution test as well.

4.2 DISINTEGRANT PROPERTY

4.2.1 Effect of disintegrant type and concentration on the hardness and friability of tablets

Table 8 shows that increasing concentration of the test materials as disintegrants led, in each case, to decreasing hardness and increasing friability values. A similar trend was obtained with maize starch. A probable explanation for these observations is that the disintegrants used here in their pure dry forms possess poor compressibilities and since the extragranularly incorporated disintegrant has not in any way been wetted by the binder solution used in wet granulation, increase in its concentration will lead to a decrease in the number of points of contact between particles where strong solid bonds could possibly be formed, poor compressibility of materials and excess fines. Intragranular incorporation of disintegrants, on the other hand,

Table 8: PROPERTIES OF TABLETS CONTAINING DIFFERENT CONCENTRATIONS OF VARIOUS FORMS OF DETARIUM POWDER/MUCILAGE AS DISINTEGRANTS

BATCH	H	P	F	D	T	W	DISSOLUTION RATE			REMARKS
							Diss at 45mins	t_{75}	t_{90}	
SMD 10	6.2	0.76	2.3	14.0	2.4	151.2	101.57	15	15	pH 4.50
							(88.12)	(40)	(50)	pH 9.53
5	6.5	0.78	2.1	10.5	2.4	148.3	90.43	10	15	
2.5	7.5	0.78	0.9	9.0	2.4	145.0	79.08	25	>120	
SCD 10	6.3	0.86	1.2	12.3	2.6	171.0	80.58	30	>120	
5	7.5	0.88	0.9	7.5	2.3	153.9	84.84	25	>120	
2.5	7.3	0.83	1.4	7.5	2.4	152.1	80.42	15	>120	
BMD 10	4.6	0.76	1.7	9.0	2.6	162.2	96.10	30	40	
5	6.0	0.84	1.3	9.7	2.3	153.4	91.12	25	35	
2.5	6.5	0.82	0.9	8.5	2.4	152.3	88.98	30	>120	
BCD 10	4.4	0.83	1.7	31.8	2.5	162.8	79.11	45	50	pH4.50
							(100.39)	(20)	(20)	pH9.53
5	5.8	0.86	1.3	13.8	2.4	159.4	75.67	45	>120	
2.5	6.7	0.79	1.1	12.3	2.5	151.6	94.91	25	30	
MSD 10	5.7	0.85	2.0	6.5	2.7	171.7	95.18	10	20	
5	7.0	0.82	1.4	7.0	2.5	155.5	97.73	10	15	
2.5	7.4	0.85	1.0	8.0	2.4	154.9	67.74	>120	>120	
DO	7.4	0.86	1.7	8.0	2.2	144.2	91.68	10	15	

Key:

H = Hardness (Kgf)

P = Packing fraction

F = % friability

D = Disintegration time (mins)

T = Thickness (mm)

W = Mean weight (mg)

will result in disintegrant particles with thin residual binder coating acquired during the wet granulation process. Asperitic melting during compression and subsequent cooling and solidification will result in strong bond formation (York and Pilpel, 1972). This is so because the thin binder coating on each particle will now fuse with the coating on any other particle at the point of contact so that only one layer of binder material ultimately exist at the interparticular spaces. Since binders are known to impart cohesiveness on powder particles (Carter, 1972(iv)), strong solid bonds result. Again, since hardness and friability are parameters used to measure the mechanical strength of tablets, decrease in strength of interparticulate bonding will reflect by way of decreased hardness and increased friability values. The models shown in Figure 15 illustrate this explanation.

Model A represents intragranular incorporation of disintegrant material and Model B that of extragranular incorporation of the same material. In Model A, monolayers of binder material hold the powder particles together resulting ultimately in relatively firmer tablets than in Model B where such uniformity is lacking.

Figure 15: Models showing the effect of method of incorporating disintegrant on the mechanical strength of the tablet



Key: = Disintegrant particle intragranularly incorporated with thin residual binder coating acquired during wet granulation process.

= Disintegrant particle extragranularly incorporated and devoid of binder coating.

= Particles of other tablet components

4.2.2 Effect of disintegrant type and concentration on the disintegration and dissolution times of tablets

Table 8 shows that all the test materials prolonged the disintegration time of the tablets and the extent to which this prolongation took place increased with increase in concentration of the test material. The nature of the material also affects the extent of prolongation. For example, at 10% w/w the disintegration times of the tablet batches were of the order BCD > SMD > SCD > BMD > MSD. BCD tablets actually failed the disintegration test at this concentration. In contrast, maize starch reduced the disintegration time and this effect progressively increased with increase in concentration up to the maximum of 15% w/w investigated. Figure 16 illustrates these effects.

The purpose of incorporating disintegrants in tablet formulations is to facilitate the rapid disruption of the tablet in aqueous medium so that maximum dissolution and subsequent absorption of the incorporated drug can take place and the minimum effective concentration reached within the shortest possible time. Table 9 shows that all the tablet batches containing the test materials met the official specification of 70% dissolution within a period of 45 minutes (British Pharmacopoeia, 1980) despite the fact that none of the test materials performed well as tablet disintegrant but in some cases - SMD 2.5, SCD 2.5 , SCD 5, SCD 10, BMD 2.5 and BCD 5 -

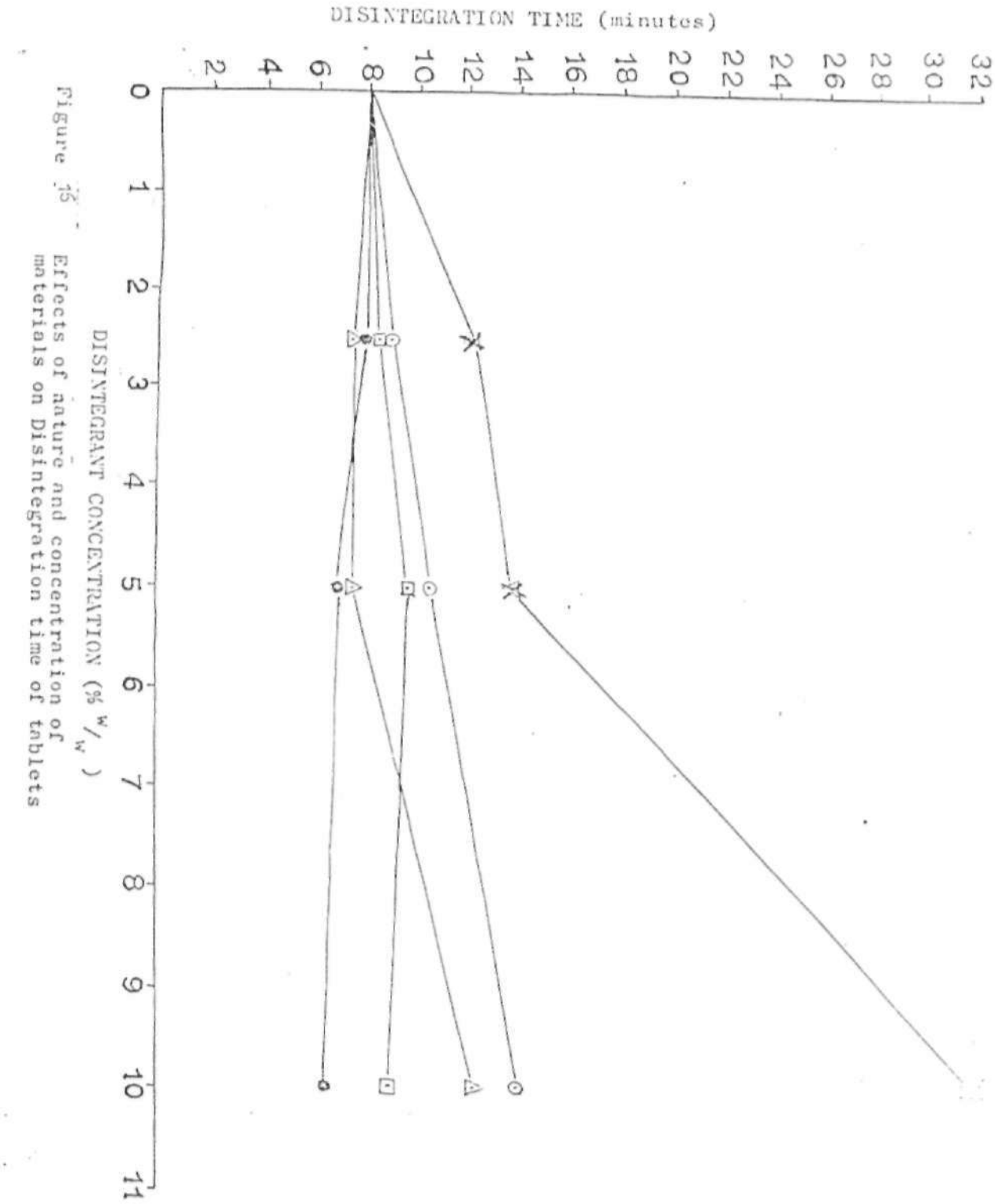


Figure 15 - Effects of nature and concentration of materials on Disintegration time of tablets

o SMD; Δ SCD; ⊡ BMD; ✕ DCD; ⊙ MSD .

Table 9: Investigation of disintegrant property - Result of Dissolution Test II

TIME (MIN) BATCH		2mins	4mins	6mins	8mins	10mins	15mins	20mins	25mins	30mins	35min
SMD 10	a	0.034	0.065	0.092	0.124	0.147	0.186	0.218	0.210	0.212	0.214
	b	14.44	29.87	43.32	59.25	70.79	90.12	106.05	102.07	103.06	104.1
SMD 5	a	0.102	0.131	0.137	0.152	0.162	0.195	0.194	0.193	0.196	0.199
	b	46.66	60.61	63.49	70.71	75.52	91.39	90.91	90.43	91.87	93.31
SMD 2.5	a	0.048	0.076	0.093	0.109	0.121	0.145	0.157	0.165	0.173	0.170
	b	20.61	34.03	42.18	49.84	55.60	67.10	72.85	77.16	80.52	79.08
SCD 10	a	0.043	0.061	0.083	0.094	0.105	0.118	0.139	0.161	0.181	0.186
	b	16.73	24.68	34.35	39.19	44.03	49.76	59.00	68.69	77.50	79.70
SCD 5	a	0.047	0.065	0.083	0.094	0.116	0.141	0.165	0.179	0.188	0.188
	b	19.47	27.82	36.16	43.55	51.46	63.05	74.18	80.67	84.84	84.84
SCD 2.5	a	0.055	0.084	0.109	0.136	0.157	0.175	0.184	0.181	0.181	0.182
	b	22.85	36.10	47.52	59.86	69.45	77.68	81.79	80.42	80.42	80.88
BMD 10	a	0.038	0.060	0.064	0.071	0.078	0.096	0.124	0.148	0.176	0.194
	b	15.32	25.53	27.39	30.64	33.89	42.25	55.25	66.39	79.39	87.74
BMD 5	a	0.051	0.068	0.085	0.105	0.121	0.139	0.166	0.185	0.196	0.200
	b	21.39	29.29	37.19	46.49	53.93	62.30	74.85	83.68	88.80	90.66
BMD 2.5	a	0.045	0.044	0.061	0.072	0.088	0.112	0.140	0.160	0.177	0.200
	b	18.25	17.80	25.55	30.57	37.87	48.83	61.60	70.73	78.49	88.98
BCD 10	a	0.040	0.051	0.056	0.069	0.079	0.091	0.108	0.119	0.131	0.146
	b	16.19	21.28	23.59	29.61	34.24	39.79	47.65	52.74	58.29	65.23
BCD 5	a	0.015	0.020	0.036	0.061	0.063	0.083	0.107	0.123	0.145	0.152
	b	4.48	6.72	13.88	25.07	25.97	34.92	45.67	52.83	62.68	65.82
BCD 2.5	a	0.049	0.064	0.083	0.103	0.116	0.140	0.166	0.193	0.205	0.211
	b	20.17	27.05	35.76	44.93	50.89	61.90	73.82	86.20	91.70	94.45
MSD 10	a	0.101	0.116	0.143	0.160	0.181	0.209	0.217	0.219	0.223	0.233
	b	42.11	48.68	60.53	67.98	77.19	89.47	92.98	93.86	95.61	95.61
MSD 5	a	0.076	0.100	0.133	0.154	0.177	0.208	0.217	0.219	0.219	0.217
	b	32.58	43.59	58.73	68.36	78.92	93.14	97.27	98.19	98.19	97.27
MSD 2.5	a	0.024	0.062	0.072	0.093	0.099	0.114	0.139	0.149	0.151	0.153
	b	8.52	25.57	30.06	39.48	42.17	48.90	60.12	64.60	65.50	66.40
DO	a	0.089	0.106	0.138	0.160	0.177	0.203	0.201	0.200	0.200	0.201
	b	39.49	47.49	62.53	72.87	80.87	93.09	92.15	91.68	91.68	92.15
a = Absorbance (b) = % w/w Dissoluton											
SMD 10	a	0.048	0.054	0.052	0.073	0.073	0.060	0.067	0.070	0.074	0.125
(pH9.53)	b	21.41	24.40	23.40	33.86	33.86	27.38	30.87	32.36	34.35	59.75
BCD 10	a	0.060	0.061	0.076	0.085	0.129	0.132	0.206	0.238	0.233	0.225
(pH9.53)	b	25.45	25.91	32.85	33.01	57.37	58.76	92.99	107.80	105.48	101.3

Table 9 continued:

TIME(mins) BATCH		40mins	45mins	50mins	55mins	60mins	75mins	90mins	105mins	120mins
SMD 10	a	0.216	0.209	0.218	0.216	0.214	0.212	0.212	0.213	0.214
	b	105.05	101.57	106.05	105.05	104.06	103.06	103.06	103.56	104.06
SMD 5	a	0.193	0.193	0.192	0.193	0.194	0.194	0.190	0.190	0.190
	b	90.43	90.43	89.95	90.43	90.91	90.91	88.99	88.99	88.99
SMD 2.5	a	0.165	0.170	0.170	0.167	0.173	0.170	0.172	0.168	0.181
	b	76.58	79.08	79.08	77.64	80.52	79.08	80.04	78.12	84.35
SCD 10	a	0.188	0.188	0.186	0.188	0.188	0.187	0.188	0.186	0.185
	b	80.58	80.58	79.70	80.58	80.58	80.14	80.58	79.70	79.26
SCD 5	a	0.185	0.188	0.186	0.185	0.185	0.184	0.186	0.185	0.184
	b	83.45	84.84	83.91	83.45	83.45	82.99	83.91	83.45	82.99
SCD 2.5	a	0.185	0.181	0.187	0.180	0.182	0.180	0.180	0.184	0.190
	b	82.25	80.42	83.16	79.96	80.88	79.96	79.96	81.79	84.53
BMD 10	a	0.210	0.212	0.211	0.216	0.211	0.212	0.209	0.209	0.215
	b	95.12	96.10	95.64	97.96	95.64	96.10	94.71	94.71	97.42
BMD 5	a	0.200	0.201	0.200	0.199	0.199	0.200	0.200	0.199	0.199
	b	90.66	91.12	90.66	90.19	90.19	90.66	90.66	90.19	90.19
BMD 2.5	a	0.177	0.200	0.177	0.177	0.178	0.177	0.176	0.178	0.180
	b	78.49	88.98	78.49	78.49	78.94	78.49	78.03	78.94	79.85
BCD 10	a	0.157	0.176	0.206	0.206	0.207	0.208	0.206	0.209	0.209
	b	70.32	79.11	92.99	92.99	93.45	93.92	92.99	94.38	94.38
BCD 5	a	0.162	0.174	0.184	0.184	0.195	0.187	0.185	0.186	0.188
	b	70.29	75.67	80.14	80.14	85.07	81.49	80.59	81.04	81.93
BCD 2.5	a	0.213	0.212	0.213	0.209	0.210	0.212	0.212	0.212	0.211
	b	95.37	94.91	95.37	93.54	93.99	94.91	94.91	94.91	94.45
MSD 10	a	0.221	0.222	0.222	0.224	0.219	0.221	0.223	0.222	0.222
	b	94.74	95.18	95.18	96.05	93.86	94.74	95.61	95.18	95.18
MSD 5	a	0.218	0.218	0.219	0.217	0.218	0.218	0.217	0.218	0.218
	b	97.73	97.73	98.19	97.27	97.73	97.73	97.27	97.73	97.73
MSD 2.5	a	0.157	0.156	0.150	0.149	0.151	0.153	0.152	0.150	0.151
	b	65.50	67.74	65.05	64.60	65.50	66.40	65.95	65.05	65.50
DO	a	0.201	0.200	0.200	0.200	0.199	0.200	0.199	0.199	0.200
	b	92.15	91.68	91.68	91.68	91.21	91.68	91.21	91.21	91.68

a = Absorbance (b) = % w/w Dissolution

SMD 10	a	0.174	0.182	0.211	0.220	0.212	0.217	0.212	0.203	0.211
(pH9.53)	b	84.14	88.12	102.56	107.04	103.06	105.55	103.06	98.58	102.56
BCD 10	a	0.215	0.222	0.210	0.208	0.209	0.200	0.211	0.210	0.211
(pH9.53)	b	97.15	100.39	94.84	93.92	94.38	90.21	95.30	94.84	95.30

- two hours was not sufficient for the attainment of 90% dissolution.

The dependency of disintegration and dissolution on the ease of water penetration into the tablet matrix has been reported (Udeala and Chukwu, 1985 (ii)) and a plausible explanation for the observed prolongation of the disintegration time by the test materials is the formation of a viscous gel following swelling of the test material on getting into contact with water. The material then functions as both binder and disintegrant in the same manner as had previously been postulated for methylcellulose (Esezobo, 1989).

4.2.3 Effect of pH of the dissolution medium on the dissolution rate of tablets prepared with the test materials as disintegrants

Figure 17 shows the dissolution rate profiles of SMD 10 and BCD 10 in acid and alkaline media. It could be seen that tablets made from SMD 10 released their medicament in both media more completely than those made from BCD 10 probably because BCD 10 had greater propensity for gel formation than SMD 10. The gel would then constitute a barrier to further penetration of water into the tablet matrix and subsequent dissolution of the active ingredient. However, the graphs show that the actual rate of release of the active medicament in SMD was faster in acid medium and there was a marked biphasic pattern of dissolution in the

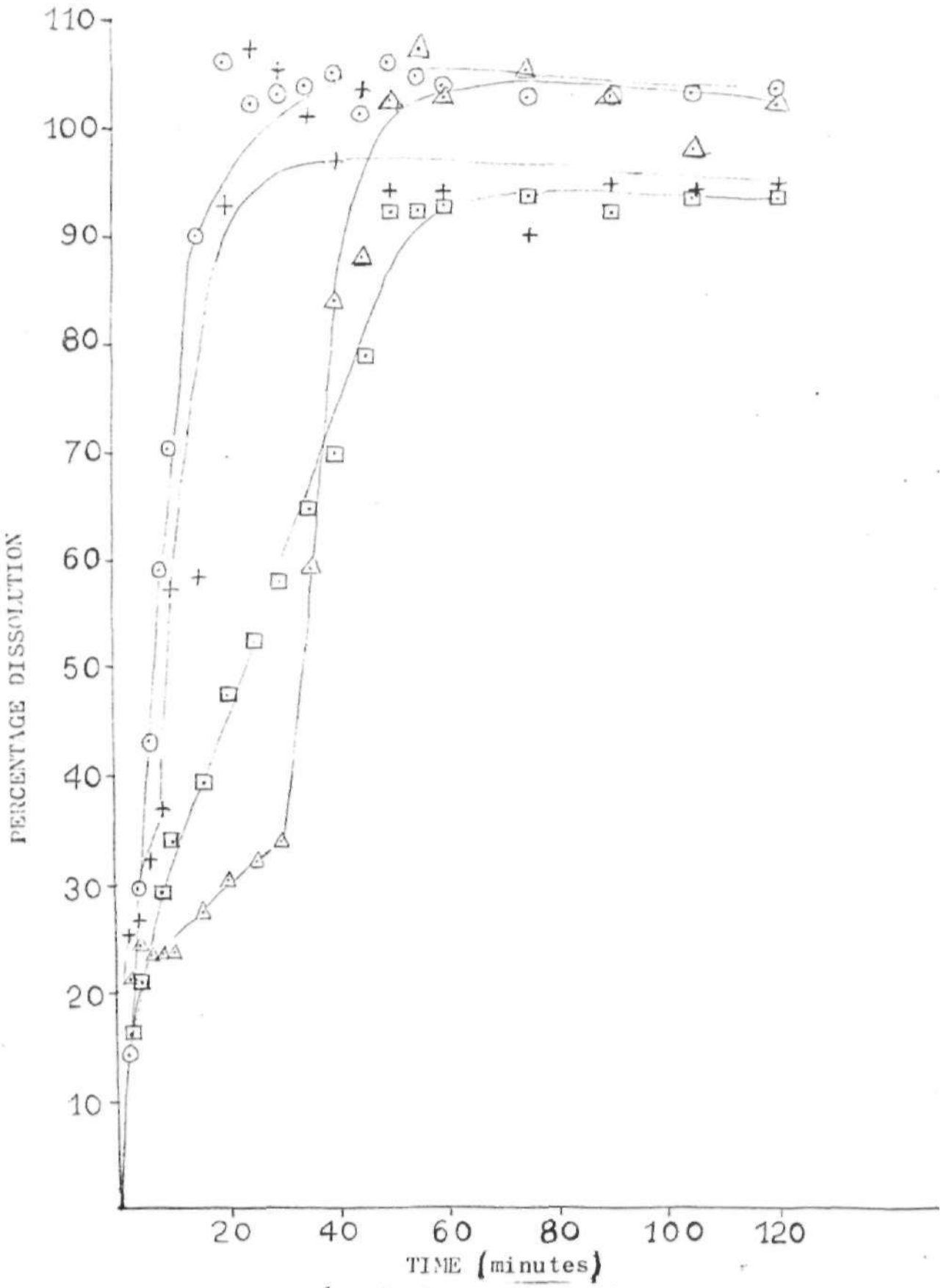


Figure 17: Dissolution rate profiles of SMD 10 and BCD 10 at pH 4.5 & 9.53.

⊙ SMD 10 (pH 4.50); △ SMD 10 (pH 9.53)

⊡ BCD 10 (pH 4.50); + BMD 10 (pH 9.53)

alkaline medium. Dissolution was slow within the first 30 minutes at the end of which only 34.35% dissolution was achieved and then sharply increased to attain the peak dissolution within the next 30 minutes. In contrast, BCD 10 dissolved faster in alkaline medium reaching the peak percentage dissolution of 107.80 in 25 minutes. Its dissolution in acid medium within the same time limit was 52.74%. It can also be seen that BCD gave a slight biphasic dissolution profile. The reason for these biphasic dissolution profiles is not clear. It could be that the disintegration process was slow initially and dissolution was only taking place from the intact tablet at the initial stage of the dissolution test and the subsequent sharp rise in the dissolution rate was due to dissolution from disintegrated tablets and fine particles of larger effective surface area.

It should be noted that there are a number of differences between the test materials, SM and BC, used in formulating the two batches of tablets. For instance SM was obtained from alcohol extraction of aqueous dispersion of SC and some percentage of mineral matter may have been lost during the extraction process. Secondly, BC is a product of pre-boiling of the Detarium seed and the heat treatment may have led to a disruption of the molecular structure of the seed polysaccharide. One or both of these factors may have contributed to the observed differences in the dissolution rate profiles

4.3 DIRECT COMPRESSION STUDIES

4.3.1 Effect of test materials on hardness and friability of tablets

Table 10 shows the results of the tests carried out on the tablets prepared from the various binary mixtures. It can be seen that the test materials, SC and BC, decreased the mechanical strength of the tablets containing them. This effect was manifested in decreasing hardness and increasing friability values as the concentration of the test material in the binary mixture increased. The hardness-friability ratio, therefore, decreased progressively. The trend was the same but to varying degrees in all the tablet batches prepared from binary mixtures containing the test materials.

In the test material - Lactose binary mixtures, BC had a greater lowering effect on the hardness-friability ratio than SC. The order of this lowering effect was also the same in test material - Avicel and test material - Starch 1500 binary mixtures. In contrast, increasing concentration of the proven direct compression excipients, Avicel and Starch 1500, led to increasing hardness and decreasing friability values with corresponding increase in hardness-friability ratio. Figures 18, 19 and 20 illustrate these results.

Table 10: MECHANICAL STRENGTH AND DISINTEGRATION CHARACTERISTICS OF TABLETS PREPARED FROM BINARY MIXTURES OF EITHER OF TWO FORMS OF CRUDE DETARIUM POWDER AND LACTOSE, AVICEL OR STARCH 1500

BATCH	MEAN WEIGHT (mg)	DISINTE-GRATION Time(min)	% FRIABILITY	MEAN HARDNESS (Kgf)	HARDNESS FRIABIL-ITY RATIO	THICK-NESS (mm)	PACKING FRACTION
LACTOSE100%	176.2	4.3	-	2.8	-	2.63	0.79
AV-L 25:75	160.9	0.8	0.63	11.2	17.8	2.46	0.79
50:50	158.4	19.8	0.65	14.8	22.7	2.53	0.78
25:25	166.1	> 60	0.32	17.0	53.1	2.56	0.83
100:0	161.7	> 60	0.34	17.0	50.0	2.34	0.90
St-L 25:75	174.3	0.1	1.27	6.1	4.8	2.56	0.81
50:50	179.8	1.5	0.68	7.9	11.5	2.78	0.78
75:25	188.2	8.8	0.67	8.7	13.0	2.90	0.79
100:0	185.0	20.5	0.39	6.4	16.4	3.04	0.75
SC-L 25:75	176.8	> 60	1.54	5.6	4.3	2.75	0.77
50:50	180.0	> 60	1.40	5.2	3.7	2.80	0.78
75:25	173.7	> 60	2.08	2.6	1.2	2.84	0.75
100:0	168.8	> 60	8.97	1.0	0.1	3.10	0.68
BC-L 25:75	180.0	> 60	4.40	3.1	0.7	2.81	0.70
50:50	169.9	> 60	3.36	1.1	0.3	2.74	0.63
75:25	164.6	> 60	11.85	0.3	0.0	2.86	0.54
100:0	165.5	> 60	-	0.1	-	3.10	0.46
BC-AV25:75	176.6	> 60	1.64	5.1	3.1	3.40	0.62
50:50	210.3	> 60	7.26	2.1	0.3	3.65	0.63
75:25	236.5	> 60	10.76	0.4	0.0	3.85	0.60
BC-St25:75	223.5	> 60	-	0.1	-	3.70	0.69
50:50	205.0	> 60	-	0.1	-	3.80	0.57
75:25	202.1	> 60	-	0.1	-	3.80	0.51
SC-Av25:75	170.7	> 60	2.17	6.7	3.1	3.50	0.63
50:50	169.7	> 60	2.20	3.1	1.4	3.30	0.66
25:75	181.5	> 60	10.00	1.0	0.1	3.45	0.66
SC-St25:75	219.8	> 60	3.60	1.8	0.5	3.80	0.71
50:50	214.2	> 60	7.11	1.4	0.2	3.75	0.71
25:75	209.1	> 60	-	0.9	-	3.75	0.69

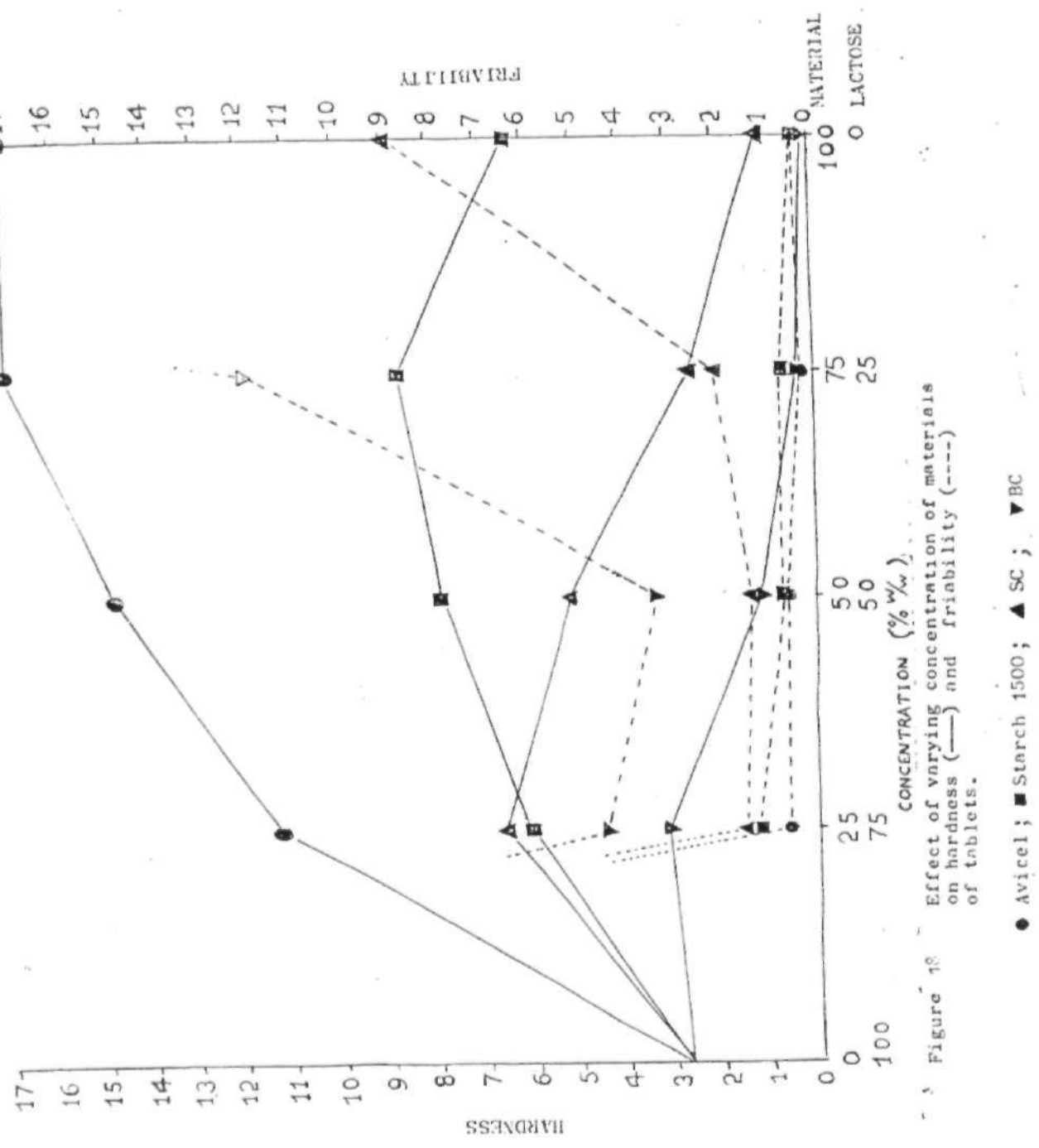


Figure 18 Effect of varying concentration of materials on hardness (——) and friability (----) of tablets.

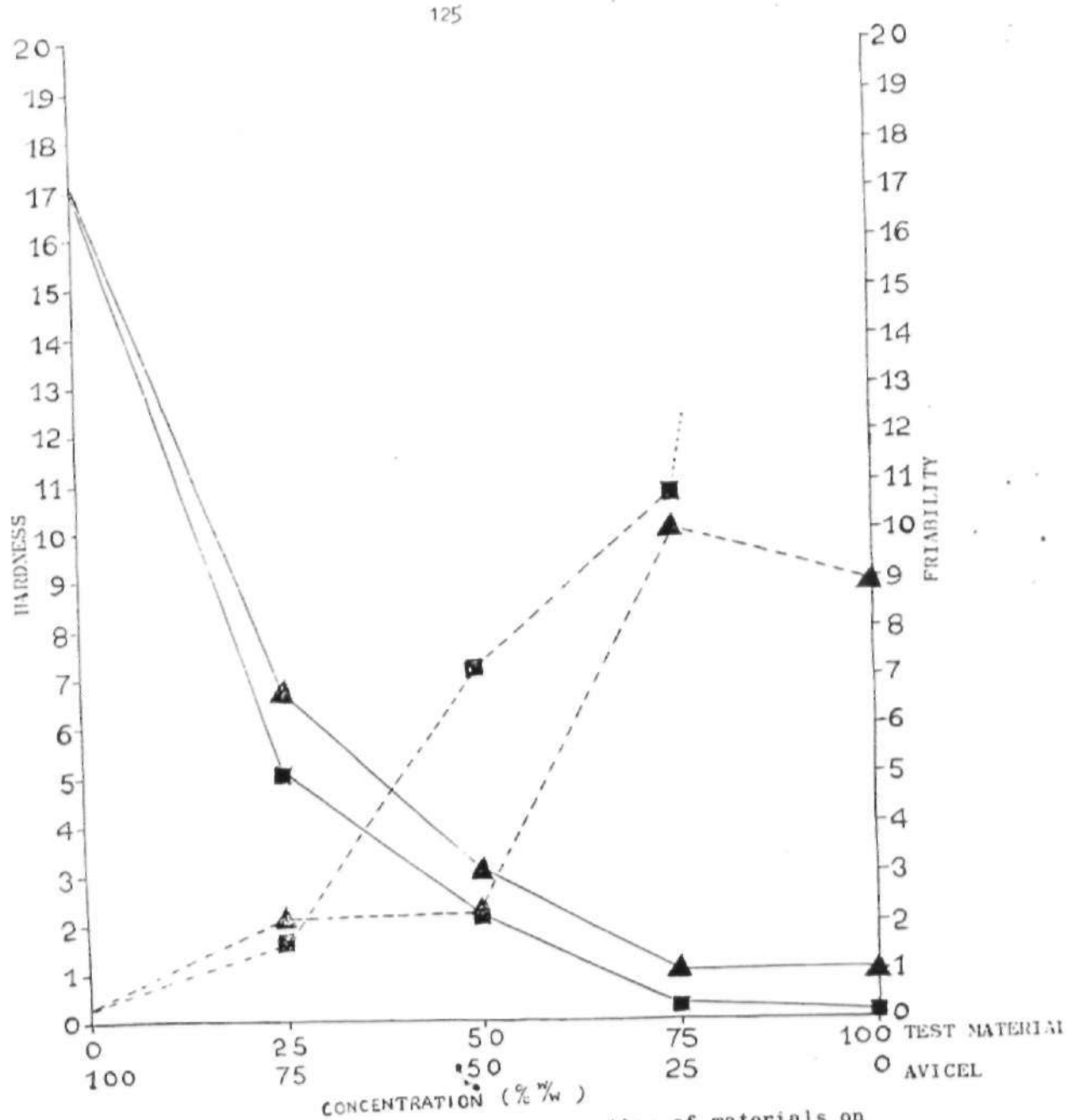


Figure 12. Effect of Varying concentration of materials on direct compression property of avicel.

▲ SC ; ■ BC

(——) Hardness (----) Friability

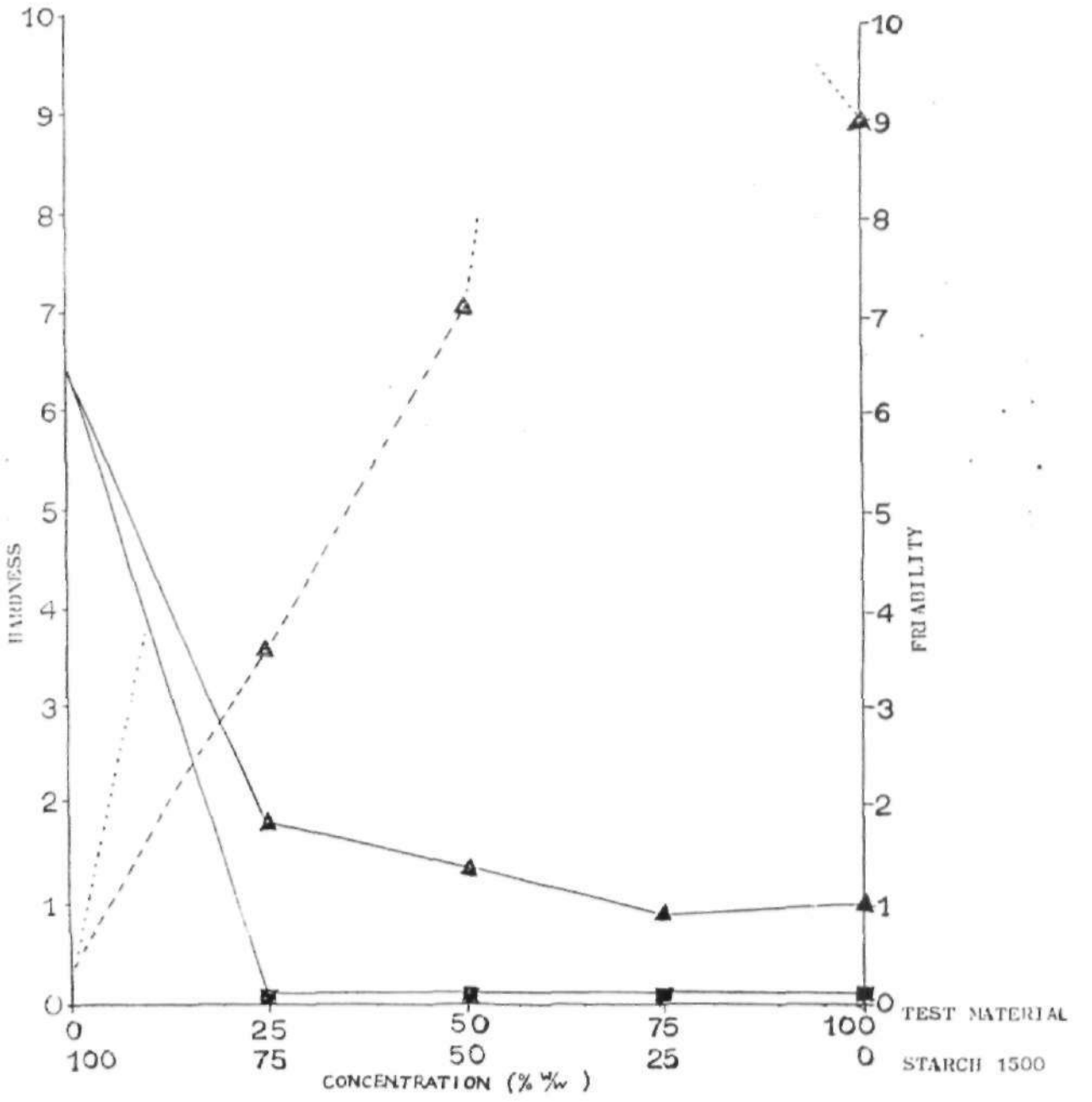


Figure 20 Effect of Varying concentration of materials on direct compression property of starch 1500

▲ SC ; ■ BC .

(——) Hardness (---) Friability

4.3.2 Effect of test materials on the disintegration time of tablets

At low concentrations Avicel (25% w/w) and Starch 1500 (25-50% w/w) reduced the disintegration time of lactose tablets from 4.3 minutes to 0.8 minutes and 0.1 to 1.5 minutes, respectively. This effect on the disintegration time was, however, reversed at higher concentrations of these materials in the binary mixtures. This was because at low concentrations, both Avicel and Starch 1500 absorbed water, swelled appreciably and exerted a high bursting influence on the tablets thus leading to the rapid disintegration of the tablets. However, as the concentration of Avicel increased, there was a general decrease in the interparticulate void spaces as evidenced by increasing packing fraction values. This might have led to greater difficulty in the penetration of water into the compact tablet hence the observed prolongation of the disintegration time. On the other hand, increasing concentration of Starch 1500 led to increasing proportion of void spaces in the tablet as evidenced by decreasing packing fraction values. Although this is expected to make for greater ease of water penetration into the tablet, swelling and subsequent disintegration, it also made for greater room to accommodate the swollen particles. Consequently, the bursting power of the latter might have considerably diminished and the disintegration time prolonged

The test materials, SC and BC, in contrast, prolonged the disintegration times of the tablets of binary mixtures containing them including those in which they combined with Avicel or Starch 1500 such that complete disintegration could not be achieved within the maximum time limit of 1 hour for which the test was run. This extension of disintegration time resulted from absorption of water by the test materials shortly after the tablet made contact with the aqueous disintegration medium. This was followed by swelling and formation of viscous gel which enveloped the tablets and functioned as a barrier to further penetration of water into the tablet matrix.

CHAPTER 5

SUMMARY AND CONCLUSION

Mucilages have been obtained from the seeds of Detarium microcarpum using two methods of extraction - pre-soaking and boiling the seed. The Detarium seed mucilage was found to be neutral and contained polysaccharide(s) that may be classified as "amyloid" and appeared to be composed of glucose and xylose as the building units. Pre-soaking the seed is to be preferred to pre-boiling on account of colour appeal, preservation of the polysaccharide structure and viscosity of aqueous dispersion of the resultant product as well as its binding capacity in tablet formulations.

Aqueous dispersions of the seed mucilage exhibited pseudoplastic behaviour and structure viscosity. At 4% w/v concentration, all the aqueous dispersions of the defatted powders and extracted mucilages gave very viscous solutions which were difficult to pour and were, therefore, not pharmaceutically acceptable. Results have shown that the binding capacity of a tablet binder increases, up to a point, with increase in the viscosity of its aqueous dispersion. However, it does not follow that a binder material having a comparatively lower viscosity value than another of same concentration at any given rate of

shear will bind less efficiently. The nature and concentration of the material seem to be the more determinant factors. 5% w/v gelatin, for instance, yielded firm tablets while the same concentration of maize starch did not despite the latter's comparatively higher viscosity at any given rate of shear. Increase in binder concentration generally led to decreased friability, increased hardness and increased disintegration and dissolution times of the tablets. This may be attributed to increased extent and strength of interparticulate bonding.

The mucilage derived from the pre-soaked seeds performed very well as tablet binder in chloroquine phosphate tablet formulations when its aqueous dispersion was employed as a granulating fluid in concentration range of 1-2% w/v. Its binding property was comparable with those of maize starch (10-15% w/v) and gelatin (5-15% w/v). The Detarium seed mucilage, therefore, has potential use as a local raw material and binding agent in tablet formulations because of the other properties such as local availability, the low cost of both the seed and its processing, and the comparatively low effective concentration required.

The defatted powders and extracted mucilages failed as tablet disintegrants since they prolonged the disintegration time of tablets. In addition, they lowered the mechanical strength of the tablets.

The Detarium seed mucilage has been shown to have high affinity for water to the extent of trapping from the atmosphere as much as 56.4-62.6% of its own weight of water within a period of 13 days of storage at high humidity levels (first at R.H. ≈ 85% for 7 days and then at R.H. ≈ 90% for the next 6 days) under normal room storage conditions with its attendant temperature fluctuations. The rapidity and near completeness of loss of its water content when transferred to a dry environment (R.H. ≈ 0% for 4 days) suggested that the water uptake occured by an adsorption process.

The defatted powders did not perform well as direct compression excipients since they decreased the mechanical strength and packing fraction as well as delayed the disintegration of the tablets containing them to over one hour.

Used as binder or disintegrant, the effect of increasing the concentration of the defatted powders and extracted mucilages as binders or disintegrants was the prolongation of the disintegration and dissolution times of tablets. Using SC as an example, the highest quantity used as a binder made a final concentration of 0.6% w/w of the finished tablet and this was responsible for prolongation of disintegration time from 5.8 to 10.5 minutes. The highest concentration of the same material used as a disintegrant was 10% w/w and it increased the disintegration time from 8.0 to 12.3 minutes. Used in binary

mixtures compressed into tablets, it increased the disintegration time to over one hour even at a concentration of 25% w/w. The binding efficiencies of the mucilages are in decreasing order SM > BC > SC > BM and as disintegrants, the efficiencies decreased in the order BC > SM > SC > BM. During the investigation for direct compression property, the defatted powders imparted similar disintegration characteristics on the tablets containing them in the sense that the disintegra-tion times of the tablets were prolonged beyond one hour. It can, therefore, be concluded that the potential of the Detarium seed as a source of prolonged-release tablet excipient may yet turn out to be a reality and, consequently, needs further investigation. The greenish-yellow fixed oil with specific gravity of 0.897 that it contains may also be investigated for its possible application in pharmacy.

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APPENDICES

Appendix 1: Shear stress values of various granulating fluids at varying rates of shear

SHEAR RATE(rpm)	SM 4%	SM 2%	SM 1%	SM 0.5%	SC 4%	SC 2%	SC 1%	SC 0.5%
0	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
10	62	12	1.5	1.5	23	5.5	1.5	1.25
20	72	15	2.0	1.5	27	7.0	1.5	1.25
30	27	17	2.25	1.5	29.5	8.0	1.5	1.25
40	80	18	2.75	1.5	30.5	8.5	1.75	1.3
50	83	19.5	3.0	1.5	32	9.0	2.0	1.3
60	85	20.5	3.25	1.5	33.5	9.5	2.25	1.3
70	87	21	3.5	1.6	34	10.0	2.25	1.5
80	89	21.5	3.75	1.75	34.5	10.5	2.25	1.5
90	91	22	4.0	1.8	35	10.75	2.25	1.5
100	91	22	4.0	2.0	35.5	11.0	2.5	1.6
90	89.5	21.5	3.8	1.75	34.5	10.5	2.25	1.3
80	87.5	20.5	3.75	1.5	33.0	10.0	2.0	1.3
70	85.5	20	3.5	1.5	32	9.5	1.75	1.25
60	83.5	19	3.25	1.5	30.5	9.0	1.6	1.2
50	81	18	3.0	1.5	29	8.5	1.5	1.2
40	78.5	17	2.75	1.5	27.5	7.5	1.3	1.2
30	75	15.5	2.25	1.5	26	7.0	1.3	1.0
20	70.5	14.0	1.75	1.5	24	6.0	1.25	0.8
10	62	11	1.50	1.5	20.5	4.5	1.25	0.8
0	6	1.5	0.8	1.0	1.5	0.8	0.8	0.8
RANGE	XI	XI	XI	XI	XI	XI	XI	XI

Appendix I (Contd.)

SHEAR RATE(rpm)	BM 4%	BM 2%	BM 1%	BM 0.5%	BC 4%	BC 2%	BC 1%	BC 0.5%
0	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
10	30	7.75	1.5	1.25	28.5	7.5	1.5	1.25
20	35.5	10.5	2.0	1.25	33.5	10.0	2	1.26
30	38.5	12.0	2.0	1.3	37.0	11.25	2.5	1.3
40	40.5	13	2.25	1.3	39	11.25	2.75	1.3
50	42.5	14	2.3	1.3	40.5	13.25	3.25	1.3
60	44	15	2.75	1.3	42.0	14	3.5	1.5
70	45.5	16	3.0	1.5	43.5	14.75	3.75	1.5
80	46.5	16.75	3.2	1.5	44.5	15.5	4	1.5
90	47.5	17.25	3.25	1.5	45.5	16	4.25	1.6
100	48	17.75	3.25	1.5	46.0	16.25	4.3	1.6
90	47	17	3.2	1.3	45.5	15.5	4.2	1.5
80	46	16.5	3.0	1.25	44.5	14.8	3.75	1.3
70	44.5	15.5	2.75	1.2	43.5	14.25	3.5	1.3
60	43.5	14.75	2.3	1.2	42.0	13.5	3.2	1.3
50	41.5	13.5	2.2	1.0	40.5	12.5	2.75	1.25
40	39.5	12.5	2.0	1.0	38.5	11.5	2.5	1.2
30	38.5	11	1.5	1.0	36.5	10.5	2	1.2
20	34	9.75	1.25	0.8	33.5	9	1.5	1.0
10	28.5	7	1.25	0.8	28.5	6.75	1.3	0.8
0	2.5	0.8	0.8	0.8	0.8	0.8	0.8	0.8
RANGE	XI	XI	XI	XI	XI	XI	XI	XI

Appendix 1 (contd.)

SHEAR RATE(rpm)	Gelatin 15%	Gelatin 10%	Gelatin 5%	Maize starch 15%	Maize starch 10%	Maize starch 5%
0	0.8	0.8	0.8	0.8	0.8	0.8
10	1.5	1.5	1.25	20.5	10	1.25
20	2.0	1.5	1.25	30.5	15	1.5
30	2.5	1.5	1.25	36.0	18	1.5
40	3.25	1.75	1.25	40.0	21	1.5
50	3.75	1.8	1.25	43.5	23.5	1.5
60	4.25	1.8	1.25	46.5	25.5	1.5
70	4.75	2.0	1.25	48.0	27.5	1.75
80	5.5	2.2	1.25	48.5	29	1.80
90	6.25	2.25	1.25	49.5	30	2.0
100	7.25	2.25	1.25	51.0	31.5	2.0
90	7.0	2.2	1.25	48.0	28.5	1.8
80	6.75	2.0	1.25	45	26	1.5
70	5.25	1.8	1.25	42	23.5	1.25
60	4.25	1.75	1.25	39	21	1.25
50	3.50	1.75	1.25	36	18.5	1.25
40	2.75	1.5	1.25	33	16	1.25
30	2.0	1.25	1.25	29	13.5	1.2
20	1.5	1.2	1.25	24	10.5	1.0
10	1.5	1.0	1.0	17	7	0.8
0	0.8	0.8	0.8	1.75	1.25	0.8
RANGE	XI	XI	XI	X2	XI	XI

Appendix 2: Determination of True Densities of Tablet Components and Oil Extract

	TABLET COMPONENT								OIL
	CHLOROQ-UINE	MAIZE STARCH	STARCH 1500	SC	BC	BM	LAC-TOSE	AVICEL	EXTRACT
A: LIQUID USED	Liquid paraffin	Petroleum ether						Tap water	
B: VOLUME OF PYCNOMETER (ml)	50	50	25	25	25	25	25	25	25
C: WEIGHT OF MATERIAL IN AIR (g)	5.0	5.0	2.0	2.0	2.0	2.0	2.0	2.0	
D: WEIGHT OF LIQUID HELD IN PYCNOME-TER (g)	41.21	29.33	15.63	15.63	15.63	15.63	15.63	25.22	22.42
E: TOTAL WEIGHT OF BOTH (g) (C + D)	46.21	34.33	17.63	17.63	17.63	17.63	17.63	27.22	
F: WEIGHT OF LIQUID AND IMMERSED MATERIAL (g)	43.47	32.21	16.85	16.85	16.81	17.44	16.89	25.89	
G: SPECIFIC GRAVITY OF LIQUID (D/B)	0.82	0.57	0.63	0.63	0.63	0.63	0.63	1.01	0.897
H: LOSS OF WEIGHT IN WATER $\frac{(E-F)}{G}$	3.32	3.62	1.24	1.25	1.31	0.30	1.18	1.32	
I: SPECIFIC GRAVITY OF MATERIAL C/H	1.51	1.38	1.61	1.60	2.29	6.72	1.69	1.52	0.897

Appendix 3: Particle Size Analysis of granules of Chloroquine Phosphate tablet formulations

SIEVE SIZE (µm)		SM 4	SM 2	SM 1	SM 0.5	SC 4	SC 2	SC 1	SC 0.5
75	*	0.417	0.144	0.272	0.332	0.270	0.345	0.323	0.172
	**	2.623	0.973	1.833	2.054	1.809	2.116	2.071	1.290
	***	2.623	0.973	1.833	2.054	1.809	2.116	2.071	1.290
125	*	0.068	0.113	0.027	0.034	0.011	0.030	0.028	0.041
	**	0.428	0.764	0.182	0.210	0.074	0.184	0.10	0.307
	***	3.051	1.737	2.015	2.264	1.881	2.300	2.251	1.597
150	*	0.268	0.119	0.147	0.162	0.122	0.182	0.148	0.111
	**	1.686	0.804	0.991	1.002	0.817	1.116	0.949	0.832
	***	4.737	2.541	3.006	3.266	2.698	3.416	3.200	2.429
250	*	1.145	0.478	0.569	0.656	0.625	0.912	0.684	0.472
	**	7.202	3.230	3.835	4.059	4.187	5.594	4.385	3.539
	***	11.939	5.771	6.841	7.325	6.885	9.010	7.585	5.968
500	*	5.453	2.844	2.206	3.442	3.474	5.105	2.468	1.869
	**	34.298	19.219	14.868	21.296	23.272	31.311	15.821	14.013
	***	46.237	24.990	21.709	28.621	30.157	40.321	23.406	19.981
1000	*	8.548	11.100	11.616	11.537	10.426	9.730	11.949	10.673
	**	53.764	75.010	78.291	71.379	69.842	59.679	76.591	80.020
	***	100.001	100.000	100.00	100.000	99.999	100.00	100.02	100.001
MEAN PARTICLE SIZE (µm)		732.17	857.16	869.93	833.72	827.92	770.82	859.18	881.71

* = Weight of granules that passed through sieve (in grams)

** = % w/w of granules that passed through sieve

*** = Commulative % undersize

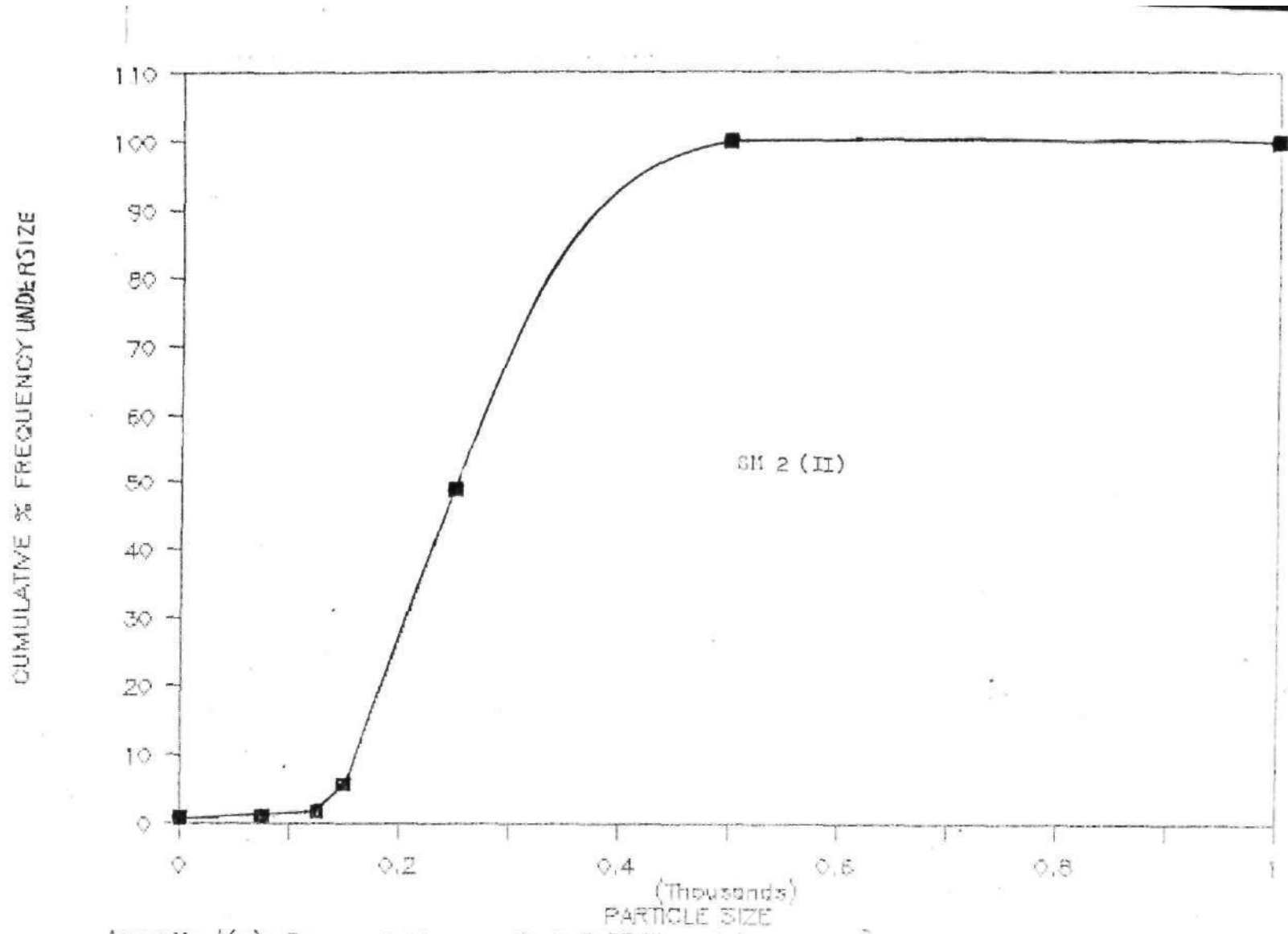
Appendix 3: (Contd.)

SIEVE SIZE (µm)		BM 4	BM 2	BM 1	BM 0.5	BC 4	BC 2	BC 1	BC 0.5
75	*	0.292	0.139	0.162	0.242	0.293	0.472	0.183	0.253
	**	1.650	0.931	1.070	1.447	2.248	3.244	1.236	1.635
	***	1.650	0.931	1.070	1.447	2.248	3.244	1.236	1.635
	*	1.028	0.270	0.184	0.245	0.033	0.032	0.023	0.040
125	**	5.810	1.808	1.215	1.465	0.253	0.220	0.155	0.259
	***	7.460	2.739	2.285	2.912	2.501	3.464	1.391	1.894
	*	0.957	0.252	0.173	0.296	0.119	0.197	0.087	0.118
150	**	5.408	1.687	1.142	1.770	0.913	1.354	0.588	0.763
	***	12.868	4.426	3.427	4.682	3.414	4.818	1.979	2.657
	*	3.539	1.148	0.626	1.171	0.426	0.719	0.421	0.657
250	**	20.000	7.685	4.133	7.002	3.268	4.941	2.844	4.246
	***	32.868	12.111	7.560	11.684	6.682	9.759	4.823	6.903
	*	6.225	5.817	2.358	4.499	1.497	2.198	3.464	3.679
500	**	35.179	38.941	15.570	26.902	11.485	15.105	23.398	23.777
	***	68.047	51.052	23.130	38.586	18.167	24.864	28.221	30.680
	*	5.654	7.312	11.642	10.271	10.667	10.934	10.627	10.726
1000	**	31.953	48.949	76.870	61.415	81.834	75.138	71.780	69.321
	***	100.000	100.001	100.00	100.001	100.01	100.02	100.01	100.001
MEAN PARTICLE SIZE (µm)		713.94	708.90	860.92	771.74	887.31	844.00	843.90	825.40

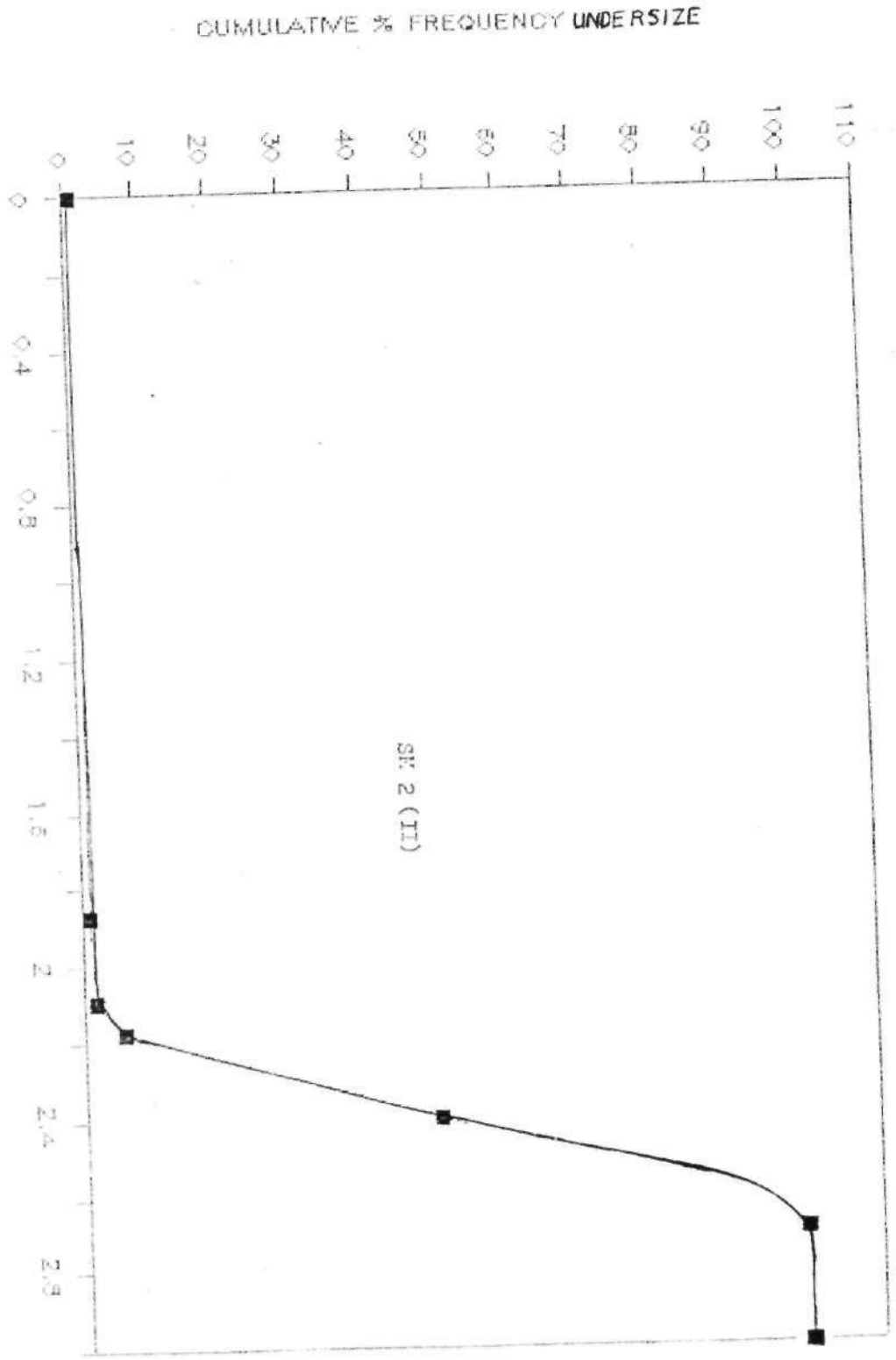
Appendix 3 (contd.)

SIEVE SIZE (µm)		MS 15	MS 10	MS 5	W	G15	G 10	G 5	SM 2(II)
	*	0.233	0.207	0.338	0.359	0.2000	0.155	0.294	2.434
	**	1.477	1.330	2.230	2.476	1.266	1.033	1.874	1.07
	***	1.477	1.330	2.230	2.476	1.266	1.033	1.874	1.07
	*	0.010	0.025	0.027	0.044	0.027	0.022	0.033	0.058
125	**	0.063	0.161	0.178	0.303	0.171	0.147	0.210	0.03
	***	1.540	1.491	2.408	2.779	1.437	1.180	2.084	1.10
	*	0.132	0.145	0.166	0.169	0.155	0.114	0.158	1.839
150	**	0.837	0.932	1.095	1.166	0.981	0.760	1.007	0.81
	***	2.377	2.423	3.503	3.945	2.418	1.940	3.091	1.91
	*	1.052	0.880	0.900	0.749	0.713	0.479	0.683	8.387
250	**	6.667	5.653	5.937	5.166	4.544	3.192	4.353	3.69
	***	9.044	8.076	9.440	9.111	6.962	5.132	7.444	5.60
	*	6.645	6.086	4.223	2.726	3.600	2.231	2.500	98.762
500	**	42.110	39.098	27.858	18.800	22.782	12.301	15.932	43.41
	***	51.154	47.174	37.298	27.911	29.744	20.333	23.376	49.01
	*	7.708	8.223	9.505	10.453	11.102	11.955	12.024	16.046
1000	**	48.847	52.827	62.702	72.090	70.257	79.668	76.625	51.00
	***	100.001	47.174	100.000	100.001	100.001	100.01	100.01	100.001
MEAN PARTICLE SIZE (µm)		718.13	740.49	784.69	831 80	830.47	882.76	859.97	738.33

SM 2 (II) = Granules prior to extragranular incorporation of test materials as disintregrant.



Appendix 4(a); Representative graph of Cumulative % Frequency undersize Against Particle size.



Appendix M(b): Demonstrative graph of cumulative % frequency undersize against log Particle size