EVALUATION OF PREGELATINISED STARCH AND MALIODEXTRIN DERIVED FROM SWEET POTATO IPOMEA BATATAS IN TABLETS

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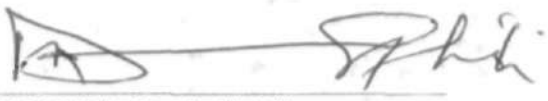
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DECEMBER, 1999

DECLARATION

I hereby declare that this thesis has been written by me and that it is a record of my research work carried out under the supervision of Dr. J.E. Ojile and Dr. J.A. Onaolapo. and that not a single part of this work has been presented in any previous applications for a degree.

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DEDICATION

This work is dedicated to my wife, Mrs. H.A. Ocheja and our children, Mustapha Alih, Fatima Alih, and Maryam Alih.

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ABSTRACT

The starch contained in potato *Ipomea batatas* was extracted by milling, suspending in water, centrifugal ion, reaction with sodium bisulphate, washing and drying. The starch complied with the B.P (1988) identification test. It was modified into pregelatiniscd starch (PGS) by drying the mucilage to form a dry powder, part of which was mixed with dilute nitric acid, subjected to prolonged heart and dried to give maltodextrin (MI)X). The modified products were characterized using the following parameters; How rate, angle of repose, bulk densities, Carr's index and moisture content.

The suitability of the modified products as various functional excipients in wet and dry granulated tablets formulation were evaluated. Direct Compression of pure and various binary mixtures as sole excipients were carried out.

The high dose 50()mg per tablet contains sulphamcthoxazolc, a non -self compressible drug, while the low dose requiring maximal sole excipients as diluent contained in 5mg folic acid, thereby constituting only 6.6% w/w. While a Pelletizing machine was used to compact excipients and active ingredients to slugs that were comminuted into granules through the sieve to form granules, the eccentric tablet press/machine was used to compact the granules into tablets, the properties of the tablets evaluated included weight uniformity, thickness, hardness, friability, packing fraction, compact density, tensile strength and disintegration time. Apart from thickness and friability, which were inversely related, the other parameters were directly related to the compression pressure. The results are traceable to densification of compacts.

In direct compression, Avicel® and maltodextrin produce more coherent tablets thereby showing a high level of binding action than pregelatiniscd starch which exhibited higher disintegranl properties. Thus, a binary mixed powder depending on the proportion enhanced better bioavailable properties with AVL/PGS and MDX/I'GS binary mixtures, for those tablets which bioavailibility arc governed by the rate at which the tablets disintegrate. Paradoxically the highest sole dry binder excipients containing 30% compared with 20% and 10% of the modified products and Avicel® in sulphamcthoxazolc tablets produced the solles tablets. This could be attributed to higher content of fines.

The thickness was in the following order; MDX/AVL® < AVL®/ PGS < MDX/PGS.

The more plastically compressible a compact the thinner is the compact.

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SYMBOLS

Avl	=	Avicel [R]
F/A	=	Folic Acid
MDX	=	Maltodextrin
PGS	=	Pregelatinised Starch
PTS	=	Potato Starch
SMZ	=	Sulphamethoxazole

CHAPTER ONE

1.0 INTRODUCTION

STARCHES

Starches are widely distributed and readily available in abundant quantities. They are used for both domestic consumption and for industrial uses. One of the earliest work on the use of locally available starches as pharmaceutical raw material was by Mital and Ocran (1968). They evaluated the binding and disintegrant properties of starch from yam and cassava tubers in tablet formulation. Other workers such as Khan and Rhodes (1972), also reported the disintegrant properties of starch. Nasipuri (1972), equally evaluated the use of cassava starch as a binder and disintegrant in tablet formulation. Cassava starch was reported to act as fillers, binders and disintegrant in dextromethophan hydrobromide tablets (Budaye, Ojile and Bangudu (1994).

Jaiyeoba and Opakunle (1978), have also shown the suitability of yam and cassava as diluents and glidants in tablet formulations. Esezobo and Ambujam (1982) reported that starch mucilage produced from *Musa Paradiasica* is used as a binder and provide sufficient strong force between particles to produce very good coherent tablets. Most of the evaluation of the effects of binder on granules and tablets have been carried out by employing a single volume of the binder while varying the concentration (Esezobo and Pilpel 1976, Pilpel et al 1978, Esezobo and Ambujam 1982, Iwuagwu et al 1986).

However, other workers (Ganderton and Hunter 1971, Opakunle and Spring 1976, Chalmers and Elworthy 1976, Nasipuri and Akala 1986) have shown that by varying the volume of binder and keeping its concentration constant also provided changes in physical properties of granules and tablets.

Pharmaceutical grades starch are derived from maize grain, potato and cassava tubers. The use of starch from other sources have been extensively investigated. Current advances in tablet technology especially in the use of high speed multistation tablet press and direct compression techniques have necessitated the use of excipient with good flow and compression characteristics. Work on forming modifications of starch has been scanty in this country. Sta-Rx 1500 which is derived from starch has been known to possess some direct compressible characteristics. Its unavailability has led to the use of Avicel® which is microcrystalline cellulose which is closely and chemically associated with starch as glucosidic units polymers and which was used for comparative purposes.

1.1 TABLET AND TABLETING

Tablets are solid preparations each containing a unit dose of one or more active ingredients. They are obtained by compressing uniform volumes of particles intended for oral administration. Some are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated.

The particles to be compressed consist of one or more active ingredients with or without auxiliary substances such as diluents, binders, disintegrants, glidants, lubricants, which are substances capable of modifying the behaviour of the active ingredients in the digestive tract, while authorized colouring and flavouring agents. Although it is possible to manufacture tablets in a wide range of shapes, official tablets are defined as circular discs with flat or convex faces (B.P., 1988). Today, they are the most popular dosage form of administering medicaments (Gunsel and Kanig, 1975). When properly formulated and manufactured, they confer the following properties on

the tablets. They are able to withstand the rigours of the mechanical treatment involved in the:

- production, packaging, shipping and dispensing.
- free from defects, contamination and are able to release the medicaments in a reproducible and predictable manner.

1.1.1 Advantages of the Tablet Dosage Form

Tablets owe its popularity to a number of reasons, among which are the followings;

- they offer means for repeated accurate dose of a drug without resorting to use of a metering unit, so the presence of a trained personnel is not required;
- they allow the incorporation of two or more incompatible drugs in one dosage form;
- the unpleasant taste can be masked by coating;
- they can be handled and transported easily by both the manufacturer and patient;
- they are very stable and therefore have long shelf-lives;
- they are amenable to mass production and the economies of high scale production.

1.1.2 Types of Tablets

There are different types of tablets which include the following:-

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1.1.2.1 Compressed Tablets:

This can be either plain (uncoated) or coated tablet. A plain tablet is prepared by compressing a particulate solid in a die by the application of forces via two punches upper and lower (Anon 1955). Coated tablets are those that, after the normal compression of the tablet, the coating materials are applied, the coating material could be sugar coating, film coating or press coating (Hogan 1983). Advantages in coating tablets include protection of ingredients from the environment particularly light and moisture. Many drugs have a bitter or otherwise unpleasant taste, Coating provides an efficient method of taste masking tablets which are easier to swallow. It aids patient compliance with the dosage schemes. It aids in the rapid identification of product by the manufacturer, dispensing pharmacists and patients. Coating also facilitates handling in high speed automatic filling and packaging equipment. It helps to add mechanical strength to the tablet core. Cross-contamination is also reduced in the manufacturing plant as dusting from tablet is eliminated. Functional film coating are used to impart enteric or controlled release properties to the coated tablet.

1.1.2.2 Sublingual and Buccal Tablets:

Tablets placed under the tongue sublingually or in the side of the cheek (buccally) can produce an immediate systemic effect by enabling the drug to be directly absorbed through the mucosa. Examples are isoprenaline sulphate (bronchodilator) and glyceryl trinitrate tablets (vasodilator). These tablets are usually small and flat, they do not contain a disintegrant and are compressed lightly to produce a fairly soft tablet. A sweeting agent like surose is used to impact sweetness.

1.1.2.3 Chewable Tablets:

Chewable tablets can be taken at any time or place without water or for the patients with difficulty in swallowing or for children who have not yet learnt how to wash tablet down with water. Mannitol is normally used as a chewable base diluent, since it has a pleasant cooling sensation in the mouth and can mask the taste of some objectionable medicaments. Chewable tablets are prepared by wet granulation but the granules are not too hard and normally contain a high proportion of flavouring agent to aid palatability which can include chocolate base. A disintegrating agent is not required, since the teeth perform this function. Examples include antacids.

1.1.2.4 Effervescent Tablets:

When tablets containing alkali metal carbonates or bicarbonates are combined with tartaric, or citric acid, carbon dioxide will be liberated, when the tablet is placed in water thus enhancing quick dissolution of the active ingredient. Effervescent tablets can be produced by wet fusion and heat fusion. With wet fusion techniques citric acid is moistened and added to sodium bicarbonate and granulated in a suitable mixer, the moist citric acid acting to partially fuse the powders. The granules are then tableted and then dried in an oven at 70°C before being packaged in moisture - proof container or aluminium foil. The heat fusion technique requires all the powders to be blended dry with the citric acid being in the form of citric acid monohydrate. The mixed powders are then heated to liberate the water of crystallization in the citric acid which acts as the granulating agent.

1.1.2.5 Lozenges

Lozenges are compressed tablets usually at least 18mm in diameter which do not contain a disintegrant and are sucked to dissolve in the mouth.

Generally, there are two types depending on the required action. The first type produces a local effect in the mouth or throat. This usually ,contains antiseptic (e.g. benzakonium) or antibiotic. It is palatable and slowly soluble. The formulation thus contains some sucrose in fine powder, lactose and gelatin solution to impart a smooth taste. The formulation is compressed between flat-faced punches to allow greater pressures to be applied. Flavours are normally incorporated to assist palatability. The second type of lozenges produces a systemic effect. An example is the lozenge which contains vitamin supplements. It is also required to be sucked. It is a palatable way of administering vitamins. Flavours are normally included in the lozenges.

1.1.2.6 Implants

Implants are very small pellets composed of drug substances only without excipients. They are normally about 2 to 3 cm in diameter and are prepared in an aseptic manner and are therefore sterile.

By the use of surgical procedures, implants are inserted into the body tissues from where they are absorbed very slowly over a period of months (Camphell et al 1958). Implant pellets are used largely for the administration of hormones such as stillboestrol, testosterone and dioxycortone acetate. Implants are produced on a single station tablet press using the punch and die set which must also be sterilized. The die is filled by hand since the drug does not flow. Particle size is large to produce slow rate of absorption and to achieve a gradual release.

1.1.2.7 Suppositories And Pessaries

These are solid preparations each containing one or more active ingredients. They are normally administered as a single dose for local action or systemic absorption of the active ingredients. They are inserted into the rectum, vagina or the urethra. After insertion, suppositories soften, melt or dissolve in the cavity fluids.

They are used by both adults and children. There are three types of suppositories:-

Rectal suppositories: The U.S.P(1980) describes rectal suppositories for adults as tapered at one or both ends and usually weighing about 2 g each. Infant rectal suppositories usually weigh about one-half that of adult suppositories. Drugs, having systemic effects such as sedatives, tranquilizers and analgesics may be administered as rectal suppository. However, the largest single use category is probably that of haemorrhoid remedies. The 2g weight for adult rectal suppositories were based on the use of cocoa butter as the base. When other bases are used, the weights may be greater or less than 2g.

Vaginal suppositories: The U.S.P.(1980) describes vaginal suppositories as usually globular or oviform and weighing about 5g each. Vaginal medication are available in a variety of physical forms e.g. creams, gels, or liquid which depart from the classical concept of suppositories. Vaginal tablets however do meet the definition and represent convenience both of administration and manufacture.

Urethral suppositories: Urethral suppositories or bougies are not described specifically in the U.S.P. either by weight or dimension. Urethral suppositories are an unusual dosage form and seldomly encountered.

1.2 TABLET MANUFACTURE

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

The machines consists essentially of:-

(1) hopper for storing the materials for compressing;

(2) feed frame for distributing the materials into the die;

(3) dies for controlling the size and shape of the tablet;

(4) punches for compacting the materials within the dies and shaping the tablet;

(5) cams for guiding the punches.

All other parts of the tablet press are designed to control the functioning of those listed above. Generally, there are two types of tablet compression machines - the single punch and the multi-station rotatory press. These machines are similar in their principles of operation and only differ in such aspects as the output, mode of compression and the mechanical features designed to control the compression processes.

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

- the ability to flow freely to give even fill of the die;
- cohesiveness for formation of strong tablets and
- lubrication to reduce frictional effect on the die wall.

1.2.1 Production Of Flowable And Compressible Materials

Since most materials have none or only some of these properties, formulations and preparations have been developed to impart these desirable characteristics to the material to be compressed. The process of granulation is usually used to achieve this. The two main reasons for granulation are:-

(i) to convert the powder into a free flowing form suitable for compression.

(ii) to aid cohesion or compressibility of the material during compaction in order to form firm tablets

1.2.2 Ways for Achieving these 2 Objectives of Flowability and Compressibility

i) granulation forms larger and more spherical particles which ensure free flowing of the particles. This is because spheres minimize interparticulate friction.

ii) granulation presents a range of particle size distribution that resemble a normal distribution curve. This implies a small percentage of coarse and fine particles with the rest in a narrow range in-between.

iii) granulation allows a uniform distribution of all the ingredients in the formulation thereby ensuring dose uniformity.

iv) granulation inbuilds compressible components that will confer physical strength and form to the tablets. When the dose of the drug is low, the diluent largely govern the physical properties of the granules and tablets but when the dose is high the drug will have the greatest influence.

There are basically three main methods for manufacturing compressed tablets, namely:-

(1) wet granulation;

(2) dry granulation (or slugging);

(3) direct compression.

1.2.3 Wet Granulation Method

This is the oldest and the most widely used method for the compressed tablets. The active ingredients and any diluent and part of the disintegrant required in the tablet formulation are mixed thoroughly. The effectiveness of this mixing stage determines the distribution of the active ingredients and therefore affects dose uniformity among the tablets produced. The granules are now formed by adding liquid binder. Mixing continues until uniform dispersion is attained and all the mucilage has been activated. The amount of binder solutions added is dependent mainly upon the formulative ingredients and the nature and the concentration of the binder. The wetted mass is then passed through a screen of the desired mesh size. This results in the breaking up of the wet mass into coarse granules or aggregates. It is usually done by an oscillating granulator which prepare the granulation by extrusion through the screens with large perforations. The purpose of this step is to increase the surface area from which moisture can be lost and thus increase the rate of drying of the granulation. The granules are then dried in one of the several equipments available.

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

After drying the granules are again sieved by passing them through a screen, the size of which depends on the size of the tablet to be made. This step helps to break down caked aggregates that might have been formed during the drying process. The lubricants are now added to the granules after any lumps or aggregates in the lubricants

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have been broken down to increase their conveying power. Any disintegrant that is left to be added is now added at this stage. This is mainly referred to as exodisintegrant.

Advantages of Wet Granulation

(1) the cohesiveness and compressibility of powder is improved due to added binder which coats the individual powder particles causing them to adhere to each other to enable them form agglomerates called granules,

(2) high dosage drugs having poor flow or compressibility properties must be prepared by wet granulation to obtain a suitable flow and cohesion for compression; in this case, the proportion of binder required to impart adequate compressibility and flow is much less than the proportion of dry binder needed to produce a tablet by direct compression,

(3) good distribution and uniform contents for soluble low dosage drug and colour additive are obtained if these are in the binder solution of a wet granulation,

(4) wet granulation prevents aggregates of components of a homogenous powder mix during processing, transferring and handling,

(5) the dissolution rate of a hydrophobic drug may be improved by wet granulation with the proper choice of solvent and binder.

Limitation of wet granulation is that it is a very expensive process because of labour, time, equipment and space required. Thermolabile and hydrolysable materials cannot be prepared by this method since they require both wetting and drying.

1.2.4 Dry Granulation

In this method large masses of the mixture (drugs and excipients) are compacted and subsequently crushed through a sieve to be sized into smaller granules. For this

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method to be used, either the active ingredient or the diluent must have cohesive properties in order for the large masses to be formed.

First, the ingredients are mixed thoroughly. The powder is then compressed into large tablets or slugs. The slugs are then broken up by a mill through a screen of desired size. Extra-granular excipients e.g. disintegrants, glidants and lubricant are added and the granules are now ready for compression.

Compacting mills can also be used to produce sheets as opposed to slugs in the compaction method. The powder to be densified passes between high pressure rollers which compress it and remove the air. Excessive pressure which may be required to obtain cohesiveness of certain material may result in a prolonged dissolution time (Kovac, 1962).

Compaction mills available include the Chilsonator made by FitzPatrick and Hutt Compactor. The pre-compression method which is also referred to as double compression method is extremely valuable for those materials which cannot be compressed directly and are at the same time thermolabile and/or moisture sensitive and also for preparing effervescent tablets since the dried acid and bicarbonate remain fully inactive until the tablet is immersed in water. However, granules made by dry granulation tend to be friable and a considerable amount of fines tend to be produced during the comminution.

1.2.5 Direct Compression Method

The direct compression is the process of preparing tablets from the mixtures of active ingredient and excipient powder (Rubinstein, 1993). This technique provides simplicity to the tableting process with an improved reliability and enhanced

acceptability. The direct compression techniques involve only the blending of the drug and the excipients and then followed by compression.

The selection of direct compression excipients is however critical as the success of the techniques depend largely on it. Apart from the advantages of saving space, machinery, personnel and time, the direct compression techniques provide improved chemical and physical stability compared to tablets produced by wet granulation method. Other advantages of the direct compression techniques include the attractive tablets produced, the faster rate of drug release and the ease of automation of the tableting process (David and Augsberger, 1977).

In formulations where active ingredients are moisture sensitive, such as aspirin and ascorbic acid, the replacement of wet granulation method with the dry granulation or direct compression techniques would increase chemical stability. Lamberson and Reynor (1976) concluded that low cost and rapid production are certainly the greatest attributes of the direct compression over the conventional techniques.

The ideal, direct compression tablet excipient should possess the following properties:-

High Capacity: Depending on the type of active ingredient to be incorporated, the suitable direct compression excipient should be able to produce stable tablets, containing a high proportion of non-compressible material (Armstrong, 1993).

High compressibility: A tablet containing a high proportion of non-compressible material should have an excipient which is highly compressible producing non-friable tablets with good hardness and pressure profile. Such excipient should also be capable of withstanding reworking with no loss of flow or compressibility.

Stability: The ideal excipient should be chemically compatible with drug substances, it should be colourless, tasteless, produce a good mouth feel and be non-hygroscopic.

Good fluidity: The ideal direct compression excipient should be free flowing, allowing continued uniform flow of the powder through the dies of the tableting press.

Bioavailability: The Ideal direct compression excipient should exhibit prompt disintegration and allow the dissolution of the active drug substance necessary for systemic absorption.

Economy: A tablet excipient should be readily and locally available and be relatively cheap. As a result of the extensive research on the physical and/or chemical modifications of diluents, disintegrants, binders and lubricants, more versatile direct compression excipients are now available. Since vast majority of medicinal agents are not directly compressible, directly compressible vehicles may be used. Other excipients of significance in direct compression techniques include anhydrous lactose, spray dried lactose, microcrystalline cellulose, amylose, dicalcium phosphate, granular mannitol and crystalline sorbitol (Gunsel and Kanig, 1976). Though these properties enumerated above are not embodied in a single material, in practice, it is desirable to blend two or more compressible aids together (Wells and Lagridge, 1981).

Disadvantages of direct compression arise due to different particle sizes and bulk density which can lead to stratification in handling and variations in drug content of the resultant tablet. Static charges may develop on the drug during mixing. This may prevent uniform distribution and inadequate mixing.. Good earthing of mixers/blenders are thus essential.

1.2.6 Other Methods of Producing Granules for Tablet Production

1.2.6.1 Fluidized Bed Granulation

An attempt to reduce handling cost in wet granulation process has necessitated the introduction of this method. Here the drug and filler are loaded into a chamber

through which a current of warm air is passed which thoroughly blends the mixture. The binder solution is sprayed as a stream of droplets onto the fluidized powder and thus granulation takes place as the particles are suspended in air. After granulation is completed, the spray is stopped but the fluidizing hot air is continued and the product dried as in a fluidized bed drier. This speeds up the process and still involves water and heat. Granules can be produced very effectively in this type of equipment and to some extent the granule size can be controlled.

1.2.6.2 Spray Drying Method

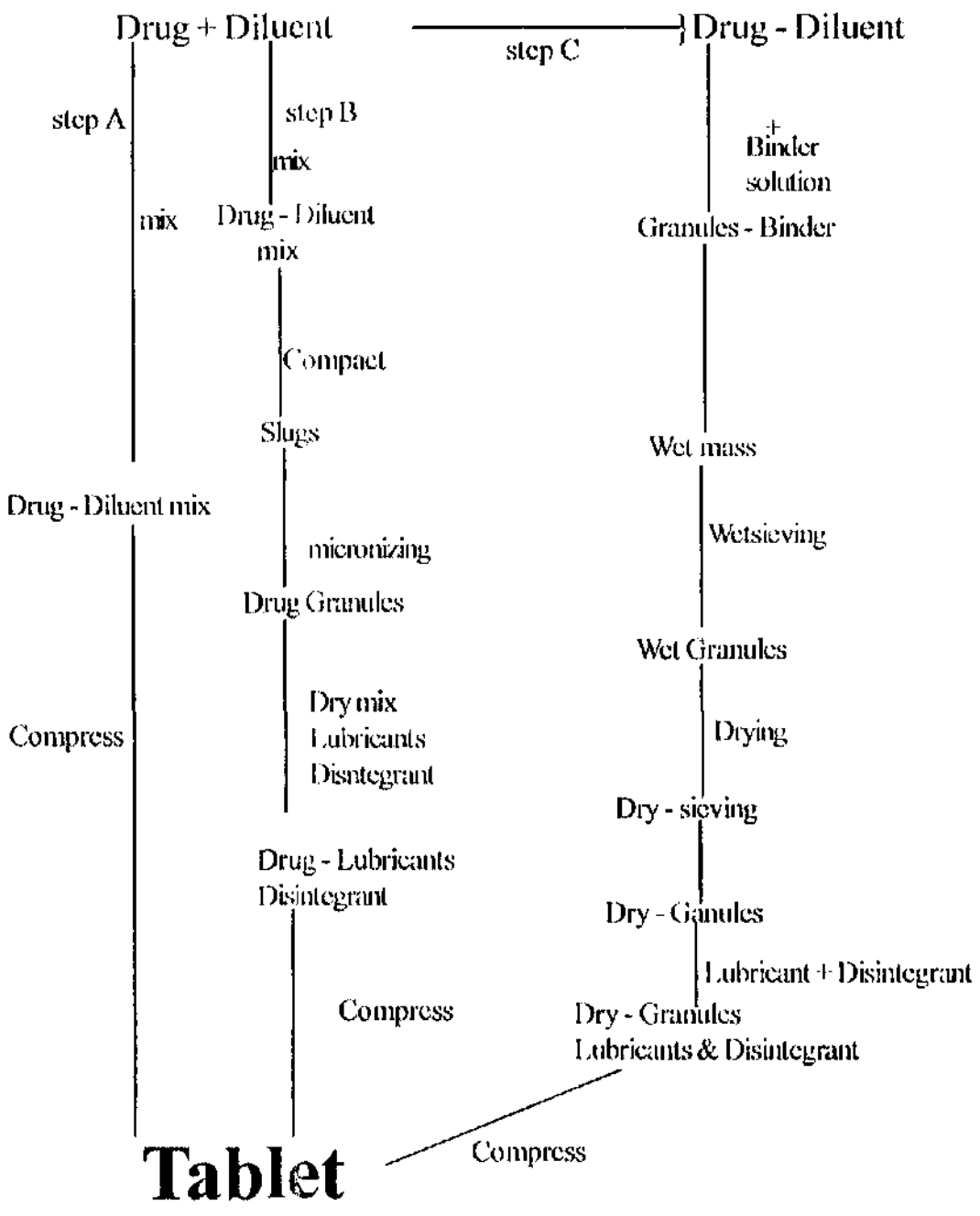
Granules can be produced directly by this method. All the components of the formulation - diluent, binder, disintegrant and lubricant are suspended in a suitable vehicle to form a solution, suspension or a slurry to achieve a concentration of about 50 to 60% w/w. The slurry is then spray-dried to produce nearly spherical granules of uniform diameter 0.1 - 0.25 mm in size.

The spray-dried product is usually free flowing. The spray drying process could have been used on a very large scale but due to a very high capital cost, the advantages of this process are usually outweighed by the high investment involved in installing this specialised piece of equipment.

The three methods of tablet manufacturing may be represented by the flow diagram as shown in Figure1 below:

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FIGURE 1 FLOW DIAGRAM REPRESENTING THE THREE METHODS OF TABLET MANUFACTURE.



Step	A	=	Direct Compression
Step	B	=	Dry Granulation Method
Step	C	=	Wet Gmulation Method

1.2.7 Factors Influencing the Choice of Granulation Methods

1.2.7.1 Drug Properties:

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

1.2.7.2 Dose of the Drug:

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

1.2.8 Factors Affecting Granulation

These can be divided into process and product variables.

Process variables are those factors which crop up during the process of granulation and may vary depending on the method of granulation. They include the speed of agitation, load of mixer, liquid, flow rate, type of binder and its concentration, methods of addition of the binder, massing time and amount of liquid.

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

of the particles, solubility of the components and the type of powder used for granulation.

1.2.9 Forces Responsible for Cohesiveness of Powders

The forces are of various origin. Basically there are two groups, mechanical and natural. The mechanical forces are applied with either the paddle or the tumble mixer. They bring the particles close enough to themselves for more important natural forces to act. There are various natural forces in operation between particles.

The most important ones are the van der Waals forces, valency and electrostatic forces and mechanical interlocking of the particles.

1.2.9.1 Van der Waal's Forces:

These forces result from molecular attraction due to dipole-dipole interactions. Bipolar molecules tend to align themselves with their neighbours so that the negative pole of the next results in molecular attraction. The distance separating the two particles is very important since these forces usually operate at a maximum range of $100\mathring{A}$ beyond which their effects are not pronounced.

The nature of the particles' surface, that is, its roughness also affects the operation of these forces, since it determines to a large extent how close the particles can be to each other.

1.2.9.2 Electrostatic Forces:

These develop as a result of the rubbing together of the particles with the associated loss or gain of electrons. Charges, either positive or negative, are thus developed on the particles depending on whether electrons have been gained or lost.

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Since opposite charges will be developed on different particles, there is an attraction between such particles.

1.2.9.3 Mechanical Interlocking:

This is the most important in the case of fibrous materials that are spongy in nature with rough surfaces. These surfaces can give rise to frictional forces.

1.2.10 Forces Responsible for Formulation of Tablets

The binder solution contribute in two important ways. These are:

a. By the crystallization of soluble components. Some materials, which are soluble in the binder solution, crystallise out on drying or evaporation of the wet mix. This results in cementing of those particles together.

b. By the hardening of the binder on drying. The viscous binder thus form solid bridge between the particles. The presence of a liquid which in most cases is water can also exert capillary forces that can hold solid particles together. This is due to the formation of liquid bridges. The nature and strength of the forces depend on the amount of water present in the formulation.

1.2.11 Stages of Water in Solid Particles

There are three main stages of water when it is added to solid particles. These are:-

a. **Pendular stage:** The solid particles are held together by lens shaped rings of liquid with air spaces between the particles. A force is thus developed. This force can be represented by the Fischer (1926) equation:-

$$F = \frac{2\pi r T}{(1 + \tan 0)} \qquad (1)$$

where F = pendular force between the particles

r = Radius of the solid particles

T = Liquid surface tension

0 = Contact angle between solid and liquid.

T = a circle constant which is equal to 22/7.

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

c. **Capillary stage:** All the air voids have been completely eliminated but the particles are still held together by the liquid. The forces by which the particles are held together are capillary forces. It can be represented by the Rumf's equation (1958 and 1963).

$$C = \frac{6(1-E)}{E} \frac{T}{d \cos 0} \quad .2$$

where C = Capillary forces

E = Porosity (void fraction)

T = Surface tension

d = diameter of particles

0 = Solid/liquid contact angle

The heat produced during compression can cause the melting of asperities and/or the binding agents at temperature below their conventional melting points. If cooling occurs, solid bridges are formed (Kurup and Pilpel; 1979).

Solid bridges can also be formed when crystalline substances are heated by friction during compression and then cooled (Murray, 1968). The water of

crystallisation liberated during compression partially dissolves some of the solid and finally reform a crystalline bridge (Kurup and Pilpel, 1979).

1.3 FUNDAMENTALS OF POWDER COMPRESSION

1.3.1 Compression

Prior to compression of granules into tablets extra-granular disintegrants, lubricants and glidants are added to the prepared granules and mixed thoroughly. Suitable pressure is then applied by the punches to compress the mixture into coherent tablets in the die.

During the compression process depending on the nature of the materials, plastic deformation, mechanical fragmentation or asperitic melting or combination of two or all are possible mechanisms which occur to produce a coherent tablet (York and Pilpel, 1973).

a. Plastic Deformation

This is one of the stages distinguished by several authors during the compression of powder in dies (Heckel 1961). Heckel plots was able to give the various types of powder compressional characteristics. And also use it to assess plasticity of the materials. By this mechanism the materials deform irreversibly with increase surface area for bonding to form a coherent tablets (Garr, 1988). Particle size and shape affect hardness of compact, the smaller the particle size the higher the surface area and thus the higher the probability of more bond formation between the particles.

Iwuagwu et al, (1986) has shown that the points of contacts increase with increase in particle surface area and therefore more bonds are formed. Materials that compact by plastic deformation have physical properties of the compact been affected. by the particle size of the materials. Since particles do not fragment under pressure for

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such material but undergo flow to increase surfacearea available for bond formation, it therefore means that the smaller the intial particle size the larger will be surface area under pressure and so more bond formation occur resulting in harder tablets with lesser friability.

b. **Mechanical Fragmentation:** is that mechanism by which coherent tablets are obtained when brittle particles are compressed. On application of pressure the particles shatter into pieces which is accompanied by percolation of those smaller pieces of the particles into spaces in-between bigger particles with the formation of bonding.

c. **Aspertic Melting**

York and Pilpel (1972) proposed aspertic melting as the third mechanism of formation of tablets based on temperature melting.

During tableting, high pressure exist at the minute contact point between particles where pressure is transmitted. In addition, the heat of interparticle friction is generated at these points and this combination of high pressure and high temperature provide the conditions for the phenomenon of asperity melting with subsequent bonding to occur (York and Pilpel, 1972). Thus York and Pilpel (1973) found that low melting point materials like stearic acid and gelatin when present in reasonable amounts could melt during compression even below their conventional melting points. Thus, during decompression and as a result of flow of the melted mass, there is a reduction in pressure so that the materials that have melted will resolidify and form solid bonds or bridges to form coherent hard tablets.

1.3.2 Removal of the Compressive Force

If consolidation of the powder mass has occurred and an increase in the degree of interparticulate bonding has been brought about by fragmentation, the removal of the force should have no effect on the tablet since there is no way in which the fragments can rearrange themselves to recombine into the original particles.

However, purely fragmentary consolidation is unlikely to have occurred and so the effect of force removal on deformed particles must be either elastic (reversible) or plastic (permanent). The difference between the two is crucial in the consideration of tablet formation, as exemplified by the behaviour of a spring when subjected to an extensive progressively increasing load (Hooke's Law).

If the particles have deformed plastically then removal of the compress force will have no effect, since interparticulate bonds which are formed as a result of increased particle contact will not be disrupted. However, if particles tend to revert to their former shape coherence will be lost as a consequence of the reduction in the area of interparticulate contact. Most particulate systems show some elastic and plastic properties but it is obviously desirable that plastic deformation should predominate.

1.3.3 Force Transmission through a Powder Bed

Particles in the die wall of an eccentric tablet press is considered. Force is applied by the descending upper punch on the press while the lower punch remains passive and force is transmitted to it through the powder bed. The distribution of force within the powder bed will not be uniform but formed a more complex pattern caused by the force being transmitted to and reflected from the die wall (Train, 1957).

There are two zones of high force at the periphery near the moving punch and much lower in the powder mass on the vertical axis. On the other hand lower zones of

forces occur on the same axis much near the moving punch. The consequence of this on tablet strength can be profound. Particle deformation whether plastic or elastic will be proportional to the force applied. The deformation is an essential preliminary step to the formation of the interparticulate bonds on which tablet integrity depends. Thus, the porosity of the tablet and hence its strengths will vary within the tablet and the weakest points in the tablet structure will be those that receive the lowest force i.e. on the face of the tablet adjacent to the stationary punch and on the central axis near the moving punch (applicable to eccentric press). But with rotary tablet press both punches move and exert some force on the powder bed (Higuchi et al 1958).

The force distributed will be different. Here, two low density zones near the faces of the tablet and a high density zone in approximately the centre of the powder mass. Here because of non-uniform density some areas of the tablet are stronger than others. Furthermore, after the compressing force is removed elastic recovery will occur to a greater or lesser extent which will result in a reduction in the strength of interparticulate bonds and overall weakening of the tablet (Jarosz et al, 1982). It therefore follows that if the tablet is to be disrupted by elastic recovery this is most likely to occur at its weakest point which is just below the top surface and is a phenomenon often encountered in tablet manufacture known as capping or lamination.

However, by considering the non-uniform density distribution in the tablet it can be seen that the weakness is not caused by the relative absence of solid material in those parts of the tablet which have high porosity. If this place is compressed it follows that the pores are filled with air at elevated pressure which will obviously assist in the disruption of the tablet. Thus, anything which obstructs the expression of air during compression will exacerbate capping, although it is not the fundamental cause. Such factors include clearance between punch and die, the speed at which the force is applied

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and presence of small particles in the granules making the passage of the air through the tablet more tortuous.

Similarly, any stress which exceeds the breaking strength of the tablet will cause the tablet to break at its weakest point. A number of stresses occur when the tablet is removed from the die after compression. First, wear may occur at the point in the die where the tablet is compressed i.e. the die is fractionally wider at this point than elsewhere. Thus, when the tablet is ejected it is forced through an aperture of a diameter slightly less than the tablet itself. This will obviously stress the tablet and the interparticulate bonds may be overcome at their weakest points (Nelson, 1954). As the tablet is extruded from the die, elastic expansion will occur not just in the axial direction but also radially. The latter occurs progressively i.e. one segment of the tablet is free to expand while the one below it is still constrained by the die. Disruption of some interparticulate bonds is an inevitable consequence.

1.4 TABLET DEFECTS

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

1.4.1 Capping

Gunsel and Kanig (1976) defined capping as an expression which describes the partial or complete separation of the top of a tablet from the main body. The type and state of both punch and die sets can be responsible for capping.

The concave or bevelled-edge faces of punches gradually curve inward with use, and form a claw which can pull the top of the tablet too loose. Dies develop wear in the area of compression. A ring develops and enlarges to a point which the tablet

diameter is too large to pass easily through the narrower orifice above the ring. Improper setting of the press can also cause capping. Others include high elastic recovery, polymorphic forms of drug, particle size where there are excess fines leading to air entrapment in the compacts. Inadequate binding and moisture content variations are other possible causes of capping in tableting. Scored tablets are more prone to capping (Rippie et al, 1981).

1.4.2 Lamination

This is said to occur when there is separation of tablet into two or more distinct layers. The most important cause is usually ascribed to the entrapment of air among the granules which does not escape during compression but afterwards when the pressure is released.

Granules that contain large amount of powder due to insufficient binders are prone to this difficulty. Inadequate die wall lubrication can also lead to lamination of tablets on ejection.

1.4.3 Chipping

In less severe cases of improper setting of the press the tablet may merely chip. Another possible cause of chipping is the setting of the sweep-off blade. If it is set too high the tablet can chip partially under it and break off. A chip may then enter the feed frame and may affect the other tablets. Tablets with flat faces or bevelled-edges are more prone to chip when they strike each other than those with convex faces which tend to shingle (inter leave) more readily and reduce the amount of edge contact.

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1.4.4 Picking

This describes the removal of material from the surface of tablet and its adherence to the face of the punch. Picking of tablet may also result from micro-expansion of tablet immediately after compression. Tablets increase by about $1/100^{th}$ of their original sizes immediately after compression due to the elastic nature of the granules resulting from improperly dried granules.

1.4.5 Sticking

This is the adhesion of granules to the die wall. When it occurs the lower punch fails to move freely with consequent strain on cam tracks and punch heads. The term may also refer to build up of materials on punch faces. Binding and sticking lead to grunting of machine and pitting of the tablet. Insufficient lubrication of granules may cause sticking and picking. Low melting point substance either active ingredients or additives such as stearic acid and polyethylene glycol may soften from heat of compression to cause sticking. Dilution of the active ingredients with additional high melting material and a consequent increase in weight may help to solve this problem. Excessive moisture and further drying of the granules are then required. Sticking are normally indicated by tablet faces which are dull.

1.4.6 Spontaneous Cracking

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

1.4.7 Weak Equator

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

1.4.8 Weight Variation

When granulation is unsatisfactory each tablet made from it may vary in weight beyond acceptable limits. The cause of weight variation in tablet include: the size and distribution of granules being compressed where excess large granules interfere with the filling of the void spaces leading to weight variation. Poor flow of granules may lead to incomplete filling of the die in some cases. Poor mixing of the lubricants and glidants with the granules lead to inefficient filling of the dies. Poor mixing is sometimes revealed by the grunting sound of strain during tablet ejection. When the lower punches are of unequal lengths leading to change in volumetric fill of the die, weight variation can also occur.

1.5 EVALUATION OF TABLET QUALITY

Drug manufacturers are aware that tablets must meet some physical specifications in order to guarantee the quality of the tablets. These specifications include hardness, disintegration time, friability, weight uniformity, thickness and dissolution rate (Gutsel and Kanig, 1976). These specifications must be controlled within the production of a batch of tablets as well as from batch to batch in order to guarantee not only the outward appearance of the product but also its therapeutic efficacy. While some of these quality control tests are official, others are not but are

only being added by various manufacturers to ensure that their tablets are of high quality.

1.5.1 Tablet Hardness

A tablet should be sufficiently hard to resist breaking during packaging, shipment and normal handling and yet soft enough to dissolve or disisntegrate properly after administration. Numerous instruments have been devised to test the hardness of tablets. This is a non-pharmacopocial evaluation but very important since it is an attempt to show how tablets withstand packing, handling and transportation.

Such appliances include:-

(i) **Monsanto Hardness Tester**

This consist of a barrel containing a compressible spring held between two plungers. The lower plunger is brought into contact with the tablet, pressure is then applied to the spring by rotating a screw.

This force the upper plunger against the spring and the force is transmitted to the tablet. The instrument has a calibrated gauge on the barrel with a zero adjustment which expresses the crushing force in kilograms (kg). In the industry, a force of about four (4 Kg) is considered to be the minimum permitted for a satisfactory tablet (Ansel, 1981) depending on the diamter and the thickness of the tablet.

(ii) **Pfizer Hardness Tester**

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

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(iii) **Strong-Cobb Hardness Tester**

It measures the applied force required to break a tablet across its diameter. The tablet is held between two jaws and pressure is applied by means of a hydraulic pump. A dial indicator records the final breaking force. These instruments are very popular because of their ease of operation and maintenance. But they suffer from some important defects which must be considered when they are being used. These are inconsistencies in the zeroing of the instrument which might vary depending on the operator. The rate and nature of application of force are important determinants of the values given by the instrument since this can vary from one operator to another and even when used by the same operator at different times. The results obtained become usually subjective and difficult to correlate. Finally, it should be noted that all of these instruments actually measure resistance to crushing and not the tablet hardness per se.

A number of more exact instruments which do not suffer from most of the defficiencies of the instruments discussed above are available. They include the Instron Tester and Transverse Tester which measure the tensile strength of tablets. They also take into consideration the dimension of the tablets. Okhamafe et al (1992) gave the equation for tensile strength of a tablet as follows:-

$$T_s = \frac{2F}{\pi dt} \qquad 3$$

where T_s = tensile strength (Kgf/cm^2

F = crushing strength (kgf)

d = tablet diameter (cm)

t = tablet thickness (cm)

1.5.2 Friability

A tablet must be sufficiently robust to withstand chipping, capping or breaking. These problems, are most frequent as a result of friction and shock. That is why equipment such as Roche Friabilator are used to measure the resistance of tablets to these problems.

Usually, twenty tablets are weighed and placed in the drum in which a curved baffle is mounted. The drum is rotated at twenty-five rotation per minute (25 r.p.m) for four minutes making the tablets to be scooped up and banged. The tablets are then removed, dusted and weighed. Not more than one percent decrease in weight of the free fall within the drum resulting in the breakage of excessive abrasion of the tablets considered suitable to withstand shipment without being damaged. The hardness and friability of tablets are measures of their mechanical strength. They give an indication of the extent of cohesiveness among the particles in the tablet.

1.5.3 Uniformity of Weight

Testing for weight uniformity is an attempt to minimize dose variation in tablets. Since the tablet weight is adjusted to give the quantity of granulation that will contain a unit dose of the medication, any variation in weight will result in dose variation assuming uniform dispersion of the active ingredients in the tablet mix. The standard requires that twenty tablets be taken and their average weight determined. The tablets are then weighed individually and deviation in tablet weight must be within the official (U.S.P, B.P) limits.

There are various factors that could affect the die fill and as such result in weight variation among tablets. These are poor flow, properties of the materials, bridging of the materials in the die or particles' segregation during flow through the

hopper. Since the tablet mix may consist of particles of widely different sizes, segregation could occur during flow through the hopper. Thus, there may be excessive more coarse materials at the start of the run resulting in more porous packaging and therefore lower tablet weight. At the end of the run, there may be a higher amount of fines resulting in the presence of more compact bed within the die leading to an increase in tablet weight. The tablet should therefore be checked at given time intervals during production to avoid excessive weight variation.

1.5.4 Content Uniformity

This test for dose variation in tablets, that are of the same weight Such variation arises from a non-homogenous distribution of drug in the tablet granulation.

Twenty tablets or other numbers, as may be indicated under the appropriate monographs, are used for the assay. The tablets are crushed and analysed as may be stated in the individual monographs of the official books. The limit of deviation in content from the stated amount are also given in the official books and the content must be within the stated limits.

1.5.5 Thickness and Diameter

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

The thickness of tablets can vary due to:-

i. size segregation within the hopper which can lead to weight variation and consequently difference in tablet thickness if the same compression pressure is applied;

ii. change in compression pressure:- the diameter is controlled by the die and punches and so does not vary much. But the constant compression of tablets in a particular area of a die might result in a widening of that portion of the die with time resulting in the diameter of the tablet on formation being larger than the diameter of the top of the die. This can result in the crubbling of the tablets during ejection.

iii. Thickness could give a measure of plasticity or compressibility of the same tablet weight compressed at the same compaction force using varying excipients.

1.5.6 Disintegration Test

This is an official method available in official books like the B.P.and U.S.P. The equipment as specified in the B.P. (1988) consist of a perpex tube with the bottom end of which is sealed with a number ten (10) mesh which is 1700μm screen.

Six tablets are placed in the tube which is attached to an arm and is raised and lowered at thirty cycles per minute through a water-bath thermostated at 37 ± 1°C. It should be adjusted such that at the top of the stroke the mesh must just break the surface of the water while at the bottom of the stroke the top of the tube must remain above the water level. As the machine is set in motion the tablets steadily break-up and the pieces pass through the mesh. All the tablets, except enteric coated, must pass through the mesh in fifteen minutes B.P. standard or 30 minutes U.S.P standard unless otherwise stated in the monographs.

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1.5.7 Dissolution Studies

The dissolution of the drug from the fine particles is the most important and the rate limiting step in drug dissolution and absorption. This provides a means of determining the rate at which a drug goes into solution and therefore its rate and extent of absorption from the tablet formulation, thus the bioavailability of the drug can be predicted.

Therefore, the *in-vitro* dissolution test is carried out for two major reasons;

i. to ensure that the active medicaments in the tablet are totally released on time and

ii. to ensure uniformity in the release of active ingredient in all batches.

B.P. (1988) dissolution apparatus consists of four main parts:

(a) a water-bath

(b) a cylindrical stainless steel basket in which the tablet is placed

(c) a covered vessel - one litre in volume in which (b) is immersed.

(d) a variable speed motor – say at 50, 100, 150 oscillations per minute.

One tablet is placed in the basket situated 2.0 cm above the bottom of the vessel which contain 900 ml of the medium specified in the individual drug monographs. The medium is maintained at a temperature of $37^{\circ} \pm 0.5^{\circ}C$. The basket is driven by variable speed motor at the rate specified in the monographs. Samples are withdrawn at specified intervals or as recommended by the B.P. after forty-five minutes for quantitative analysis. Unless otherwise specified, not less than 70% of thje stated content of the tablet should have dissolved. Five replicate are carried out, if one of these fails to meet the standard, then five more tablets are tested and none should fail.

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The dissolution area under the curve can also be measured and compared with the dissolution at any point in time to give the extent of dissolution. Factors that can affect the dissolution test include the dissolution medium, PH, temperature, rate of rotation of the basket and formulation factors such as particle size, amount of binder, lubricants and compression pressure.

A direct correlation of result obtained in the dissolution tests outlined above with *in-vitro* conditions is not often found (Levy, 1963) since it is very difficult to design an apparatus that will exactly simulate *in-vivo* conditions in-vitro.

In-spite of all these the dissolution test still serves as a convenient means of testing to ensure that drug is released from the tablet and that there is a batch to batch uniformity of release pattern.

1.6 TABLET EXCIPIENTS

Tablet excipients are used to convert pharmacologically active compounds into solid dosage forms suitable for administration to patients (Wells and Aulton, 1993). These are also referred to as additives or adjuvants and are indispensable in pharmaceutical formulations without which very few products would be suitable or convenient for administration. The selection of such excipients is very important in tableting.

Among other applications, excipients as pharmaceutical aids are used to impart aesthetics to drug products, enhance drug stability, control drug release, mask an unpleasant taste and give a suitable physical form to drugs. It is believed that the number of important excipients currently in extensive use are about twenty-five but their range of properties are such that they meet the needs of the six major categories (Okhamafe, et al, 1992). These include diluents, binders, lubricants, disintegrants,

colourants and sweetners. Additives are classified according to the primary functions they perform in the tablet. Many additives will also often, have secondary functions which may or may not be of a beneficial nature in good solid design of oral dosage forms.

Some fillers or diluents may facilitate tablet dissolution which is beneficial while others may impair dissolution. The most effective lubricants are water repellent by their nature (hydrophobic) which may retard both disintegration and dissolution.

Bavitz and Schwartz, (1974) concluded in a paper evaluating common tablet diluents that their proper choice becomes more critical when formulating water insoluble drugs. They showed that inert ingredient can profoundly affect the properties of the final dosage form. A knowledge of the properties of additives and how they affect the properties of the total formulation is necessary to provide guidelines in their selection. This is particularly true when the drug concentration is small. The drug plays a more significant role in determining the physical characteristics of the tablet as the drug concentration increases.

The two major classification of additives by function include;

those which affect the compressional characteristics of the tablet i.e. diluents, binders (adhesives), lubricants, adherents and glidants and those which affect the biopharmaceutics, chemical and physical stability and marketing considerations which include disintegrants, colorants, flavours and sweetners.

1.6.1 Diluents

They are also referred to as fillers and are used to increase the bulk of the tablet so as to enable a formulation to become suitable for compression. It is generally not feasible to make a tablet with less than fifty milligram (50 mg) weight. Fillers are

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selected to improve the binding and flow properties of the formulation. The list of most common diluents was presented (IIPE, 1993). These include lactose, starch, Avicel®, dicalcium phosphate, sucrose, mannitol and sorbitol.

It is essential that fillers be inert and stable. Compatibility and solubility must be considered in the selection of diluents e.g. the combination of amine salts with lactose in the presence of alkali lubricants resulted in tablet which discoloured on aging (Browley and Lachman, 1963). An ideal diluent should be relatively cheap and inert, and be compatible with the active ingredients.

1.6.2 Binders

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

A substance used as a binder when added in the right amount should impart just the degree of cohesiveness that will require minimum compression pressure to compact granules to tablets. There are various binders in use depending on the method of granulation to be used or whether manufacturing is to be direct compression or not. Those used in wet granulation include acacia which is used in solutions with concentrations ranging from 10-20% or even higher depending on how much water the mixed powder can tolerate.

Gelatin must be used when warm since it hardens on cooling and its dissolution is enhanced if it is first suspended in cold water and then heated in a water- bath. Starch is one of the most useful binders, especially in mucilage form when the drug is insoluble and in high concentration. It is usually used in an amount equal to two percent by weight of the formula while the volume of the mucilage could vary from

1.4 to 3.0 percent depending on the net solubility and particle size of the mixed powder being granulated (Ojile et al, 2000. It is used as a paste prepared by suspending it in one to one and half part of cold water with the addition of four times as much as boiling water. Other binders are methyl cellulose, sucrose, sodium carboxy methyl cellulose and polymers such as polyvinyl pyrollidone (PVP). These binders can also be added dry blended with the diluents and drug and then activated by the addition of water or other solvents, although it is now known that the same binder added as a solution or mucilage is more effective than when added dry to the formulation before activation. Dry binders are used in the direct compression of tablets. Those used for this purpose include Avicel®, amylose, and polyethyleneglycol (PEG).

The concentration of liquid binders used varies, depending on the binder and the powdered materials to be granulated (Ojile et al, 2000). In turn, the concentration of the binder, along with its nature and mode of incorporation, influences the compressional characteristics of the tablets to be prepared from the granules. It is therefore important to know the effects of these binders on tablet properties and take steps to eliminate those of them that are adverse. The presence of binders in granules used in tablet manufacture has some effects on properties of the tablets. Its most noticeable effect is on the hardness and friability of the tablets which consequently affect the disintegration and dissolution rate.

Jacob and Plain (1968) investigated the effect of increase in binder concentration on tablet properties they found that it resulted in decrease dissolution rate of phenobarbitone. Shubair and Dingwall (1977) using three different drugs showed that invitro release levels of the drugs were affected by the amount of binder (starch mucilage). Nasipuri et al (1986) also reported the variation in starch mucilage concentration produced by wet granulation. They found out that the mucilage up to

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10% w/w resulted in variation of granule size distribution but at concentration of 15% w/w mucilage there was a decrease in mean granule size from the optimum size obtained at 10% w/w. They also found that at a higher mucilage concentration the more viscous mucilages produced pasty masses which were not easily screened, which they explained as being due to a decrease in bond formation that also resulted in the production of higher amount of fines.

Sakr et al (1972) reported that as the concentration of binder (gelatin) was increased in lactose tablet formulation, the friability of the tablets decreased while the disintegration and dissolution rates decreased. The retardation effect on disintegration and dissolution rates are not the only effects of using excessive binder in tablet formulation. In a few extreme examples, excessive binder can result in tablet capping. Premature wear out of tablet punches and dies is also another possible result of regular compression of formulations with excessive binder. Inadequate addition of binders can result in the production of excessively soft tablets which will not withstand handling effectively.

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

1.6.3 Disintegrants

A disintegrant is an agent added to compressed tablets for the purpose of causing them to break apart (disintegrate) in the fluid. Its major function is to oppose the efficiency of the tablet binder and the physical forces that act under compressions to form the mechanical body of the tablet. An ideal disintegrant is one that can cause the break-up of a compressed tablet at the proper time and place within the alimentary tract

(G.I.T.) so that the active ingredient can be released to achieve maximum absorption at the fastest possible rate or as desired.

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

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

Disintegrants have been classified chemically into starches, clays, celluloses, alginates and gums by Feinsten and Bartiluci (1966).

Fakouli et al (1963) based their own classification on the mechanism of action of the disintegrants:

(a) agents which react with moisture to constitute a foam.

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

(c) substances which react with moisture and swell.

The starches among which are corn, potato, wheat, rice, sago, cassava and cocoyam are undoubtedly the most popular class of disintegrants. Some of these starches like corn starch and potato starch have been used for decades as disintegrants in the manufacture of compressed tablets and today are still the disintegrant of choice in most parts of the world. Many authorities consider starch as the best tablet disintegrants available and the frequently used are corn starch and potato starch as standard for evaluation of other disintegrants or in the evaluation of agents which might serve as disintegrants (Mital and Ocran [1968], Khan and Rhodes [1972], Nasipuri

[1979].) Some derivatives of starch are also used as disintegrating agents with some of them having better disintegrating properties than starch itself. One of these is sodium carboxymethyl starch which is able to swell several times in water without its granules rupturing. Unlike starch, it is not hygroscopic and disintegration time is unaffected by aging when it is used in compressed tablets.

Gums, both natural and synthetic, are also used as disintegrants. They are used because of their ability to swell in water but because of their tendency to become adhesive when wetted they are capable of becoming in situ binding agents rather than disintegrants and so are not normally used. These include locust bean gum, Karaya gum, guar gum, tragacanth and agar, methylcellulose, sodium carboxymethyl cellulose, alginate, polymer cation exchange resins and synthetics, like cross-linked PVP (polyvinylpyrollidone) are also used as disintegrants, although not frequently. The disintegration time of tablets as a function of binder concentration has been shown by various workers; - Esezobo and Pilpel [1976], Pilpel, Otuyemi and Kurup [1978], Esezobo and Ambu-Jam, [1982]. Udeala and Chukwu [1985], Esezobo [1986], Garr [1988].They all showed that increasing the binder concentration caused a corresponding increase in the disintegration times of all tablets formulated.

1.6.3.1 Incorporation of Disintegrant in the Tablet Formulation

Although there is complete agreement as to the usefulness of disintegrants in the formulation of compressed tablets, the mode of incorporation of the disiintegrants in the tablet varies. Opinion is divided regarding the best method of addition. The main point of divided opinion is with regards to whether the disintegrating agent should be utilised intra- or extra- granularly (i.e. whether it should be added before granulation or after granulation just before compression). Some workers (Rubinstein and Body, 1976) added the total amount of disintegrants to granulation before compression arguing that

the agent must be as dry as possible for efficient activity and that this state can be best controlled at this point in process. Others added the disintegrant to the active ingredients and diluent during preparation of the granules. This is based on the assumption that much finer particles are obtained during disintegration than when the disintegrant is incorporated extragranularly (Shotton and Leonard, 1972).

The method most commonly employed is to add part of the disintegrant to the powder formula prior to granulation while the other part is added with lubricant prior to compression. In a study of deaggregation of compressed tablets Rubinsten and Body (1976) using tablets of dibasic calcium phosphate containing varying proportions of intra and extragranulary maize starch, found that the optimum starch combinations that produced the maximum surface area in a tablet formulation was either 2.5% intragranularly to 12.5% extragranularly or 15% intragranular starch. The proportion of disintegrant incorporated into a tablet formulation depends on the particular formulation, although a range of 5-20% of the total granular weight is recommended. The specific disintegrant to be used also affects the quality . In general, the higher the percentage of the disintegrant in the tablet formulation, the shorter is the disintegration time, but Commons et al (1968) investigated the influence of starch concentration on the disintegration time of tolbutamide and found that there appears to be a critical starch concentration for different granule sizes above which disintegration time increases with further increase in proportion of disintegrant.

1.6.3.2 Mechanism of Action of Disintegrating Agents

The means by which disintegrant cause the rupture of tablets have been the source of much controversy among research workers. A review of the proposed theories explaining the mechanism of action of tablet disintegrants are presented by,

Billups and Cooper (1964) who oberserved that the most widely held opinion is that tablet disintegration is by absorption of water by the disintegrating agent and development of pressure within the tablet by swelling or expansion of the disintegrating agent.

In their study they concluded that while water absorption is a common qualitative characteristic of many disintegrating agents, it is not a quantitative measure of their effectiveness. Disintegrating agents with the highest rate of water absorption did not produce the fastest disintegration times. Some evidence supported the view that disintegrating agents with the highest rate of water absorption produced the longest disintegration time. Their results also showed that the amount of water absorped by corn starch dried to a constant weight after exposure to ninety-eight percent relative humidity was only 0.5% in fifty minutes.

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

(1) **Swelling-Rupture Theory**

This theory states that a disintegrant, for example, starch when added to dry granules before compression will swell and mechanically disrupt the tablets. This is based on the observation by some investigators and generally accepted view that most disintegrating agents swell when exposed to water (Kanig, 1976).

Crisaffi and Becker (1958) have demonstrated that starch will absorb about twenty percent of its weight of water when exposed to ninety-five percent relative humidity at 27 °C. Patel and Hopponen (1966) found that corn starch dried for two hours (2 hrs) at 110 °C when suspended in water at 23 °C increased in volume by seventy-eight percent within five seconds. They also showed that in aspirin tablets

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where contact of starch grains were continuous in the interparticle spaces disintegration was rapid and effective. However, where contact was not continuous, disintegration was slowed and appeared to depend on the degree of contact between starch grains and aspirin particles and on the size of interparticle spaces. These observations led to the conclusion that the primary mechanism of disintegration by starch in aspirin tablets is by swelling action. Lowenthal and Wood (1973) postulated that hydration of the hydroxyl group and sorption of water could account for slight swelling of 5 - 10% of starch obtained. Ingram and Lowenthal (1966) had earlier found that this volume of swelling could result in about seventy percent (70%) increase in volume and the swelling took a few seconds. These two combined effects of the attachment of water molecules and the increase in volume of the starch grains cause sufficient force to break-up the tablets. Workers who held opposite views to the rupture theory have pointed out the observations that the extent of swelling of starch suspended in water is not enough to cause tablet disintegration and that is why many substances are poor disintegrants. Other materials do not swell but have good disintegrating properties e.g. amylose (Manudhane et al, 1966).

Curlin (1955), testing the disintegration of aspirin tablet in cold water found by microscopic examination that starch grains were not swollen after disintegration. However, Ingram and Lowenthal (1966) found that the swelling of the starch grains observed (5-10% increase in mean grain size) did not seem to be large enough to cause tablets to rupture. They ,therefore, concluded that it did not seem possible that untreated starch will swell sufficiently at 37 °C to cause tablet disintegration. Some tablets contain disintegrants which are adhesive in the hydrated state for example, sodium carboxymethyl cellulose. The positive forces of penetration of water and swelling of particle must overcome the opposing forces of adhesion within the particles to produce

tablet disintegration. When the opposing forces are equal to or greater than the positive forces the result is a longer disintegration time.

Khan and Rhodes (1972) also found out that the disintegration time decreased steadily with increased disintegrant concentration for distintegrants which are adhesives when in contact with water.

(n) **Water Absorption-capillary Theory**

This theory maintains that a distintegrant especially starch, by virtue of its relative incompressibility, forms chains around the granules. These chains form a capillary network within the tablet and the higher the concentration of starch the greater the number of capillaries formed. The capillaries are thought to promote the rapid absorption of water into the tablet and subsequent break-up of the tablet. Commons et al (1968) using corn starch soaked in a saturated aqueous iodine solution and dried, found that the grains form continuous chain along the channel between the granules even at concentration below those required to make the tablet disintegrate. It appeared, however that as the percentage of starch was increased, thicker chains of starch were formed in the pore channels thus enlarging them and allowed water to enter the tablet more readily and cause disintegration of the tablets.

Karr (1950) stated that starch in the natural state is insoluble in cold water but appeared to absorb 25-30% water and does not swell appreciably. Crissati and Becker (1958) had also shown that starch absorbs about 20% of its weight of water in twenty-four hours, when exposed to an atmosphere of ninety-five percent relative humidity at 27 °C. The results of these works quoted above made Curlins (1955) suggest that the disintegrating effects of disintegrant is due to capillary action rather than swelling is tenable. This theory is not without criticism. Patel and Hopponan (1966) from the

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results of their investigation concluded that capillary *per se* did not appear to have a disintegrating effect, although under certain conditions, related to pore size, it may play a part in increasing the rate at which water was introduced into the tablet matrix and this was substantiated by the results of work carried out by Ingram and Lowenthal (1966). Lowenthal and Wood (1973), using a scanning electron microscope to study the location and structure of starch grains in aspirin tablets, reported that in any of the surfaces examined, there was no channel or pores within the starch which led them to propose that the theory were selected starch grains act as a "wicking agent" and draw water into the tablet should be discarded. They were only able to observe occasionally chains of starch grains which were only one grain thick and of finite length and since they were few and isolated they could not have a significant effect on tablet disintegration. The conclusion reached by Lowenthal and Burrus (1971) from the results of their study of the disintegrant on mean pore diameter and porosity is that large mean pore diameter or porosity did not always give rapid disintegration time, nor did small mean pore diameter or porosity imply poor disintegration.

This also rules out the possibility that capillary is the only mechanism by which disintegrants act.

(iii) **Evolution of Gas**

Effervescent tablets are based on their ability to evolve gas. The gas produced is carbon dioxide which is the product of the reaction of sodium bicarbonate with citric and tartaric acids in the presence of water. As carbon dioxide is released within the tablets an internal pressure develops within the tablets until the pressure is high enough to cause the break-up of the tablet with either the dissolution or release of the carbon dioxide from the reaction medium.

1.6.3.3.3 Conclusion

Generally, the mechanism of action of disintegrant is complex. It may be mediated through several unrelated phenomena. However, it seems that in most cases the principal mechanism of disintegrant, especially in starch, is pressure exerted by increased volume in the presence of water with capillary possibly facilitating the rate of penetration of water. The condition required for rapid disintegration are sufficient starch agglomerates, low pressure and presence of water (Lowenthal and Wood, 1973).

1.6.4 Lubricants

This is a substance which deforms easily when sheared between two surfaces. When interposed between tablet and die wall, it provides a readily deformed film. Hydrocarbon chain provides the deformable property. So the granule surface is covered by a hydrophobic material. This retards disintegration of tablets after ingestion. The flow of granules, adhesion of granules or powder to punches and dies and the release of tablets from its mould after compression are the three main problems associated with tablet compression which are ameliorated by the group of chemically diverse substances collectively referred to as lubricants. Cooper et al, [1958] defined lubricants in tablet technology as substances which facilitate the passage of granules through the various orifices of a tableting machine.

Based on their ability to carry out certain functions, lubricants may be classified into three groups (Gunsel et al, 1976) as follows:-

1.6.4.1 **Glidants:** These reduce interparticle friction, and eliminate the problems associated with flow of materials from larger through smaller apertures in the

tablet press. They are termed flow regulators or flow promoters. Examples are talc and starch.

1.6.4.2 **Anti-adhesives:** They are also referred to as anti-sticking agents. These are essentially deformed and prevent adhesion of tablet surface to punches and dies during compression. Examples include stearic acids and soaps.

1.6.4.3 **Lubricants:** These are the proper lubricants and reduce interparticulate friction between the die walls and machine surfaces during ejection cycle thereby facilitating tablet ejection. Examples are magnesium stearate and talc.

The absence of a lubricant during tablet ejection results in severe straining of the press and this is frequently audible as a characteristic grunting sound. Another manifestation of poor lubricants at this critical stage is the presence of vertical irregular striations or 'scratch marks' on the edges of the ejected tablets. Lubricants reduce the tendency of tablets to cap and pick. They must be added to granules properly to achieve satisfactory results. They must therefore be finely divided by passing through a 60 - 80 sieve mesh.

1.6.4.4 Method of Incorporating Lubricants

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

(i) The lubricant is added to the dried granules prior to compression. These extra-granular lubricants are thought to function by coating the surface of the granules with a film which reduces interfacial friction between the granules and the compression surfaces. Magnesium stearate and calcium stearate are good examples.

(ii) Intra-granular lubricants: Cooper et el (1958) found that it was possible to add the lubricant to the initial powdered mixture of the active ingredients and other excipients and subject them to wet granulation without loss of lubricating properties. The impression that the lubricant would be enclosed within the granules and covered by the binder, thereby losing its function was proved to be unfounded since tablets prepared by the method had good physical properties and exhibited a reduction in disintegration time.

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

1.6.5 Flavours

Taste masking in tablets are often achieved by using sweetening substances as diluents or by coating the tablet. However, it may be necessary to incorporate a flavouring agent. As these agents are often thermolabile, they cannot be added prior to an operation involving heat. They are often added as spray dried, or sprayed on the granules as solutions.

1.6.6 Colourants

A pharmaceutical colouring agent (colourant) is usually a dye material. It is a pigment or other substance made by a process of synthesis, or extraction, isolation or otherwise derived from vegetable, animal, mineral or other sources that are employed solely in a pharmaceutical product to impart a colour.

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Hess et al, (1978) said many tablets are coloured to aid identification, aesthetic value and patient compliance. They are classified according to their origin into three major groups: synthetic organic dyes, mineral pigments and natural colourants.

Judd et al (1963) evaluated that the use of colour must comply with the regulations of Food and Drug Administration (FDA) of the country in particular, so their uses may vary from one country to another.

1.7 STARCH

Starch in the pure form is a white amorphous, relatively tasteless solid which possess no odour and is insoluble in cold water and in ordinary organic solvents such as alcohol, ether and acetone.

Starches are markedly hygroscopic and will absorb water when equilibrated under normal atmospheric conditions, until the amount present is 10-17% (Leach, 1965). Under the microscope starch is seen to consist of thinly colourless, highly refractive particles, the size and shape of which are specific for each variety of starch and therefore diagnostic. Under polarized light most intact starch particles exhibit a dark cross whose centre is the hilium which is the organic nucleus around which the granules has been formed, it may be placed centrally or nearer one end than the other. The starch particle also has striations (concentric rings) which are fine lines surrounding the hilium, that result from the highly stratified structure of the majority of starch particles. The hilium often becomes replaced by a hollow fissure in commercial starches because of the removal of the crystalloid part of the amylose during the washing to which starches are subjected during preparation (Leach, 1965).

1.7.1 Structure

Reviews of starch chemistry (Green Moor, 1956, Goudah and Guth, 1965) show that it has now been established that starch is a polymolecular system. It is known to consist of chains of α-D- glucose pyranose units joined in the main body by α-D (1-4) glucosidic bonds.

By fractionation into its similar components (first carried out quantitatively by Schoch, 1945), it was found that starch is composed of the following two components which are chemically distinguishable:

1.7.1.1 Amylose-Straight Chain Polymers

Amylose: Common starch contains about 20-25% of amylose while the waxy starches such as waxy maize starch, rice and sorghum might contain less. Amylose is a linear polymer composed of α-D- glucopyranose residue linked by α-D (1-4) glucosidic bonds. Early methylation experiment indicated the presence of 0.2 - 0.4% of non-residual group in amylose which corresponded to a length of about 200 - 350 D - glucose residual units. Schock (1945) has also showed that the osmotically determined molecular weight of maize and potato amylose agreed with a chain length of 200 - 350 D - glucose residues.

They were thus the first to suggest that amylose is a linear molecule.

Bear, (1942) by studying the X-ray digaram of amylose was able to determine the arrangement of the glucose units. He found that the glucose units were not arranged in straigth chain but rather were coiled in a spiral form with the length of each spiral being 6 - D - glucose units.

1.7.1.2 Amylopectin

It contains about seventy-five to eighty percent (75-80%) of starch, consists of high molecular weight polysaccharides and have α-D gluocpyranose residues linked by α-D (1-4) glucosidic bonds. The chains normally contain twenty to twenty-five (20-25) D-glucose residues and are interlinked to form a ramified bush-like structures by means of α-D (1-6) glucosidic linkages. Evidence regarding the manner in which the glucose units are combined in the two starch components have been obtained from methylation studies (Haworth and Machener, 1932). This consists of treating the starch with dimethyl sulphate or methyl oxide in alkaline conditions until each free hydroxyl group in the starch molecules are converted into a methyl ester. The methylated starch chains are then split by hydrolysis with acid into methylated sugars which are identified and estimated quantitatively. The positions occupied by the methyl groups in fragments correspond with those of the unsubstituted hydroxyl groups in the original starch.

The main product from both the amylose and amylopectin fraction is 2:3:6 tri - o - methyl α-D- glucopyranose which confirmed the continuity as being long chain linked in the 1-4 position.

Information on the extent of branching in the molecules can be obtained by determining the molecular weight of the polysaccharides and thus calculating the number of non-reducing ends per molecule. The periodate oxidation method of Greenwood, (1956) is also another source of evidence regarding the manner in which glucose units are combined. It is based on the determination of the ratio of terminal to non-terminal D-glucose units in amylose or amylopectin by determining quantitatively the amount of formic acid produced on addition of periodic acid. One molecule of formic acid is produced from each non-reducing end unit and two molecules from each

reducing end unit of a starch molecule and one molecule of formaldelyde is also produced from each reducing end unit.

These methods in conjunction with molecular weight determination have enabled both the configuration and the degree of branching to be known. The starch granule is composed of linear and branched starch molecules associated by hydrogen bonding either directly or through water hydrate bridges to form radially oriented crystalline areas of various degree of order. An interconnected three dimensional micellar lattice is formed by the participation of segments of individual molecules in several micellar areas (Leach, 1965).

1.7.2 Occurrence

Starch is one of the most widely distributed substances in nature occurring in most plants and in abundant quantities, it is formed in the leaves and other green plants from water, and carbon doxide in the presence of light and chlorophyll. This process is called photosynthesis. Photosynthetic process is chemically represented as:-

$$\text{Chlorophyll} + H_2O + CO_2 + \text{Light Energy} \rightarrow \text{Carbohydrate} + O_2\uparrow$$

Carbohydrate is made up of starch which is stored in fruits , bulbs, tubers etc. Here starch accumulates in sufficient quantities to make its extraction commercially viable.

Different plants use different structure for starch storage. Thus in the preparation of starches for commercial purpose, many different plant parts are used as raw materials, for examples potato starch is obtained from tuber, cassava from tuber of *Manihot utilissims*, while wheat, maize and rice starches are from cereals.

The method used to separate the starch from protein and fibrous material which might also be present in the plant part depends on the structure and composition of the plant parts. The quantity of starch available in a given raw material differs from plant to plant and even the same plant of different varieties contain different amounts of starch.

Examples of quantity of starch present in some sources are corn grains (71.5%), rice grains (90.2%), potato tubers (12.5%), cassava tubers (31%), arrow root (25%) and sago (40%). These are average values.

The nature of the starch obtained also depends on the sources of the starch and differs from plant to plant. For example, starch derived from maize differs in particles size, shape, gelatinization temperature, amylose - amylopectin contents, total liquid content, paste clarity, texture and taste from that of wheat starch. Badenhuizen (1965) subdivided starch broadly into two groups according to their origin either in organs that retain a high water content or under conditions in which less water is available. The first group include starches that are deposited in tubers, bulbs, rhizomes and unripe fruits. In the second group are the cereal starches such as wheat starch and rice starch. The importance of these differences depend on what the starch is to be used for. For example, the paste clarity, taste and odour of a given starch is very important if the starch is to be used in the food industry while it is unimportant if it is to be used as a disintegrant in the pharmaceutical industry.

1.7.3 Extraction

The method of extraction of starch from the raw material (that is the plant part in which it is present) depends on the nature of such raw materials. For example, the method used for the extraction of potato starch from the tubers differs from that used

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for the extraction of maize starch from the grains. There are some steps however which are the same in principle for different raw materials.

These steps are clearing of the material, a variety of procedures to release starch from the cell and separating it from the other constituents of the plant parts and then finally drying the starch and reducing it to the desired size.

1.7.4 General Uses of Starch

Starches are widely used for both domestic consumption and industries. So its demand is highly competitive. Cultivation for such food can be stepped up to meet the desired need of both people and industries. In this case, cultivation can be embarked upon by institutions, industries or entrepreneurs who wish to use this source of raw materials. Among the uses are the following:-

1.7.4.1 Textile Industry

Starch is a very useful commodity in various industries. Starch and its derivatives are used in the textile industries in four main ways:-

(a) It is used in sizing of warp yarns. This process strengthens the grain and improves its quality and ability to withstand the mechanical operations of weaving process as well as to add weight to the yarn in some cases.

(b) It adds beauty to the fabric after it has been printed.

(c) Starch also increases the consistency of paste in printing.

(d) It is also used in the glazing and polishing and sewing thread. Corn starch is commonly used in the textile industry especially in the United States of America.

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The amount of starch used for sizing is much more than that used for other purposes in the textile industries. During sizing, the strength of the yarn is increased from ten to thirty percent.

1.7.4.2 Food Industries

Different food products make different demand on the starches used in their production. This depends on the particular combinations of viscosity, gel formation, clarity and length of paste desired and also on the effects of other ingredients present in the food.

The natural starch and their derivatives can also be used depending on the type of food being processed. Corn and sorghum starches are mainly used in the food industries. This may be due to their abundance and low cost.

Sorghum starch resembles corn starch and the two are interchangeable. They are mainly used for thickening and pudding push fillers. They are suitable for products which are to be frozen because of the tendency of the paste to retrograde under treatment.

It is used in canned food but the starch has to undergo special treatment like oxidation to remove any micro-organisms which may be resistant to heat during canning (Schopmeyer and Felton, 1941; Wurburg et al, 1962).

1.7.4.3 Paper Industries

Starch is used extensively in the paper industries. The use of starch in the paper industries dates as far back as the middle ages when starch was used as binders and stickers to bind what Egyptians used then as paper, called papyus.

Ever since then, starch is still being used in the paper industries. It is used not only as stickers and binder but also to improve the quality of the paper. It was recorded in the United States that as much as one hundred and fifty thousand tons of starch was used in the paper industries that year in 1963 (Anan, 1963). That made the paper industries the largest single industrial consumer of starch products.

1.7.4.4 Pharmaceutical Industry

Starch has many uses in medicine and pharmacy. Starch has been found to be quite effective in drying up dermatitis, lessions, where there are water exudates as a result of which it is found as a complement in such pharmaceuticals, as dusting powders, pastes, ointments and emulsions. It is also used as a bulking agent in some of these preparations. Starch finds its greatest and most important use in pharmacy in the manufacture of compressed tablets, which are very important Pharmaceutical dosage form. It is used as a binder, diluent, disintegrant and its derivatives as directly compressible vehicles. As a diluent or bulk agent, it is used as a filler, when the drug is required to be taken in very small doses. It is used for this purpose because it is bland, odourless and digestible. As a binder, it is used as a mucilage to bind powders together to form granules and add to the cohesive strength already available in the bulking agent. Starch is used here because of its ability to form pastes. It is used as a disintegrant to cause the tablet to break-up.

1.7.5 Starch as Pharmaceutical Excipient

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

and is also greatly influenced by the starch species (Gunsel and Kanig, 1976). The swelling of the starch particles is due to the penetration of water and subsequent hydration of the starch. Viscosity of the starch water mixture is high because of the crowding effect of the swollen balloon-like particles.

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

Subjecting the aqueous suspension of starch to the influence of heat weakens the micellar network within the particle by disrupting the hydrogen bonds which permit further hydration and irreversible starch particles swelling (gelatinization). This process according to Chabot et al (1970) includes the loss of birefringence, leaching of amylose into solution and tangential swelling of the starch particles resulting in the formation of a small bladder. Initially, some amylose is retained in the interior cavity but rupture, collapse and dissolution of the swollen granules occur during prolong heating.

As the starch particle swells, starch molecules that have been fully hydrated separate from the micellar network and diffuse into the medium.

Evidence has been provided by Schoch (1945) to prove that in a dilute starch paste an equilibrium is established so that the concentration of soluble starch in the water inside the swollen particle is the same as that in the surrounding aqueous phase.

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

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

The individual starch particles in any given starch do not begin to swell at the same time but rather over a temperature range of about 10 °C. This is because gelatinization begins from portions of the granules where the bonding is weakest since the degree of bonding differs in individual particles of each starch species.

The addition of certain chemicals markedly alter the properties of starches. The properties affected include gelatinization temperature, range of starch paste either enhancing gelatinization by accelerating the disruption of hydrogen bonds or inhibiting gelatinization by acting as desolvating agents.

Chabot et al (1976) found that chemical modification of corn waxy maize and sorghum starches affect starch properties such as pasting temperature, particle swelling and the paste properties. These alteration of starch properties by addition of chemicals is important in the formulation of pharmaceuticals and should be taken into consideration in formulation studies. Mansour and Guth (1968) in their investigation to

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determine the complexing property of some drugs with starch found that all the starches tested, formed complexes with the drugs used.

Amylopectin was found to be the main complexing component of starch. Chemicals such as sodium sulphate depress starch particle gelatinization, while acids and hypochloride reduce starch paste viscosity. On the other hand sodium nitrate however lowers gelatinisation temperature as does esters and ethers which increase particle swelling. In addition on cooling starch paste also has properties of interest. Starch paste are physically unstable and thus tend to become less soluble on standing, a phenomenon which is referred to as retrogradation. Retrogadation is mainly due to the amylose fraction since amylopectin solution in water are known to be relatively stable.

Amylose, because of its long molecular chains and the numerous hydroxyl groups present in it, has a great tendency for bonding between chains, thus producing bundles of amylose molecules and hence rigid gels and insoluble precipitates. The rate of retrogradation in a given starch paste depends on the amylose percentage in the starch, the method of preparation of the paste and the size of the amylose molecules (Whistler and Johnson 1948; Lanak et al, 1949). Goering et al (1975) also found the pasting peak of starch paste was due to the break-down of an amylose, fatty acid complex. The paste forming property of starch is most important in the use of starch as a binder to form granules in the manufacture of compressed tablets.

The compressibility of starch is another property that is useful in the pharmaceutical industry. Most starches are poorly compressible alone and it is possible that poor adhesion between these agents and other tablet components is an asset in disintegration efficiency since wicking activity is enhanced (Gunsel and Kanig, 1976). Poor compressibility also increases the porosity of tablets (Commons, et al, 1968). All

these properties, poor adhesion and increase in tablet porosity, are useful in the use of starch as a tablet disintegrant, although the mechanism is still not clear.

1.8 SWEET POTATO

Family - Convulascea

Species - *Ipomea batatas*

1.8.1 Distribution

The potato originated from the mountain region of South America where it has been an important food crop for a long time, from where it spread. In the 19th century, the potato was introduced to several tropical and subtropical countries mainly by colonialists from Europe. They are grown in about 140 countries and more than one hundred of them are in the tropical and subtropical zones. However, most production is still concentrated in the temperate regions in the industrialised countries.

1.8.2 Climatic Conditions

It is a warm weather crop, grown in both tropical and subtropical and warm, temperate regions of the world. Sweet potato performs best at about 24 °C. Growth is severely retarded at 10 °C. It does not tolerate forest and does best at high light intensity. It is at its best within 75 - 100 cm of rainfall per annum. Though the crop can withstand drought, the drought reduces the yield if it occurs within the first six weeks after planting. It performs best in sandy loamy soil and poor in dry soil and where there is water logged, it prefers PH of 5-6. It is sensitive to alkaline and saline soil, hence such soil should be avoided.

Potato has a relatively weak root system. Impermeable layers in the soil limit rooting depth which restrict availability of water to the plant in dry periods. As a result, soil compaction can greatly reduce potato yield. Another penalty of soil compaction or dense layers is that it readily becomes saturated after heavy rainfall or irrigation, killing the root and causing the tuber to rot. It requires two times' weeding.

1.8.3 Propagative Materials and Tubers

The potato parts used for consumption is a tuber bearing herbaceous plant. The following plant parts can be distinguished:-

(a) Haulum (foliage) leaves and stems.

(b) Tubers, stolons and roots, but only the tubers are utilized and the tuber can be considered as a part of the root tuber adapted for food storage and reproduction.

They are usually propagated from vine cuttings. Due to hard testa of potatoes seeds, it is not easily penetrated by water and oxygen hence propagation through seed is with great difficulty. In some areas, e.g. temperate zones, root sprout are used for planting. Local varieties are abundant in Northern part of Nigeria. Fertile soil is selected for high yield. Three feet ridges are prepared before planting. Planting period is between June - August but July planting may give the best yield. Tubers persist in the field vegetation from one season to the next hence serves as seed for the next cropping.

1.8.4 Manuring and Fertilizer

Potatoes respond extremely well to both farmyard manure and mineral fertilizer. The crop benefits from the application of farmyard manure not only from the amount of

nitrogen phosphate and potash but also from its improving effects on the tilth and the moisture retaining properties of the soil.

A crop yielding 30 tons of potatoes may take from soil during growth, 150 kg of nitrogen, 60 kilogrames of phosphate, 350 kg of potash, 90 kg of calcium salt and 30 kg of magnesium oxide. As only the tubers are harvested from the field, a large amount of these quantity of minerals remain behind.

1.8.5 Harvesting Operation, Transports and Storage

Harvesting potatoes include: lifting, collecting the tubers, separating the tubers and removing soil and stones.

The aim of each harvesting system is to take the tuber from the soil to the store or to the market as cheaply as possible keeping losses (e.g. quantity) to a minimum. The harvesting system used depends on the economic situation i.e. machinery cost, quantity of potatoes, labour, the size, shape, the situation of the potato field, the soil, weather conditions, and the uses to be made of the potato e.g. consumption, storage, etc.

The method of storage used depends on the purpose of the crop. Duration of storage period depends on the temperature and storage seasons, and the quantity to be stored. The method of handling will affect the storage life and the keeping quality are affected by good tubers quality and skin, proper ventilation, low temperature and humidity, light and chemicals used.

Here in Nigeria (particularly in the Northern part), tubers are stored in pits and in layers separated by grasses, sometimes ash is also sprinkled on the tubers. The pit is finally covered with a layer of grass and sealed with mud.

1.8.6 Insect and Pests

Chalfant et al (1990) reported that the most destructive insect pest of cyclespuncticolis, are the most important pests of sweet potato. Cycles Spp. feed on both leaves, tubers and oviposit mainly in the basal portions of the vines of sweet potato. The major damage is done when these pests feed on tubers. Low yield is attributed to cycles damage either from direct consumption or as predisposing factor for fungal rot and has been estimated to be about 40 - 80%.

Tubers exposed by erosion or cracks in the soil are more easily damaged. Aphids and whiteflies transmit inflective agents may which give rise to the sweet potato virus diseases. The aphids and whiteflies transmit agents that are latent in sweet potato plants and the disease is experienced only when both agents occur in the same plant. Then the leaves are distorted, yellow and die off. New growth result in reduced internode. Leaves are very much reduced in size and later die. A lot of leaf eating beetles and catarpillars destroy sweet potato leaves in the field. The degree of leaf damage can be very high.

These can be tackled by removing the affected tubers which should be burnt or buried deep in the soil. A good site (farmland) is selected and the best yielding variety is adopted. The tubers are harvested carefully immediately when matured and it is suggested that continuous crop rotation should be practised.

1.9 EFFECT OF EXCIPIENT MATERIALS ON PROPERTIES OF NAMED HIGH AND LOW DOSE TABLETS

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1.9.1 Sulphamethoxazole

It is 3 - p. aminobenzene sulponido - 5 - methylisoxazole. It is an antibacterial agent and bacteriostatic rather than bactericidal. This is due to the similarity of their

chemical structure to that of p - aminobenzoic acid which is essential to the normal development of bacteria. Therefore if the sulphamethaxozole is present in a concentration greater than that of p - amino benzoic acid, it is taken up by the bacteria enzyme system which thus becomes blocked and incapable of its normal function. Therapeutic blood level are reached within two hours of administration of the drug and may be maintained by doses at interval of eight to twelve hours of administration.

Pharmacokinetically, it is similar to trimethoprim. So it is usually used in conjunction with it. The two components act on the two successive reactions in the bacteria syntehsis of folic acid. The mixture is in combination of trimethoprim 160 to 480 milligrammes with sulphamethoxazole 0.8 to 2.4 grams daily, divided into two to three doses. The combination of trimethoprin with sulphamethoxazole which is known as co-triomoxazole is used in the treatment of gram negative and gram positive infections of the respiratory, alimentary and urinary tract, gonococci, pneumococci, staphylococi, streptoccocci, E-Coli and Shigella.

Sulphamethoxazole alone is given as initial dose of 2 g and then followed by 1 g every twelve hours. It is slightly soluble in water. The solubility at 20 °C is fifty parts of alcohol and in three parts of acetone. It is soluble in solution of akaline hydroxides. It should be stored and protected from light.

1.9.2 Folic Acid

It is insoluble in cold water and in alcohol. Soluble in five thousand parts of boiling water, soluble in a dilute sodium hydroxide and the solution yield a clear orange brown solution.

It should be stored in air tight container and protected from light. Sources are green leaf, vegetables, meat and cereals. It is present in many food parts as free folic

acid but mainly in the conjugated form with several gultamic acid residues. It is important for the maturation of megaloblast into normaloblast. It is also important for cell division in the body. It is enzymatically reduced in the body to tetrahydrofolic acid, a coenzyme that is involved in purine and pyrimidine nucleotide synthesis and some amino acid conversion.

Human requirement is 50µmg or mcg daily though the actual amount is determined by metabolic function and cell turnover rates. Deficiency leads to megaloblastic hemotopoiesis, glossitis, diarhoea, loss of weight. Deficiency occurs in pregnancy and epileptic patient on continuous administration of anticonvulsive treatment and this can lead to mental deterioration.

1.10 RESEARCH OBJECTIVES AND SCOPE

Nigeria Pharmaceutical Manufacturers depend heavily on imported raw materials for their industries. Nigeria has been blessed with plenty of arable land and conducive climatic conditions where agricultural materials can be grown in large quantities. Sweet potato (Ipomea batatas) could be cultivated with little attention as it can be grown perpetually once the soil and climatic conditions are satisfied.

Our economic recovery policy is centred on local sourcing of these raw materials. In response to the national call for local sourcing of these materials for our pharmaceutical industries, the need to look inward to exploit the locally available crude raw materials including agricultural products cannot be over-emphasised [Kio, 1987), Ojile (1994), Ojile et al (1995]. Tablet excipients rather than the active ingredients could be more easily extracted at affordable costs in a developing nations like Nigeria (Ojile et al, 1999).

One of these excipients is the starch which functions as a disintegrant, as a binder in form of a mucilage and at times as a diluent (HPE, 1995). There are so many plant sources of starch e.g. cassava (Budaye et al, 1994), yam (Nasipuri, 1986), sorghum, (Akande, 1988) cocoyam, (Kunle, 1988), maize, rice etc.

However, sweet potato (*Ipomea batatas)* was selected for this study due to its perpetual growth, being vegetative once the soil and moisture conditions are met. Thus no seasonal replanting is necessary. The starch will be modified by treatment of its suspension to form a mucilage. This would be dried to form pregelatinsed starch. Part of the starch extracted was treated with dilute nitric acid and heated for partial hydrolysis to form depolymerised products (maltodextrins).

Both will be tested for their excipient properties for tableting, including considerations for their use in direct compression of both microdose e.g. folic acid and high dose e.g. sulphamethoxazole tablets.

Generally the focus is to be able to modify starch into pregelatinised starch and maltodextrin in order to investigate whether they meet the requirement for direct compression tableting so as to explore them as substitute for the imported directly compressible vehicles.

The project would also investigate which of the modified starch products has better binding or disintegrant properties in direct compression, dry granulation and wet granulation procedures.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 MATERIALS

Materials sourced from May & Baker Rhone Poulenc Plc Ikeja Nigeria were as follows:-

Sulphamethoxazole,

Maize starch

Materials sourced from BDH Chemicals Ltd Poole England were:

Nitric Acid, Hydrochloric Acid, Talc, Sulphuric Acid, Xylene, Acetone, Sodium Bisulphate, Maltodextrin (Yellow).

Materials sourced from Hopkin and Mill Ltd England were as follows:-

Magnesium stearate, Gelatin granules.

Materials sourced from Roche Nigeria Ltd was folic Acid.

Equipment sourced from Erweka Apparatebau GMBH Germany were as follows:-

1. Tablet disintegration time test machine model ZT3
2. Water heater/bath
3. Hot plate regulator
4. Erweka tablet friability tester, model TA3R
5. Single punch and die tableting machine EKO
6. Erweka dry particles' flow tester

Other equipment used were as follows:-

7. Gallenkamp oven BS Size 3 (England)
8. Avery weighing balance (W.T Ltd, Birmingham U.K)
9. Endecott sieve shaker (MK11 Endecott London SW19 England).

10. Blender Mill (Mouline Type 242, France)

11. Analytical weighing balance (Mettler, P163, Switzzerland)

12. Microscope (Wild Mill Maire, Switzerland)

13. Centrifugal suspension (BHG Hannale, Z230, Germany

14. Specific gravity bottle.

15. Corringham pH meter (UK)

2.2 METHOD

2.2.1 Extraction of Potato Starch

Potato tubers were bought from Samaru market in Zaria Northern Nigeria. 4 kg weight was taken. This was properly washed, peeled and cut into small pieces, rewashed and grated in the centrifugal machine. The grated mass was reduced to fine pulp with the Mouline blender and was suspended in 20 litres of water. The aqueous milky suspension contains starch with a small quantity of protein, cell debris and fat. On standing, the starch separated more rapidly than other materials. This was passed through a centrifugal separator, the starch was separated from other components. At 10 minutes interval, two drops of equimolar mixture producing sulphur dioxide from concentrated sulphuric acid and sodium bisulphate were introduced. This was to prevent the discolouration of the starch product by oxidative enzymes (Treas and Evans, 1985). The starch was collected and dried in the hot air oven at 50 °C. The dried powder was screened through a 180 μm mesh of the sieve and stored in air tight transparent glass bottle.

2.2.2 Determination of percentage of starch content in the sample

The percentage of the starch content obtained from the sample was determined. The total weight of the potato starch at the initial stage before the extraction processes was noted (4 kg). After the completion of the extraction processes, the weight obtained was also noted.

$$\% \text{ starch contents} = \frac{\text{initial total weight}}{\text{final weight}}$$

2.2.3 Investigation of the Starch and its Modified Products

i. **Identification Test for starch**: The B.P. 1988 test for the identification of starch was used. One (1) g of the starch was heated with 15 ml of water for 1 min, and then cooled. Two (2) drops of 0.005 M iodine solution was added. A blue colour which disappeared on warming and reappeared on cooling was observed.

ii. **Determination of Gelatinization Temperature**: The temperature of gelatinization of the starch sample was determined by making 250 ml of 0.29% w/v suspension of the starch sample in a 500 ml beaker and heated in the Gallenkamp water bath thermostated at 40 °C. The temperature was then gradually raised by 2 °C each time when the sample was withdrawn and observed under the polarised microscope to determine the temperature at which the granules lost their polarization crosses totally.

iii. **Production of Pregelatinised Starch**: 40% w/v of sweet potato starch mucilage was spread on a try and left in Gallenkamp hot air oven thermostated at 48 °C to dry to form a solid which was milled in a mortar with pestle and sieved through a 180μm sieve mesh. This is pregelatinised starch.

iv. **Production of Maltodextria with Hcl Treatment**: 40% w/v of the starch mucilage in dilute (0.5N) hydrochloric acid (HCl) was heated at 90-100°C with

constant stirring for 6 hr on a water bath. The reaction mixture was cooled and neutralized with NaOH to a pH of 7 using Conningham pH meter. This was filtered through nylon cloth sieve. The residue was washed with water and dried at 48 °C for 6 hr in the Gallenkamp oven. The dried solid was pulverised in the mortar with pestle and screened through a 180 µm sieve. The product which was maltodextrin was stored in a transparent glass bottle.

v. **Production of Maltodextrin with HNO_3 Treatment**: 40% w/v of the starch mucilage formed with dilute nitric acid ($HN0_3$) at 90-100°C for 6 hr in water-bath. This produced a yellow armorphous substance mixture which was neutralized with NaOH to a pH of 7, washed with water and dried for 5 hr at 48 °C, to obtain a yellowish solid. This was similarly pulverised and stored with calcium chloride laden dessicator as it is highly hygroscopic. This is also maltodextrin which is yellowish.

vi. **Identification tests for Maltodextrin , Pregelatinised Starch and Avicel® B.P. 1988**

(A) One (1) g of the substance was taken and boiled in 50 ml of water. It was cooled and to 1.0 ml of the cloudy suspension 0.05 ml of 0.005 M iodine solution was added and mixed. Purple colour produced was noted

(B) Another 5.0 ml of the suspension in test (A) was taken and 2.0 ml of 2 M NaOH was added.. To this mixture was added drop-wise with shaking 0.5 ml of copper sulphate solution and boiled. Red precipitate produced was noted.

(C) Half (0.5g) of the substance was taken and dispersed in 2ml of water without heating. A gel is produced. 0.05ml of iodine solution was added. Dark blue colour produced was noted.

(D) Ten (10) mg of the substance was added on a water glass and this was dispersed in 2ml of iodinated zinc chloride solution. A violet blue colouration was to be noted.

vii. **Microscopic examination of starch and modified starch**: A small quantity of the starch powder and the modified products were mounted respectively on a slide in glycerol and viewed under the microscope. The sizes and shapes were observed.

viii. **Moisture Content Determination:** Two (2) g of starch and its modified products were weighed into the evaporating dishes respectively. They were placed in the oven at 80 °C and dried to a constant weight. The difference is expressed as percentage of the initial weight. This determination was repeated twice to obtain the mean.

ix. **Analysis of Maltodextrin using Paper Chromatography**:

(a) One-tenth (0.100) g of the prepared sample was taken and heated with 50 ml of dilute (1 N) sulphuric acid in a beaker at 100 °C for about 6 hr. This hydrolysed maltodextrin into monosacharides. It was centrifuged and was subjected to paper chromatography using ascending techniques. This was treated with alpha-naphthol solution, placed in the oven for 3 minutes and then compared with the standard.

(b) The qualitative analysis was carried out by taking 0.100 g of the prepared sample and that of the standard respectively which were mixed with 50ml of dilute 1 N sulphuric acid in a beaker and heated for 6 hr. After hydrolysis had taken place the samples were centrifuged and subjected to paper chromatography and the Reference Point (R_F) were compared (Foray, 1950).

x) **Particulate Flow Test**: The time required for 100 g of the sample to pass through the orifice of the Erweka flowability Tester was determined as follows. The sample was put in 100.0 ml of the measuring cylinder properly and tapped to the level. This was transferred into the funnel of the Erweka Flowability meter. The time was

set to zero. Then the vibration was started and the time recorded on the timer in seconds showed the flow time.

xi) **Determination of Angle of Repose**: The starch and modified products were used. A glass funnel was fitted firmly at 30 cm on the ring stand. Fifty (50) grams of the powder from each respective sample was placed in the funnel and allowed to flow forming a conical heap with the base. The angle of repose was calculated from the geometry of the powder according to the method of Iwuagwu et al, (1986).

xii) **Tapped and Bulk Densities Determination**: The bulk density (D_b) of each powder was determined by measuring 50.00 g of the powder into a graduated 100 ml measuring cylinder with 5.0 cm diameter and the volume taken. It was calculated using the equation.

$$D_b = W/V_b \qquad (4)$$

where W is the weight of the powder and V_b is the bulk volume of the powder.

The tapped density (D_t) was determined for each sample following the procedures of Neuman (1967). Fifty (50.00) g of each of the powder was weighed into a 10.0ml graduated measuring cylinder. The cylinder was tapped from a height of 1.0 cm at the rate of 30 drops per minute for 10 minutes. The tapped density was calculated from the expression:-

$$D_t = W/V_t \qquad (5)$$

where V_t is the tapped volume.

xiii) **Determination of True Densities of the Modified Products**:

This was carried out using specific gravity bottle method (Okhamafe, 1991). Here, the weight of the empty specific gravity bottle was taken and 5.00 g of pregelatinised starch and maltodextrin weighed respectively. The solvent was poured into the bottle and allowed to cool, it was cleaned and conditioned to room temperature

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and then weighed. After 5 minutes the powder was then introduced into the bottle, allowed to condition, cleaned and weighed.

The solvent used here was xylene with specific gravity value = 0.86.

$$\varrho = Ws/(a + w) - b \quad g/cm^3 \qquad (6)$$

where ϱ is the true density

a is weight of bottle + solvent + Powder

b is weight of bottle + solvent

s is specific gravity of solvent

W is the weight of powder

xiv **Determination of Carr's Index of Consolidation**

This was calculated after Schwartz et al (1975), after knowing the bulk and tapped densities.

$$CI = 100(D_t - D_b)/D_t \qquad (7)$$

where CI is Carr's Index

D_t is tapped density

D_b is bulk density.

2.3 DIRECT COMPRESSION OF MODIFIED PRODUCTS

The direct compression property of the excipient were evaluated. The binary mixtures of modified products [pregelatinised starch, maltodextrin and that of Avicel PH 101] were carried out.

Compression of the binary mixtures of each of the derived products were carried out at various concentrations and at different compression setting at 6.5, 7.0, 8.0 metric tons with the extremes compaction forces being the lowest and highest values that produced hard tablets. The effect on the tablet properties were evaluated.

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2.4 DETERMINATION OF PACKING FRACTION OF TABLET

Packing fraction F_p is given by the expression:-

$$F_p = D_b/\varrho \qquad (8)$$

where D_b is the bulk density

and ϱ is the true density of the tablet.

The true and bulk densities were calculated to obtain the value of F_p.

True density is given by Bangudu, (1985) as follows:-

$$1/\varrho_{AB} = WA/\varrho_{AB} + WB/\varrho_{AB} \qquad (9)$$

where ϱ_{AB} is true density of the tablet with component A & B (for only two components)

W_A is weight fraction of component A

W_B is weight fraction of component B

ϱ_A & ϱ_B are true densities of A & B respectively.

W_A = weight of component A/wt of component A + wt of component B

and bulk density D_b

$$D_b = 4W/\pi d^2 h \qquad (10)$$

where h is thickness of tablet (cm)

W is weight of tablet (g)

d is diameter of tablet (cm)

2.5 DENSITY OF COMPACT

Compressibility has also been evaluated from the densities of compact at corresponding compaction loads. Compact density (D_c) is obtained from the weights of compact and its volume as follows:-

$$D_c = W_c/V_c \quad (11)$$

where W_c is weight of compact

V_c is volume of compact

and volume of compact V_c was calculated from the relationship

$$V_c = \pi d^2 h/4 \quad (12)$$

where d is diameter of compact

h is thickness of compact.

2.6 THE TENSILE STRENGTH OF COMPACT

The tensile strength of compact is a better parameter for determining compact strength than hardness. This is because tensile strength is independent of the tablet dimensions. Okafor et al (1991) calculated the tensile strength(s) of the compact from the relationship

$$S = 2P/\pi dh \quad (13)$$

where P is the breaking load or hardness of compact in kilogram force

d is compact diameter (cm)

h is compact thickness (cm)

2.7 PREPARATION OF TABLETS

2.7.1 Via Wet Granulations

Two sets of dosage regimens were prepared. The microdose (5 mg dose per tablet) and the macrodose (500 mg dose pertablet).

In the microdose regimen folic acid tablets each containing 5 mg was formulated. In the high dose regimen 500 mg sulphamethoxazole is contained in each tablet which on its own is not compressible.

The batch size quantities of the active ingredient, the diluent for low and high dose, the intragranular disintegrant were weighed on the Mettler analytical balance and triturated by doubling up mixing techniques in 100 ml porcelain mortar using stainless steel spatula with a wooden handle. The pre-determined volume and strength of the binding solution or mucilage was added and evenly distributed on the surface of the dry mix and triturated for 5 minutes to form a wet doughy mass. This was force-screened through 1.7 mm sieve mesh onto a stainless steel tray and left in the oven thermostated at 50 °C to dry for 2 hr which was enough time to attain constant weight. The granules were allowed to pass through 1000 μm mesh by shaking manually. The oversized ones were force-screened through the sieve by gentle abrasion with a spatula through the sieve. The granules were homogenised and subjected to sieve size analysis (see 2.7.3 below).

The extragranular excipients were added to the granules and tumbled in the mortar using the spatula for 5 minutes. (See Tables 2 and 3).

The excipients considered were the sweet potato starch and its derivatives: pregelatinised starch and maltodextrin and Avicel® Here yellow maltodoxtrin was used for the work since folic acid which was used for the major part of the work was yellow. This would elimate differential colour distribution (white and yellow patches) .

TABLE I A: PREPARATION OF BINARY MIXTURES AS EXCIPIENTS:

WEIGHT CONTENT (G)		WEIGHT CONTENT (%)	
PGS	MDX	PGS	MDX
PGS	AVICEL	PGS	AVICEL
MDX	AVICEL	MDX	AVICEL
7.0	0	100	0
5.6	1.4	80	20

4.2	2.8	60	40
2.8	4.2	40	60
1.4	5.6	20	80
0	7.0	0	100

TABLE 1B: FORMULATION OF BINARY MIXTURES OF POTATO STARCH DERIVATIVES: PREGELATINISED STARCH (PGS) AND MALTODEXTRIN (MDX) AND AVICEL® PH101 FOR FOLIC ACID TABLETS CONTAINING 5 MG/75 MG TABLET

Binary Mixture Content	Binary Mixed Components					Drug
	0%	20%	40%	80%	100%	Folic Acid content for each binary mixture (g)
PGS/MDX (g)	7.00	7.00	7.00	7.00	7.00	0.500
PGS/Avicel® (g)	7.00	7.00	7.00	7.00	7.00	0.500
MDX/Avicel®	7.00	7.00	7.00	7.00	7.00	0.500

TABLE 2: MICRODOSE FORMULATION CONTAINING SOLE EXCIPIENT BY WET GRANULATION METHODION

	Weight/ Tablet (mg)	Weight/ Batch of 200 tabs (g)	Content %	Batch Number 1	2	3
Drug (folic acid)	5.00	1.000	6.67	Folic Acid	Folic Acid	Folic Acid
Intra-granular disintegrant	7.50	1.500	10.00	Starch	PGs	MDx
Diluent	54.70	10.940	72.93	Starch	PGS	MDX
Binder	0.30	0.060	0.40	Starch mucilage	PGS	MDX
Extra-granular disintegrant/Glidant	5.85	1.170	7.80	Starch	PGS	MDX
Glidant/ Lubricant	1.50	0.300	2.00	Talc	Talc	Talc
Lubricant/ Glidant	0.15	0.030	0.20	magnisium stearate	magnisium stearate	magnisium stearate
Net weight	75.00	15.00g	100.00%	15.00g	15.00g	15.00g
Variable parameter different from Batch 1	-	-	-	Starch mucilage binder noted	All starch replaced by PGS	All starch replaced by MDX
No. of Excipients	-	-	-	1	1	1

PGS = Pregelatinised starch

MDX = Maltodextrin

TABLE 3: NON-SELF COMPRESSIBLE HIGH DOSE TABLET FORMULATION BY WET GRANULATION METHOD

Material function	Weight/Tablet (mg)	Weight/Batch of 200 tabs (g)	% Content	Batch Number 1	2	3
Drug	500.00	50.000	79.8	SMZ	SMZ	SMZ
Intra-granular disintegrant	50.000	5.000	8.0	Starch	PGS	MDX
Binder	14.134	1.410	2.2	Starch mucilage	PGS	MDX
Extra-granular disintegrant/ Glidant	48.80	4.880	7.8	Starch	PGS	MDX
Glidant/ Lubricant	12.51	1.250	2.0	Talc	Talc	Talc
Lubricant/ Glidant	1.25	0.120	0.2	Magnisium Stearate	Magnisium Stearate	Magnisium Stearate
Variable parameter different from Batch 1	-	-	-	Starch mucilage binder noted	All starch replaced by PGS	All starch replaced by MDX
No.of potato derivatives (Excipients)	-	-	-	1	1	1

PGS = Pregelatinised starch

MDX = Maltodextrin

TABLE 4: FORMULATION OF HIGH DOSE SULPHAMETHOXAZOLE TABLETS USING POTATO STARCH DERIVATIVES - PREGELATINISED STARCH (PGS) MALTODEXTRIN (MDX) AND AVICEL AS DRY BINDER

Drug Content Sulphamethoxazole	Percent Content			
	100%	90%	80%	70%
Pre-slug content (PGS MDX or Avicel)	-	5%	10%	15%
Extra-granular content (PGS, MDX or Avicel)	-	5%	10%	15%
Total weight/tablet (mg)	500mg	555.6	625.0	714.3
Total weight/batch size of 100 tablets (g)	50	55.560	62.500	71.430

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2.7.1.1 **Compression of Granules into Tablets**: The weight of the granules containing the dose of the drug that is 5 mg of folic acid or 500 mg of sulphamethoxazole were accurately weighed respectively. This was transferred into the die (5.5 mm for folic acid tablets and 12.5 mm for sulphamethoxazole tablets), fitted with appropriate punch and die set of the Erweka single station tablet press. The compression pressure setting in metric tons was appropriately adjusted. Tablets were compressed and collected for evaluation.

2.7.2 Via Dry Granulation

In the dry granulation process, the active ingredients were mixed with the required intragranular excipient. These were blended properly and compressed into large tablets (pellets) on the Specac heavy duty hydraulic press at a pressure setting of 15 metric tons. The tablets were then comminuted through 1.7 mm sieve mesh to form granules which were then mixed with extragranular excipient and compressed into the final tablet using the Erweka tablet press.

2.7.3 Granule Size and Size Distribution

The unlubricated granules were poured onto a set of sieves stacked in the following descending order of sieve meshes: 500, 250, 150, 75 and collecting pan of the Endecotts sieves. The set was vibrated on the Endecotts sieve shaker for 15 minutes. The quantities retained on each sieve and pan were weighed. The cumulative percentage of the granules were plotted against the granule size.

Estimation of mean Granule Size, MGS: This is expressed as :

$$MGS = \Sigma(wp)/100 \qquad (14)$$

where w is weight per 100 g,

μ is the sieve-mesh in μm on which w is retained.

2.8 EVALUATION OF TABLETS

2.8.1 Hardness

The Monsanto hardness tester was used to determine the force in kilograms (KgF) required to diametrically crush the tablet. The mean and mean variation of ten tablets from each batch were calculated.

2.8.2 Friability

The friability value (F) of the tablets was determined by subjecting ten tablets of known weight (W_1) from each batch to controlled series of falling shocks in the Erweka Friabilator, the drum of which was made to rotate for 4 minutes at 25 r.p.m. The weight of the tablets after the bangings (W_2) was recorded.

$$F = 100(W_1-W_2/W_1 \quad (15)$$

2.8.3 Uniformity of Weight

10 tablets were weighed individually and collectively from each batch using the Mettler balance. The mean weight was computed. The percentage coefficient of tablet weight variation (V) was calculated according to the formula of Bollius (1988).

$$CV = 100\ s/m \quad (16)$$

where s is the standard deviation

m is the mean weight of the tablets

2.8.4 Disintegration Time

The disintegration time was determined by the B.P. 1988 method without resorting to the use of a guided disc. Six tablets were assessed at the same time in the Erweka tablet disintegration test machine. Distilled water, thermostatically maintained at 37± 1 °C, was used as the disintegrating medium. The mean and mean deviation of three of such determinations were calculated. This is a modified version of the B.P. standard which is the time taken for the last tablet to disintegrate.

CHAPTER THREE

3.0 RESULTS

3.1 PHYSIOCHEMICAL CHARACTERISATION OF THE PRODUCTS

Table 5 shows the properties of the potato starch extracted and its two modified products i.e. pregelatinised starch and maltodextrin

TABLE 5: THE PHYSIOCHEMICAL CHARACTERISTICS OF THE STARCH AND ITS MODIFIED PRODUCTS

Parameter	Starch	Pregelatinised starch	Maltodextrin
Angle of Repose(degree)	38.4	30.0	20.5
Flow Time (secs)	98	50	30
Bulk density (g/cm3	0.48	0.64	0.76
Tapped density (g/cm3	0.67	0.80	0.89
True density (g/cm3)	1.52	1.52	1.54
Compressibility (%)	28.5	20.2	15.0
Moisture content (%)	11.5	12.0	13.5
Shape	Spherical	More Spherical	Most Spherical

3.1.1 Percentage Starch Content

Initial wt = 4 kg s
Final wt = .45 kg
% Starch content = Final wt/Intial wt x 100 = .45/4 x 100= 11.25%
Therefore the percentage starch content in the sample is 11.25%

3.1.2 Identification of Starch, Maltodextrin, Pregelatinised Starch and Avicel

The results of the identification tests performed on the above excipients are as shown in table 6 below:-

Table 6:

Test	Expected result	Result obtained	Influence
1. Starch	Thick and transparent mucilage blue colour or a dark blue colour which dispersed on heating and reappeared on cooling	Thick and transpart mucliage blue colour was obtained	This confirmed the presence of starch
2. Pregelanitised starch	Presence of a gel and dark blue colour was produced	Dark blue with a presence of a gel was obtained	This confirmed pregelatinised starch.
3. Maltodextrin	The presence of purple colour and red precipiate	Purple colour with red precipiate was obtained	This confirmed maltodextrin
4. Microcrystalline cellulose (Avicel®)	Violet blue colour	Violet blue colour was obtained	This confirmed the specific presence of mcc (Avicel).

3.1.3 Gelatinization Temperature of Sweet Potato Starch

The gelatinization temperature of the sweet potato was as shown in Figure 2 below. The gelatinization temperature of potato strach is between 60 - 72^{0}C.

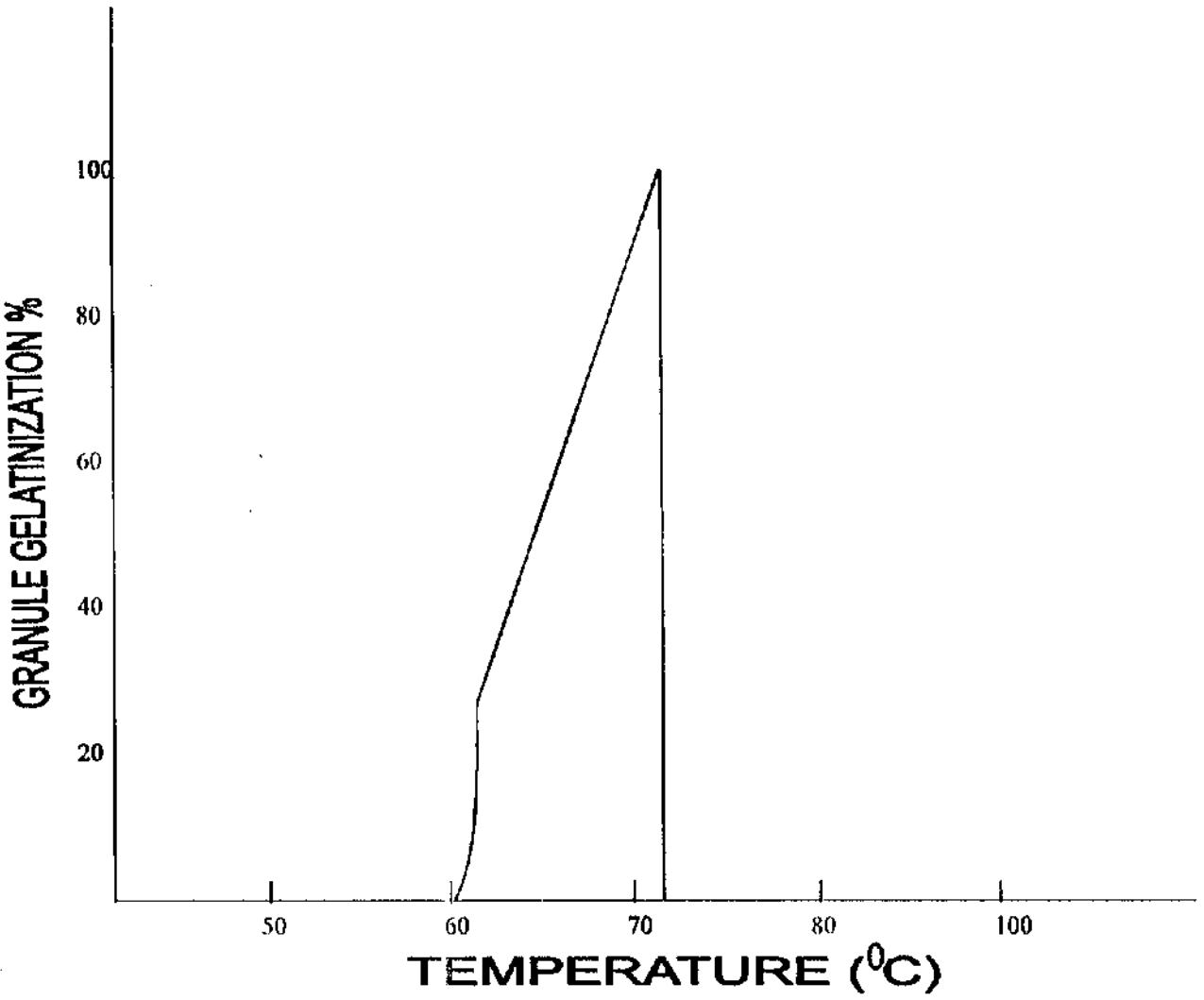


FIGURE 2: THE EFFECT OF TEMPERATURE ON THE DEGREE OF GELATINIZATION OF SWEET POTATO STARCH.

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3.1.3 Qualitative Analysis of Maltodextrin, Pregelatinised Starch

The qualitative analysis of the pregelatinised starch and maltodextrin were carried out using chromatographical techniques.

The R_F values obtained were: 0.18, 0.16 and 0.11 at 30 °C which were comparable with the values of authentic samples of D-glucose, D-galactose and maltose respectively.

3.2 DIRECT COMPRESSION PROPERTIES OF BINARY MIXTURE

TABLE 7A: DIRECT COMPRESSION PROPERTIES OF FOLIC ACID TABLETS PRODUCED FROM BINARY MIXTURE.

Tablet Properties		Weight and Weight Variations mg (±%)			Thickness (mm)			Crushing strenght (KgF)			Friability (% loss)		
Compression Pressure metric tons		6.5	7.0	8.0	6.5	7.0	8.0	6.5	7.0	8.0	6.5	7.0	8.0
MDX: PGS	0:100	75	75.0	75±0.70	4.0	3.0	2.5	2.0	4.0	6.0	1.5	0.40	0.2
	20:80	74.9	75.0	75±0.9	3.8	2.9	2.5	2.5	4.5	6.2	1.0	0.30	0.0
	40:60	75.0	74.9	75±0.9	3.7	2.8	2.5	3.2	4.6	6.5	0.6	0.20	0.0
	50:50	75.0	75.0	75±0.8	3.6	2.8	2.5	3.3	4.8	6.6	0.6	0.18	0.0
	60:40	74.8	75.0	75±0.6	3.6	2.8	2.4	3.5	5.0	6.8	0.5	0.15	0.0
	80:20	75.0	74.90	75±0.8	3.5	2.75	2.4	4.5	5.7	7.0	0.3	0.10	0.0
	100:0	75.5	75.0	75±0.7	3.5	2.7	2.4	5.0	7.0	8.5	0.1	0.0	0.0
AVICEL PGS:	0:100	75	75.0	75±0.70	4.0	3.0	2.5	2.0	4.0	6.0	1.5	0.40	0.2
	20:80	74.9	75.0	75±0.9	3.7	2.9	2.5	2.5	4.5	6.2	1.0	0.30	0.1
	40:60	75	74.9	75±0.8	3.5	2.90	2.5	3.0	4.6	6.6	0.7	0.2	0
	50:50	75	75.0	75±0.8	3.5	2.7	2.4	3.5	5.0	6.9	0.5	0.15	0.80
	60:40	74.8	75.0	75±0.6	3.5	2.7	2.4	3.7	5.9	7.0	0.4	0.1	0
	80:20	75	74.90	75±0.8	3.5	2.7	2.4	3.7	5.9	7.4	0.1	0	0.89
	100:0	75.5	75.0	75±0.7	3.5	2.7	2.4	5.1	7.0	8.6	0.1	0.0	0.2
MDX: AVICEL	0:100	75	75.0	75±0.06	3.6	2.7	2.4	5.1	7.0	8.6	0.1	0.0	0.0
	20:80	74.9	74.90	75±0.7	3.5	2.7	2.4	4.5	6.8	8.5	0.4	0.0	0.0
	40:60	74.9	75	75±0.8	3.5	2.8	2.4	4.6	6.9	8.5	0.4	0.0	0.0
	50:50	75.0	75	75±0.6	3.4	2.7	2.4	4.8	6.9	8.5	0.4	0.0	0.0
	60:40	75.0	75	75±0.79	3.4	2.7	2.4	4.8	6.9	8.5	0.2	0.0	0.0
	80:20	75.0	75	75±0.8	3.4	2.7	2.4	4.9	6.9	8.5	0.2	0.0	0.0
	100:0	75.0	75	75±0.6	3.4	2.7	2.4	5.0	7.0	8.5	0.1	0.0	0.0

TABLE 7B: DIRECT COMPRESSION PROPERTIES OF FOLIC ACID TABLETS PRODUCED FROM BINARY MIXTURE

Tablet Properties		Compact density g/cm^3			Tensile Strength Kg/cm^2			Packing Fraction (%)			Disintegration time (mins)		
Compression Pressure metric tons		6.5	7.0	8.0	6.5	7.0	8.0	6.5	7.0	8.0	6.5	7.0	8.0
MDX: PGS	0:100	0.79	1.05	1.32	5.8	15.4	27.8	52	69	83	1.0	3.0	8.0
	20:80	0.83	1.08	1.32	7.6	17.9	2.87	.54	71	83	1.5	3.5	12
	40:60	0.85	1.13	1.32	10.10	18.6	70.10	.56	74	83	1.8	4.5	14
	50:50	0.87	1.13	1.32	10.80	20.5	4.0	57	74	83	2.0	5.0	15.0
	60:40	0.88	1.13	1.34	11.30	20.7	3.2	.57	74	86	2.2	10.0	18.0
	80:20	0.90	1.13	1.34	14.90	24.0	38.8	.58	75	86	2.6	12.0	20.0
	100:0	0.91	1.13	1.34	16.5	30.0	39.50	.59	76	86	3.5	1.50	25
AVICEL: PGS	0:100	0.79	1.05	1.31	5.8	15.4	27.8	152	69	83	1.0	2.0	8
	20:80	0.83	1.09	1.30	7.8	176	28.7	160	77	89	1.2	1.8	10
	40:60	0.90	1.09	1.32	9.9	18.7	30.5	67	77	89	0.9	1.7	9.0
	50:50	0.89	1.13	1.33	11	21	31.5	067	81	89	0.9	1.6	10.0
	60:40	0.80	1.13	1.33	11.6	22	32.0	162	81	89	1	1.6	11.50
	80:20	0.89	1.15	1.34	11.9	24.4	33.0	163	82	92	1.2	2.0	13.30
	100:0	09.2	1.15	1.34	16.84	30.2	40	168	89	99	1.4	4.0	15.0
MDX: AVICEL	0:100	0.92	1.17	1.32	16.8	30.02	40	168	89	99	1.4	4.0	15.0
	20:80	0.85	1.17	1.32	14.5	29.0	39.4	163	82	92	1.6	4.7	16
	40:60	0.87	1.17	1.32	14.8	28.8	39.4	63	79	92	2.0	6.0	17
	50:50	0.89	1.17	1.34	15.4	29.60	39.40	63	82	92	2.5	11.0	20
	60:40	0.80	1.17	1.34	15.4	29.60	39.4	64	82	92	3.0	11	23
	80:20	0.90	1.17	1.34	15.8	29.0	39.5	64	82	92	3.20	13.0	24.5
	100:0	0.91	1.17	1.34	16.5	30.20	39.50	63	76	86	3.50	15.0	25

3.2.1 Effect Of Compression Pressure on Pure (100%) and 50:50 Binary Mixtures on Tablet Properties

1. **Weight and weight variation**

There was no significant differences in weight ($P \leq 0.05$). All were within ±0.9% (Table 7A)

2. **Thickness and friability**

In all instances, increase in compression pressure decreased the thickness and also decresed the friability i.e. they are inversely related to the compression pressure (Figures 3&5)

3. **Crushing strenght compact density,Tensile strength and disintegration time**

In all the formulation, the compression pressure was directly related to tablet crushing strenght, compact density, tensile strength and the disintegration tme (Figures 4,6,7,& 8).

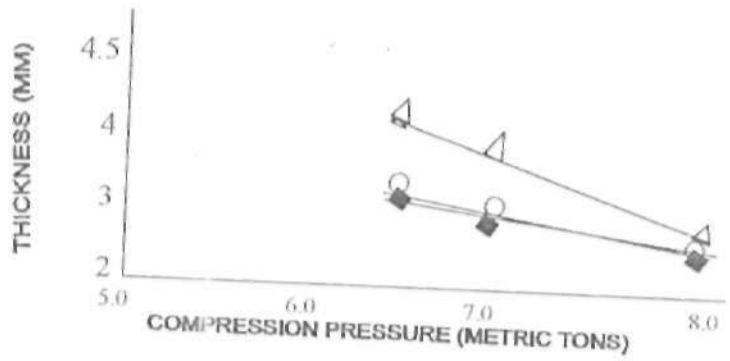


FIGURE 3: THE EFFECT OF COMPRESSION PRESSURE ON THICKNESS OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH, MALTODEXTRIN AND AVICEL®.

KEY: △ PGS ○ MDX ■ AVICEL®

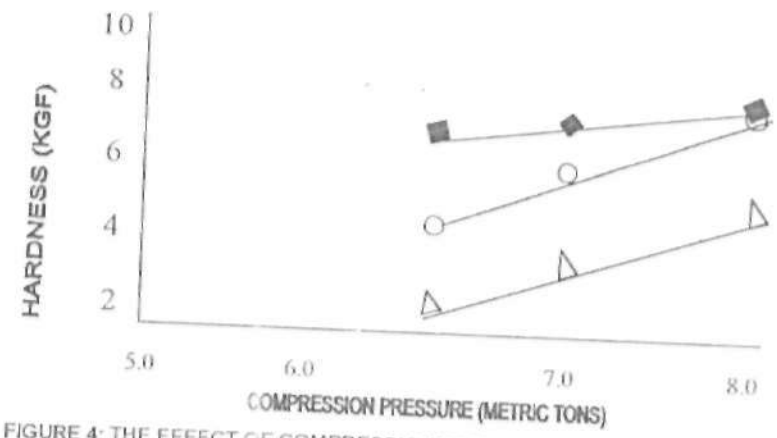


FIGURE 4: THE EFFECT OF COMPRESSION PRESSURE ON HARDNESS OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH, MALTODEXTRIN AND AVICEL®.

KEY: △ PGS ○ MDX ■ AVICEL®

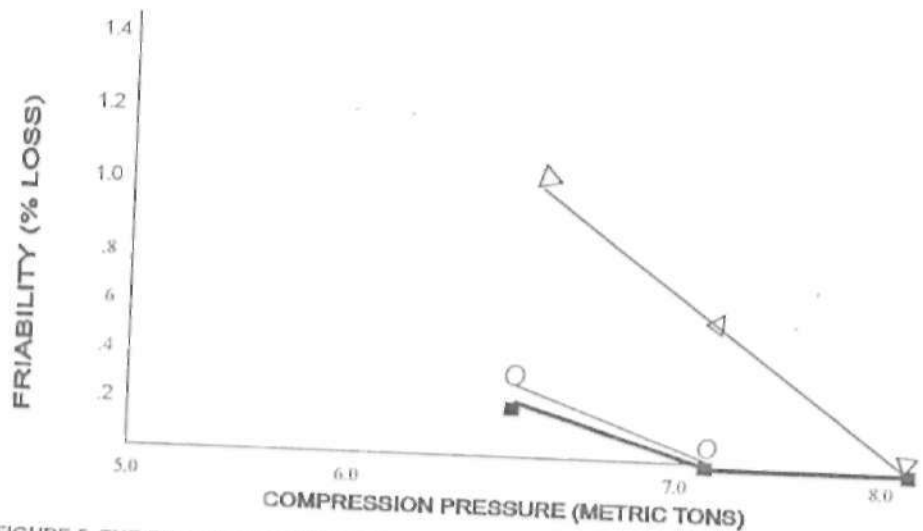


FIGURE 5: THE EFFECT OF COMPRESSION PRESSURE ON FRIABILITY OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH, MALTODEXTRIN AND AVICEL®

KEY: △ PGS ○ MDX ■ AVICEL®

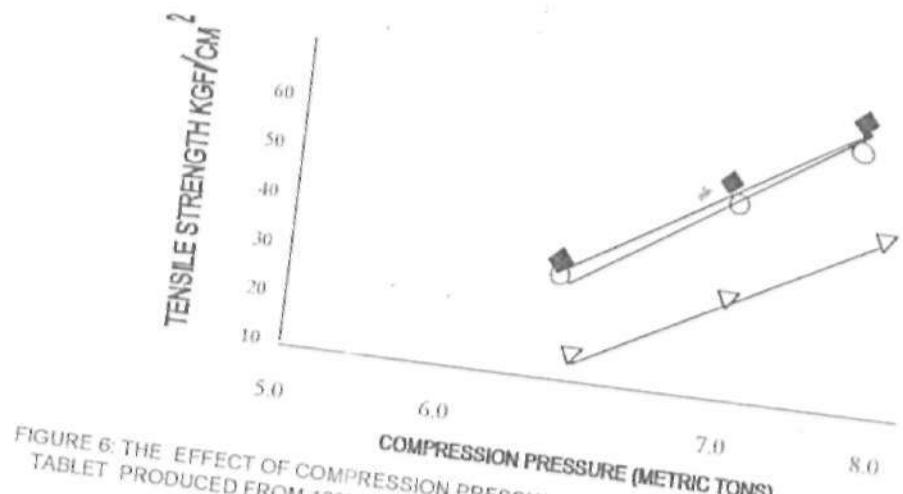


FIGURE 6: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH, MALTODEXTRIN AND AVICEL®.

KEY: △ PGS ○ MDX ■ AVICEL®

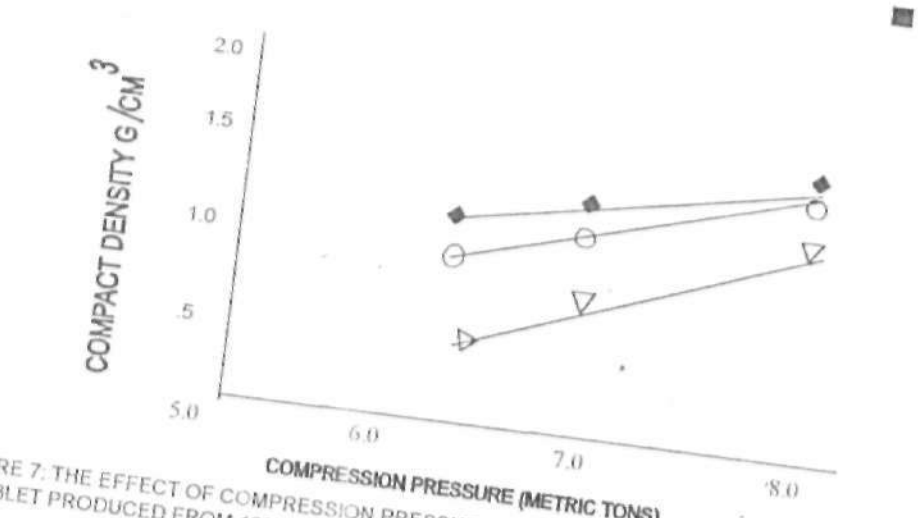


FIGURE 7: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH MALTODEXTRIN AND AVICEL®

KEY: △ PGS ○ MDX ■ AVICEL®

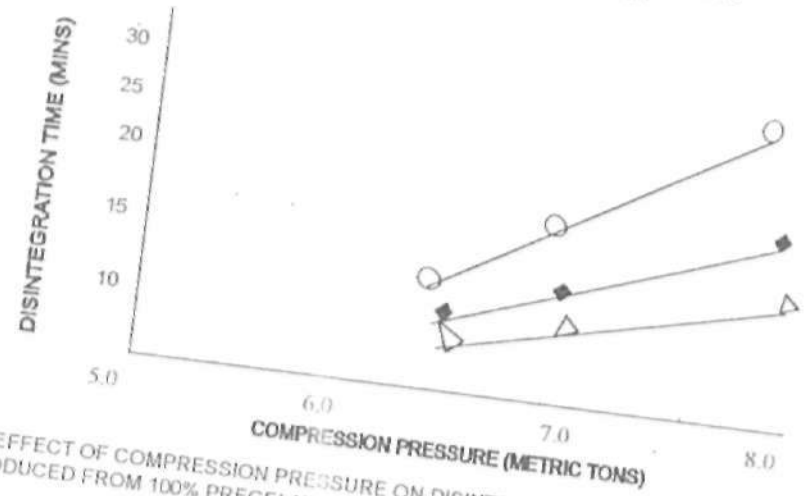


FIGURE 8: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF FOLIC ACID TABLET PRODUCED FROM 100% PREGELATINISED STARCH MALTODEXTRIN AND AVICEL®

KEY: △ PGS ○ MDX ■ AVICEL®

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b. **Effect of compression pessure on 50:50 binary mixtures on properties of tablet are shown in Figures 9, 10, 11, 12, 13, 14 and 15.**

3.2.2 Effect of Binary Components of Dry Binder on Tablet Properties at Optimum Compression Pressure of (8.0 Metric Tons)

1. Friability

While 100% pregelatinised starch component produced friability value of 0.2, other component mixtures produced 0 value of friability (Figure 16).

Crushing strength: As shown in Figure 17 MDX:PGS: The hardness increased as the maltodextrin was increased in the component, the tablet hardness value was from 6.0 to 8.5 KgF while 100% of pregelatinised starch produced tablets with hardness of 6.0 KgF that of maltodextrin produced 8.5 KgF.

AVICEL: PGS: The component of Avicel® in the binary mix with pregelatinised starch was directly related to the hardness, where 100% of pregelatinised starch produced hardness of 6.0 KgF, 100% of Avicel® produced hardness of 8.5 KgF.

MDX: AVICEL: The hardness is slightly higher in Avicel at 8.6 KgF while the hardness in MDX is 8.5 KgF.

The values for the pure dry binders were as follows:

AVICEL® 8.6 KgF > MDX > 8.5 KgF > PGS 6.0 KgF.

Packing Fraction: As shown in Figure 18 at the optimum compression pressure, the packing fraction for mixtures are given below.

MDX: PGS: When the binary mixtures were 0:100 to 50:50 the packing fraction was 0.83 but as from 60:40 to 100:0 the packing fraction increased to 0.86.

AVICEL: PGS: At 0.100 the packing fraction was 0.83 but as from 20:80 to 60:40 the packing fraction was 0.89 and then at 80:20 become 0.92 and finally 0.99 at 100:0 mix.

MDX: AVICEL: The packing fraction at 0:100 was 0.99 which decreased to 0.92 between 20:80 to 80:20 mixed component. However at 100:0 the packing fraction was 0.86 (Figure 18).

Thickness :As shown Figure 19, MDX: PGS: The thickness from binary component of 0:100 to 50:50 was 2.5mm while 60:40 to 100:0 was 2.4mm. That is 100% MDX was most thinnest.

AVICEL: PGS: The thickness from binary component of 0:100 to 50:50 was 2.5mm while 60:40 to 100:0 was 2.40 that is 100% Avicel was most thinnest.

MDX: AVICEL: Irrespective of the binary component, the thickness was 2.4mm.

Compact Density and Tensile Strength: As shown in Figures 20 & 21 the variation in the compact density appeared to synchronize with the variation of the tablet thickness while that of the tensile strength (T9) corresponded with that of the tablet hardness.

Disintegration Time: As shown in Figure 22, at compression pressure of 8.0 metric tons, only Avicel: PGS mix components produced tabets that disintegrated within the B.P. standard of ≤ 15 minutes. At 50:50 the disintegration time was 10 minutes.

MDX: PGS produced tablets that disintegrated within the B.P. standard when the component was 0:100 to 50:50 but when the component was 60:40 to 100:0, the disintegration time was above the official limit of 15 minutes.

MDX: AVICEL: Here it was when the component was 0:100 that the disintegration time was within the official limit. Other component mixtures (from 20:80 to 100:0) produced tablets with longer disintegration time which exceeded the official limit.

In this instances, the compression pressure of 7.0 MT was adopted, the disintegration time was all within the official range.

MDX 15 minutes > Avicel 4 mins. > PGS 2 mins. (See Table 7 Aand B Figure 22)

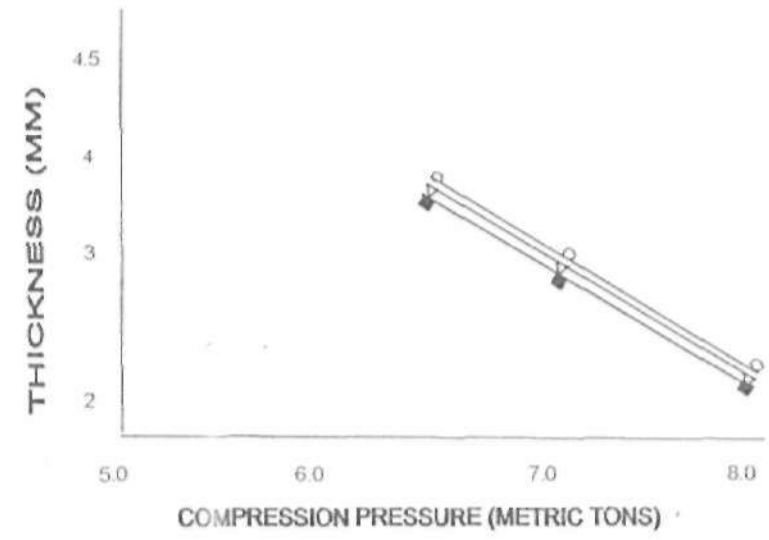


FIGURE 9: THE EFFECT OF COMPRESSION PRESSURE ON THICKNESS OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS.

KEY: ■ MDX / AVICEL® ○ MDX / PGS △ PGS / AVICEL®

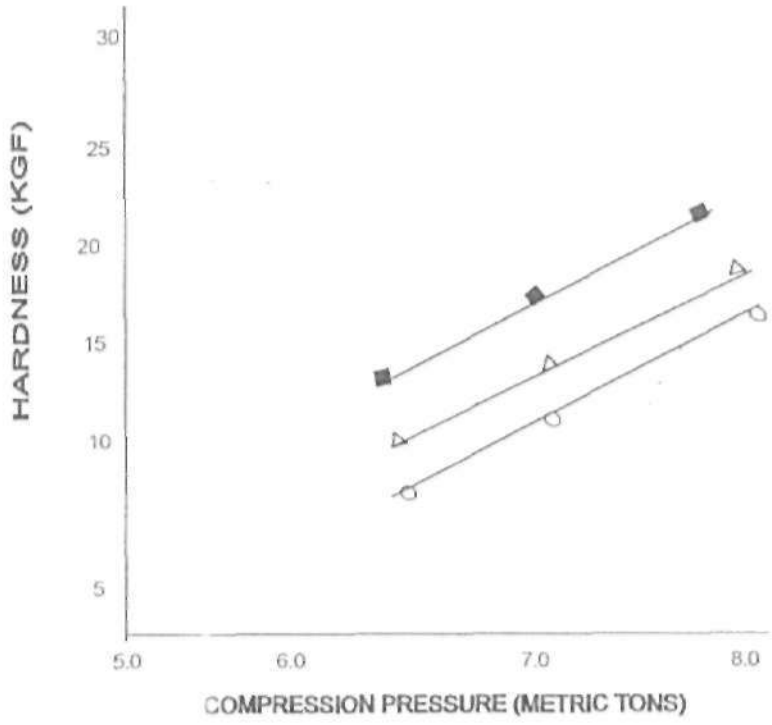


FIGURE 10: THE EFFECT OF COMPRESSION PRESSURE ON HARDNESS OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS.

KEY: ■ MDX / AVICEL® ○ MDX / PGS △ PGS / AVICEL®

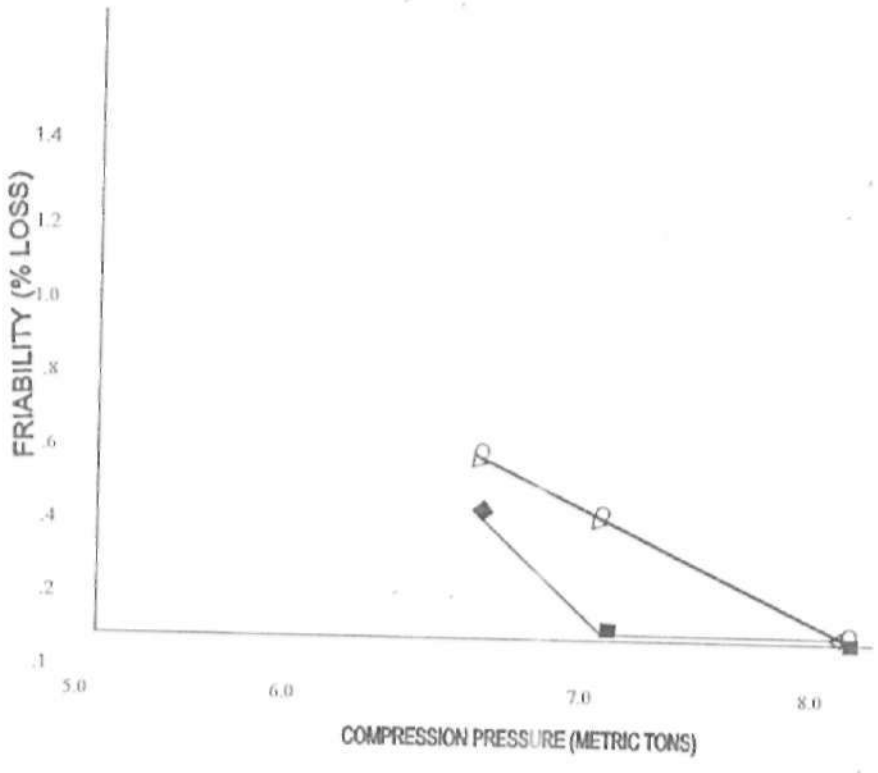


FIGURE 11: THE EFFECT OF COMPRESSION PRESSURE ON FRIABILITY OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

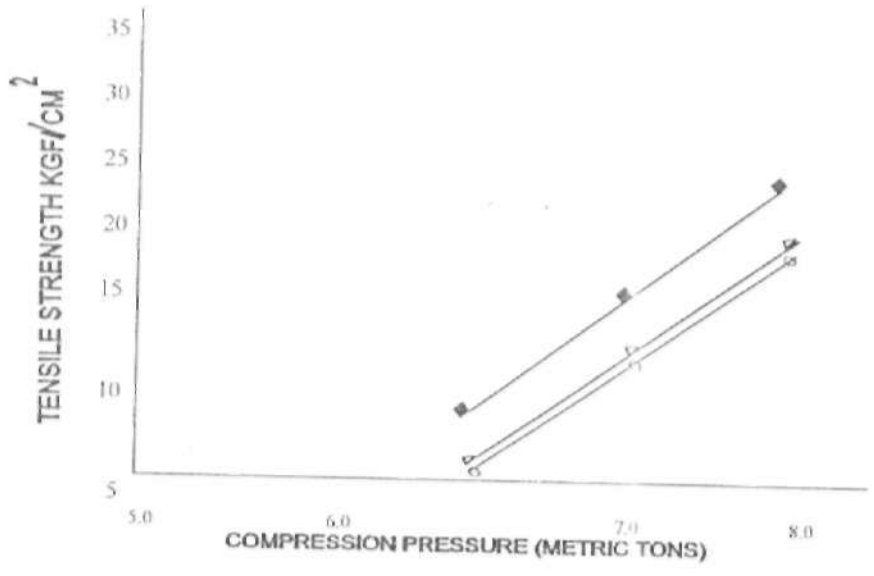


FIGURE 12: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL

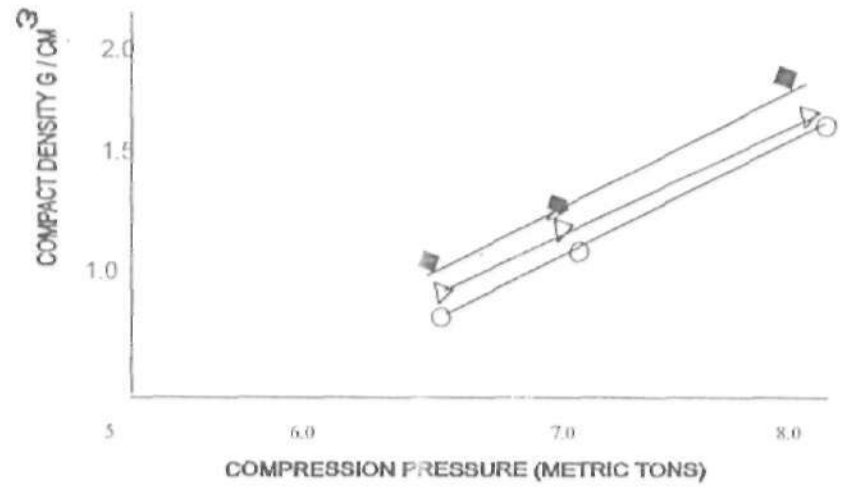


FIGURE 13: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

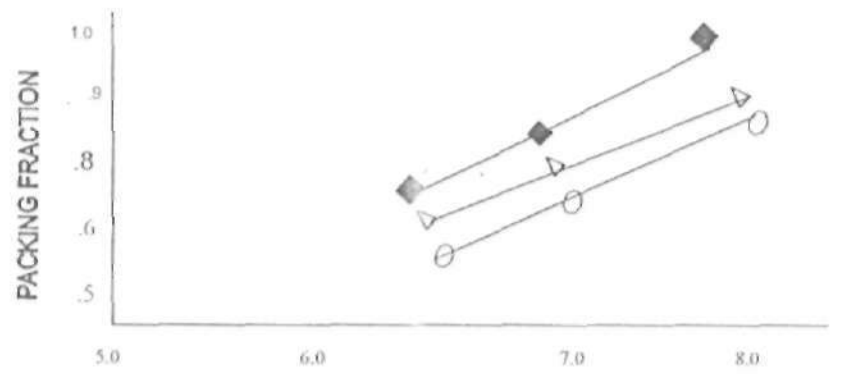


FIGURE 14: THE EFFECT OF COMPRESSION PRESSURE ON PACKING FRACTION OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

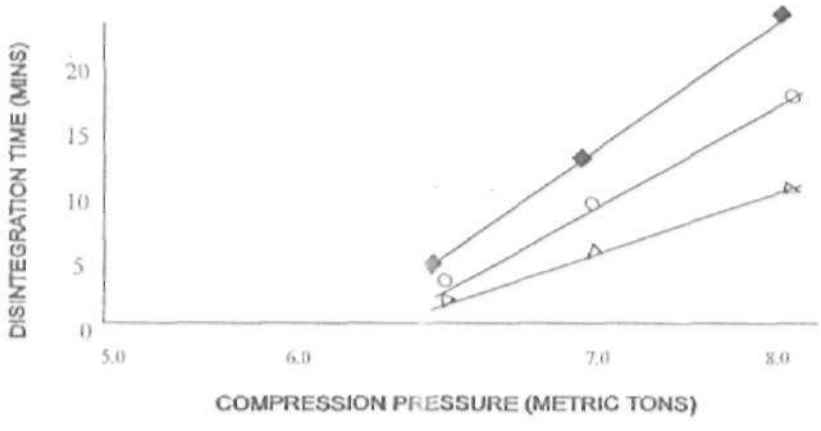


FIGURE 15: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF FOLIC ACID TABLET PRODUCED FROM 50:50 BINARY MIXED COMPONENTS.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

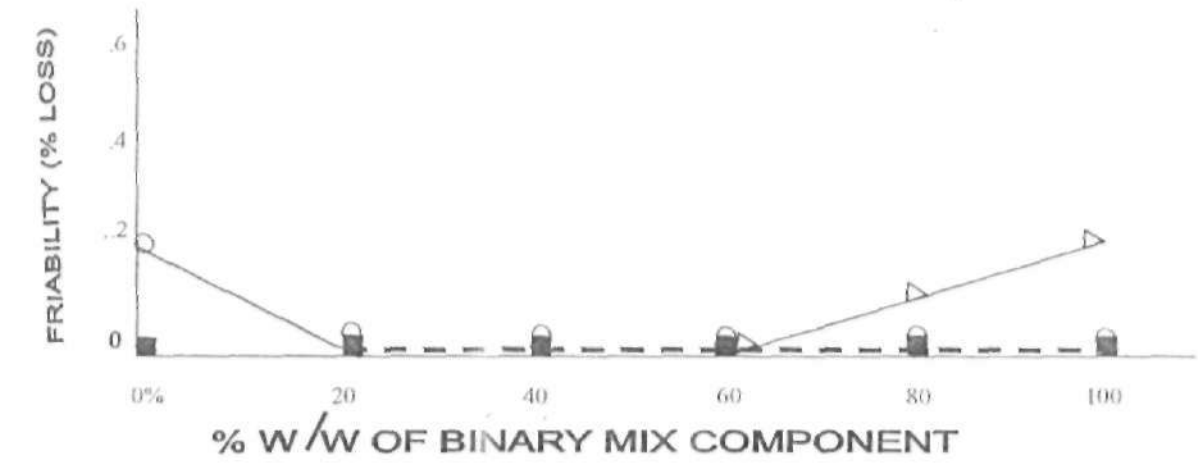


FIGURE 16: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE FRIABILITY OF FOLIC ACID TABLET.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

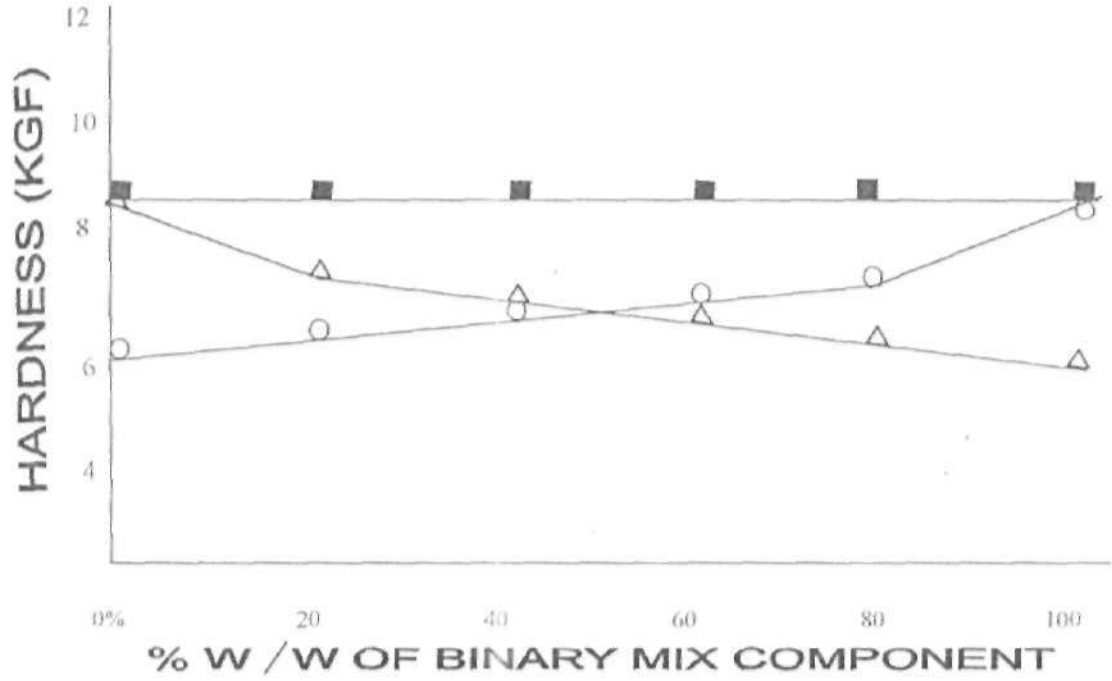


FIGURE 17: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE HARDNESS OF FOLIC ACID TABLET.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

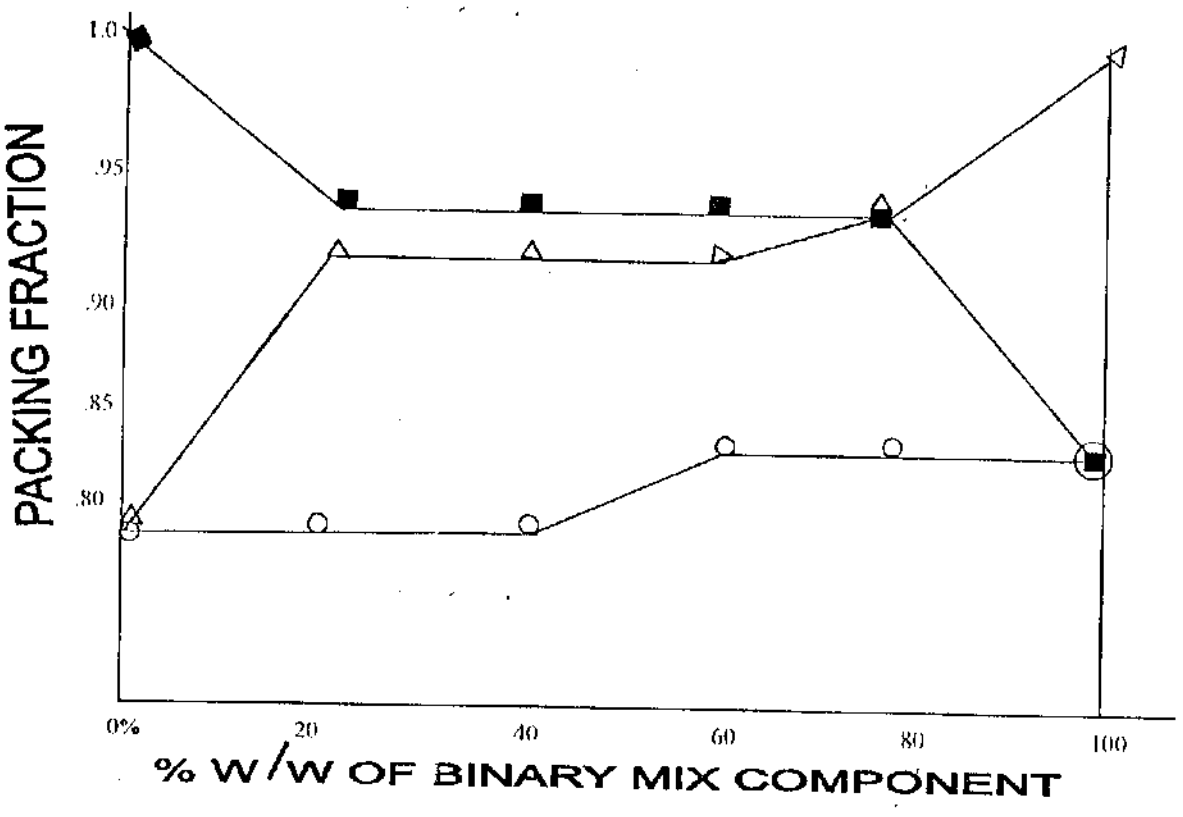


FIGURE 18: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON PACKING FRACTION.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

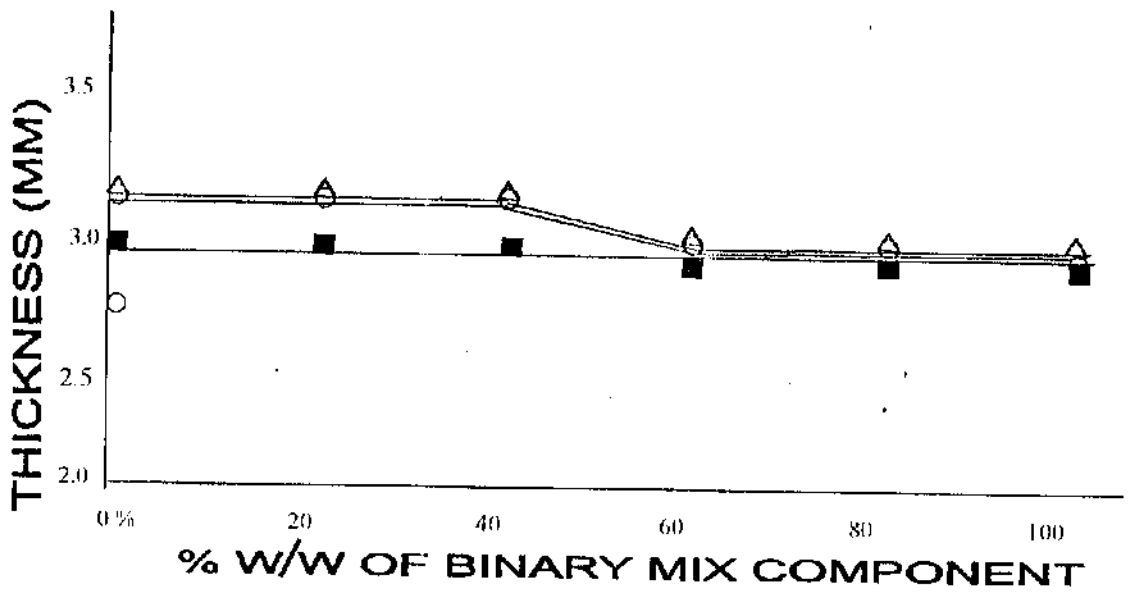


FIGURE 19: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE THICKNESS OF FOLIC ACID TABLET.

KEY: ■ MDX / AVICEL^{R} ○ MDX / PGS △ PGS / AVICEL^{R}

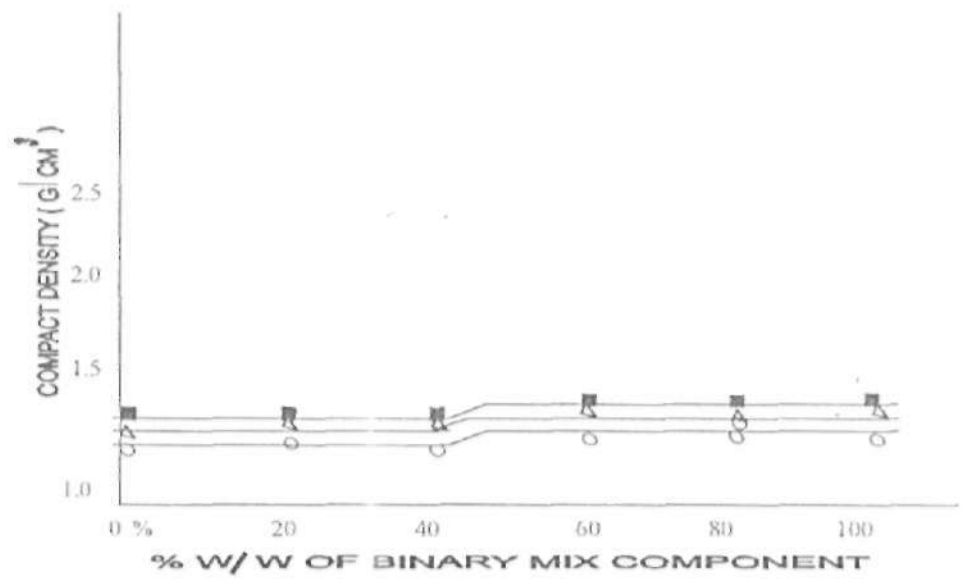
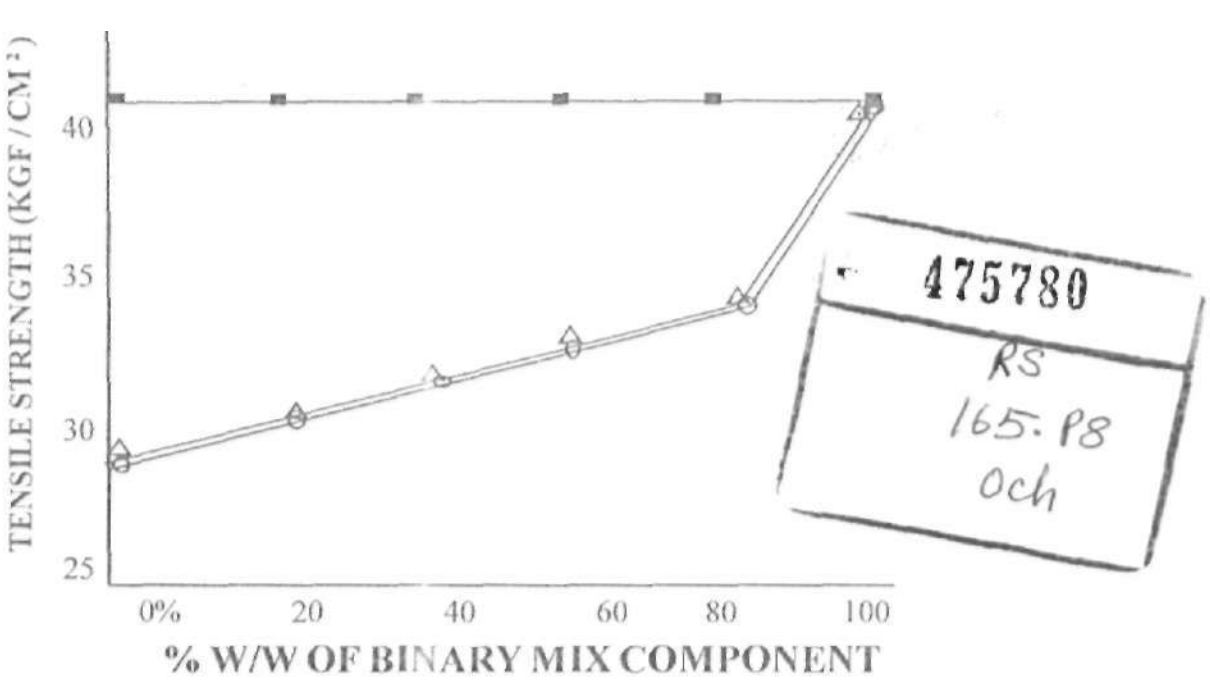


FIGURE 20: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE COMPACT DENSITY OF FOLIC ACID TABLET.

KEY: ■ MDX / AVICEL® ○ MDX / PGS △ PGS / AVICEL®

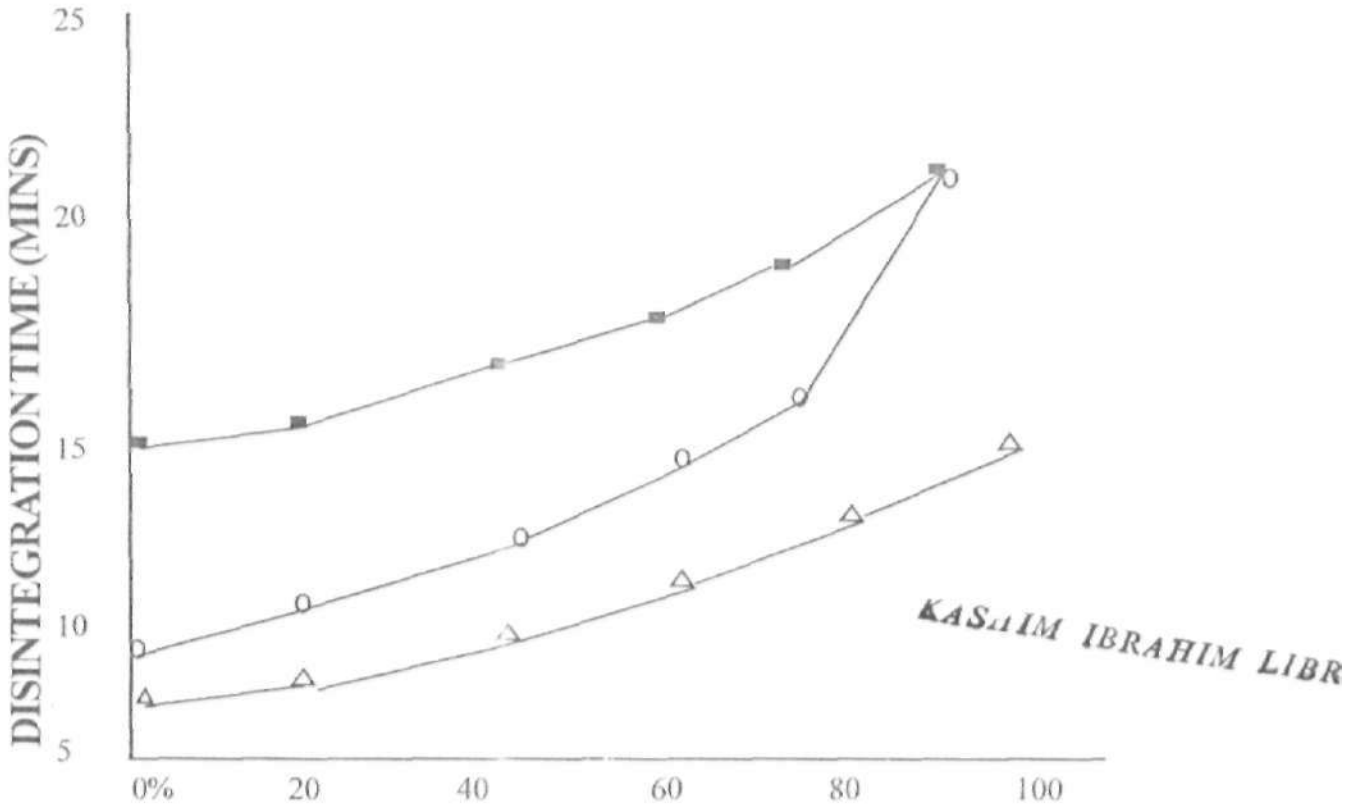


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FIGURE 21: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE TENSILE STRENGTH OF FOLIC ACID TABLET.

KEY:

■ MDX / AVICEL®, ○ MDX / PGS, △ PGS / AVICEL®



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FIGURE 22: THE EFFECT OF COMPONENT RATIO OF BINARY MIXTURE AT COMPRESSION PRESSURE OF 8.0 METRIC TONS ON THE DISINTEGRATION TIME

KEY:

■ MDX / AVICEL®, ○ MDX / PGS, △ PGS / AVICEL®

3.3 PROPERTIES OF HIGH DOSE POORLY COMPRESSIBLE SULPHAMETHOXAZOLE TABLETS CONTAINING 10%, 20% AND 30% EXCIPIENTS BY DRY METHOD

TABLE 8A: THE EFFECT OF COMPRESSION PRESSURE ON THE PROPERTIES OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10%, 20%, 30% CONCENTRATION OF MALTODEXTRIN, PREGELATINISED STARCH AND AVICEL USING DRY METHOD

Tablet Properties		Weight and Variation mg ±%			Thickness mm			Specific Thickness mm/mg x10-3			Crushing strenght KgF		
Compression Pressure (metric tons)	%	3.5	4.0	5.0	3.5	4.0	5.0	3.5	4.0	5.0	3.5	4.0	5.0
PGS	10	556 ±0.59	556 ±0.5%	556 ±0.5%	5.0	4.6	4.4	0.9	8.3	7.9	4.0	6.0	10
	20	625 ±0.6%	625 ±0.6%	625 ±0.6%	5.4	4.8	4.6	0.87	.77	73	5.0	7.5	13
	30	714 ±0.6%	714 ±0.6%	714 ±0.6%	6.0	5.6	5.2	0.84	0.74	0.72	2.5	6.0	1.0
MDX	10	556 ±0.5	556 ±0.6%	556 ±0.6%	4.6	4.4	4.0	0.82	0.79	0.72	6.5	8.5	13.0
	20	625 ±0.6%	625 ±0.2%	625 ±0.6%	5.0	4.8	4.4	0.8	0.77	0.71	8.0	12.0	14.0
	30	714 ±0.6%	714 ±0.2%	714 ±0.6%	6.0	5.4	5.0	0.84	0.76	0.70	4.8	9.0	14.0
Avicelpe	10	556 ±0.6%	556 ±0.6%	556 ±0.6%	4.2	4.0	3.8	0.76	0.72	0.68	7.5	10.0	13.0
	20	625 ±0.8%	625 ±0.8%	625 ±0.8%	4.6	4.2	4.0	0.74	0.67	0.64	8.5	13.0	14.0
	30	714 ±0.6%	714 ±0.6%	714 ±0.6%	5.0	4.5	4.2	0.70	0.63	0.59	5.8	10.5	14.0

TABLE 8B: THE EFFECT OF COMPRESSION PRESSURE ON THE OTHER PROPERTIES OF HIGH DOSE SULPHAMETHOXAZOLE TABLETS PRODUCED FROM 10%, 20%, 30% CONCENTRATION OF MALTODEXTRIN, PREGELATINISED STARCH AND AVICEL® USING DRY METHOD

Tablet Properties	Friability % Loss			Compact Density g/cm^3			Tensilse Strength Kgf/cm^2			Disintegration Time (mins)		
Compression Pressure (metric tons)	3.5	4.0	5.0	3.5	4.0	5.0	3.5	4.0	5.0	3.5	4.0	5.0
PGS %												
10	1.8	1.4	0.6	0.90	0.98	1.03	4.08	7.75	11.68	1.5	3.0	6.0
20	1.6	.90	0.20	.94	1.00	1.11	4.78	8.0	14.10	2.0	5.0	9.0
30	2.0	1.0	.30	.97	1.04	1.12	2.12	5.92	9.80	1.0	2.0	3.0
MDX %												
10	1.3	0.6	0.0	0.98	1.03	1.11	8.90	16.40	17.00	150	180	250
20	.6	0.2	0.0	1.02	1.06	1.16	5.40	8.40	16.40	5.0	220	280
30	1.0	0.20	0.0	0.98	1.08	1.16	2.50	8.50	14.50	20	90	240
Avicel %												
10	1.1	0.2	0.0	1.10	1.20	1.30	9.50	13.30	17.50	5.0	8.5	13.0
20	0.5	0.1	0.0	1.20	1.32	1.38	10.50	15.60	19.00	7.0	10.0	15.0
30	0.8	0.0	0.0	1.2	1.25	1.3	6.0	11.4	17.00	9.0	12.0	15.0

3.3.1 Weight and Weight Variation

There were no significant differences in weight ($P \leq 0.05$). All were within ± 0.9% (Table 8 A).

3.3.2 Specific Thickness and Friability

In all instances, increased in compression pressure decreased the thickness and also decreased the friability at all 3 concentrations i.e. they are inversely related to the compression pressure (Figures 23, 24, 25,26, 27, & 28).

3.3.3 Crushing strenght, Compact Density, Tensile Strength and Disintegrationtime

In all the formulations, the compression pressure was directly related to tablet crushing strenght, compact density, tensile strength and disintegration time (Figures 23, 24, 25,29, 30, 31 32, 33, 34, 35. 36,and 37).

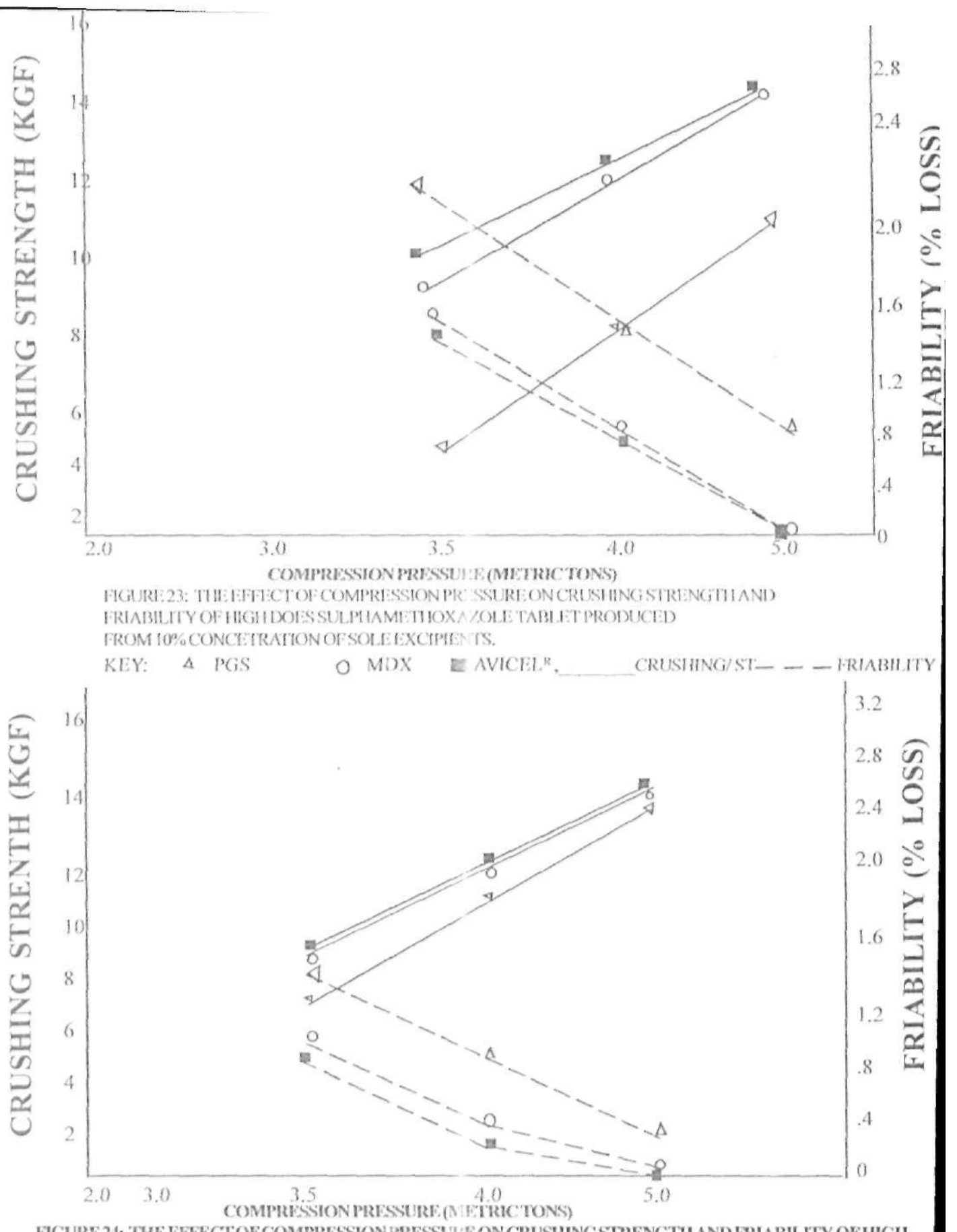


FIGURE 23: THE EFFECT OF COMPRESSION PRESSURE ON CRUSHING STRENGTH AND FRIABILITY OF HIGH DOES SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL^R, _____ CRUSHING/ST— — — FRIABILITY

FIGURE 24: THE EFFECT OF COMPRESSION PRESSURE ON CRUSHING STRENGTH AND FRIABILITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 20% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL^R, _____ CRUSHING/ST, — — — FRIABILITY

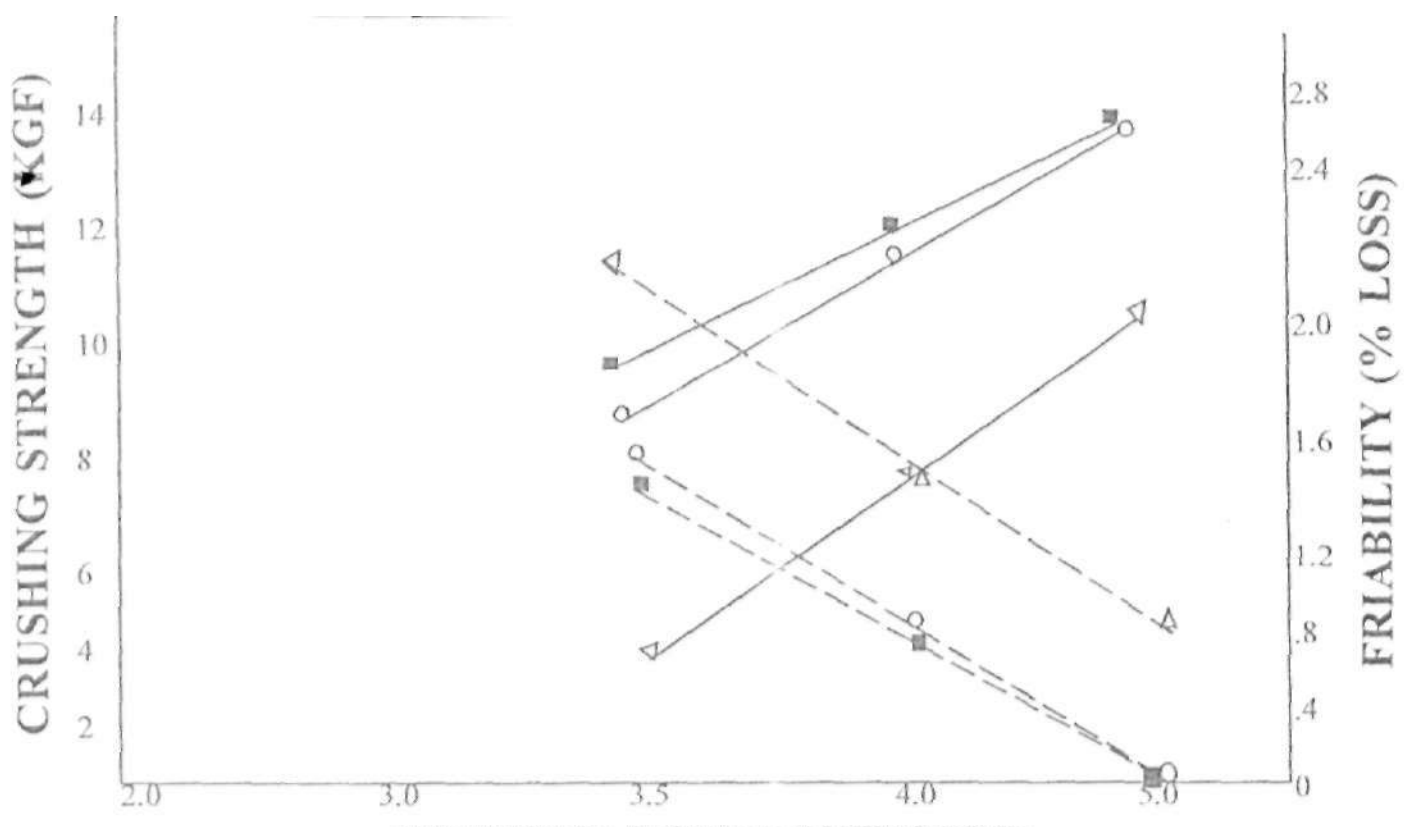


FIGURE 25: THE EFFECT OF COMPRESSION PRESSURE ON CRUSHING STRENGTH AND FRIABILITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED *FROM 30% CONCETRATION OF SOLE EXCIPIENTS.*

KEY: △ PGS ○ MDX ■ AVICEL®

_____ CRUSHING STRENGTH

– – – – – – – – – FRIABILITY

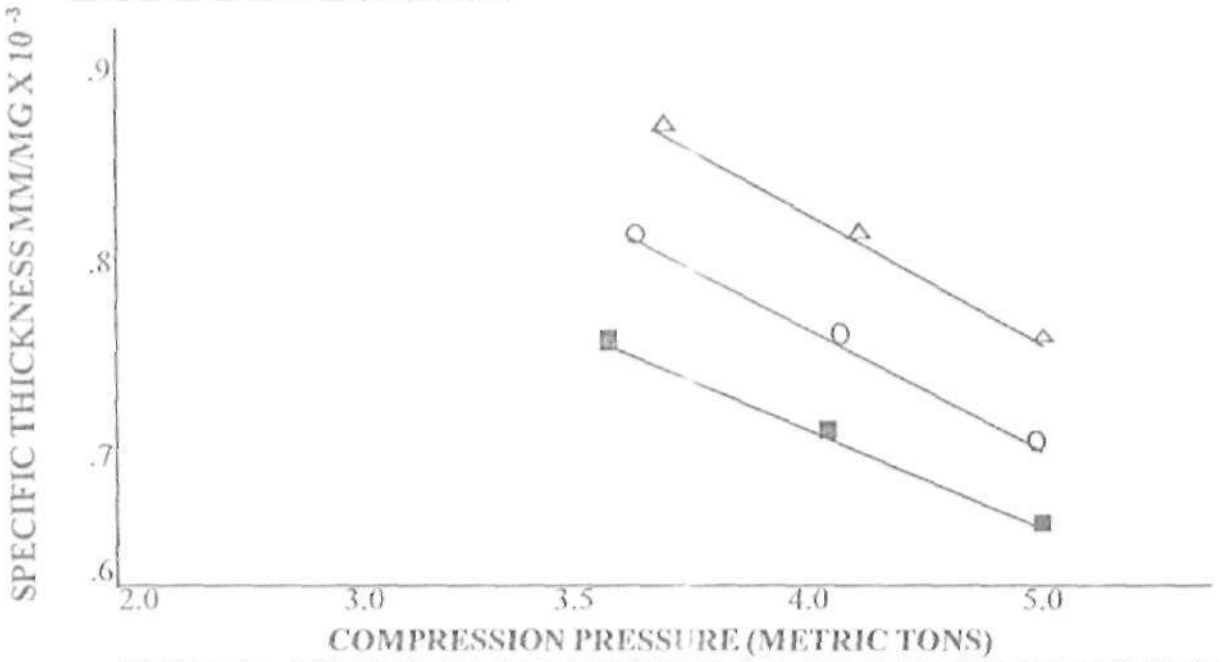


FIGURE 26: THE EFFECT OF COMPRESSION PRESSURE ON SPECIFIC THICKNESS OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL®

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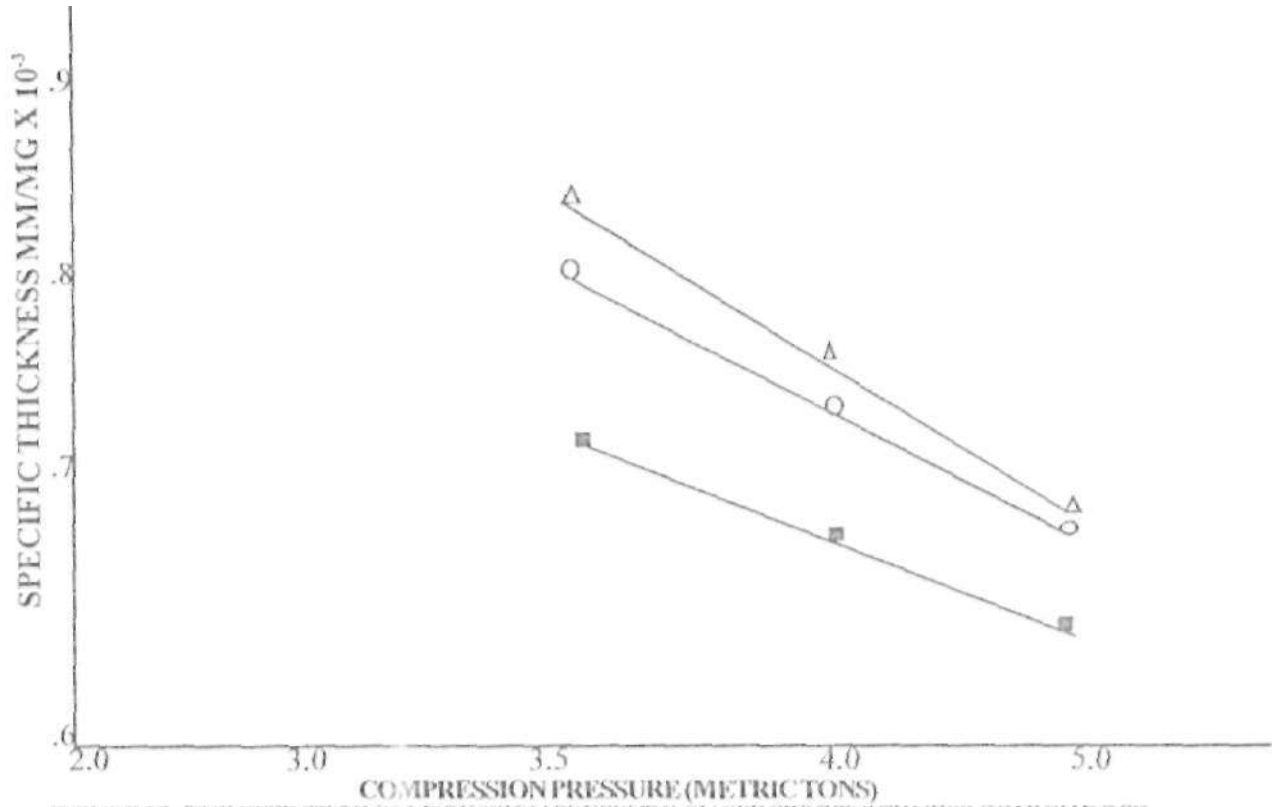


FIGURE 27: THE EFFECT OF COMPRESSION PRESSURE ON SPECIFIC THICKNESS OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 20% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]

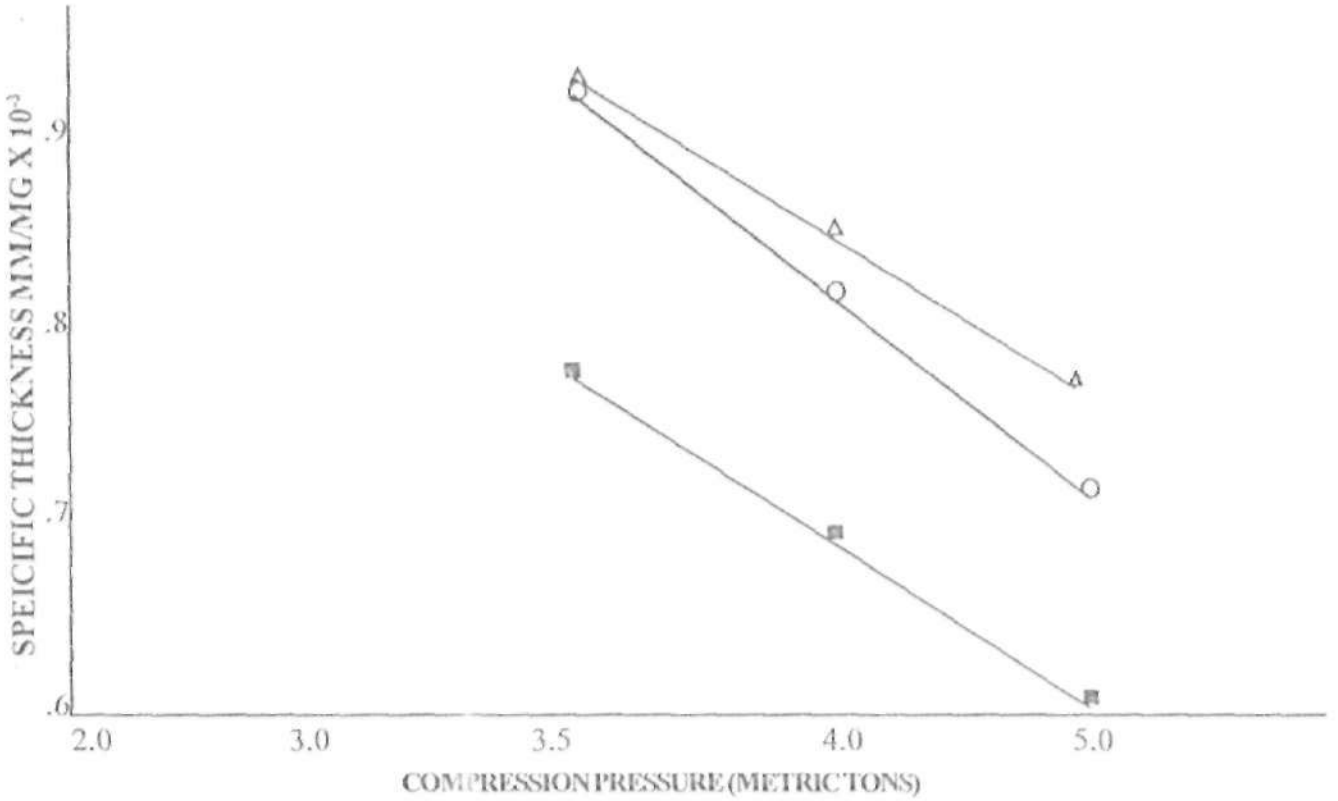


FIGURE 28: THE EFFECT OF COMPRESSION PRESSURE ON SPECIFIC THICKNESS OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 30% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]

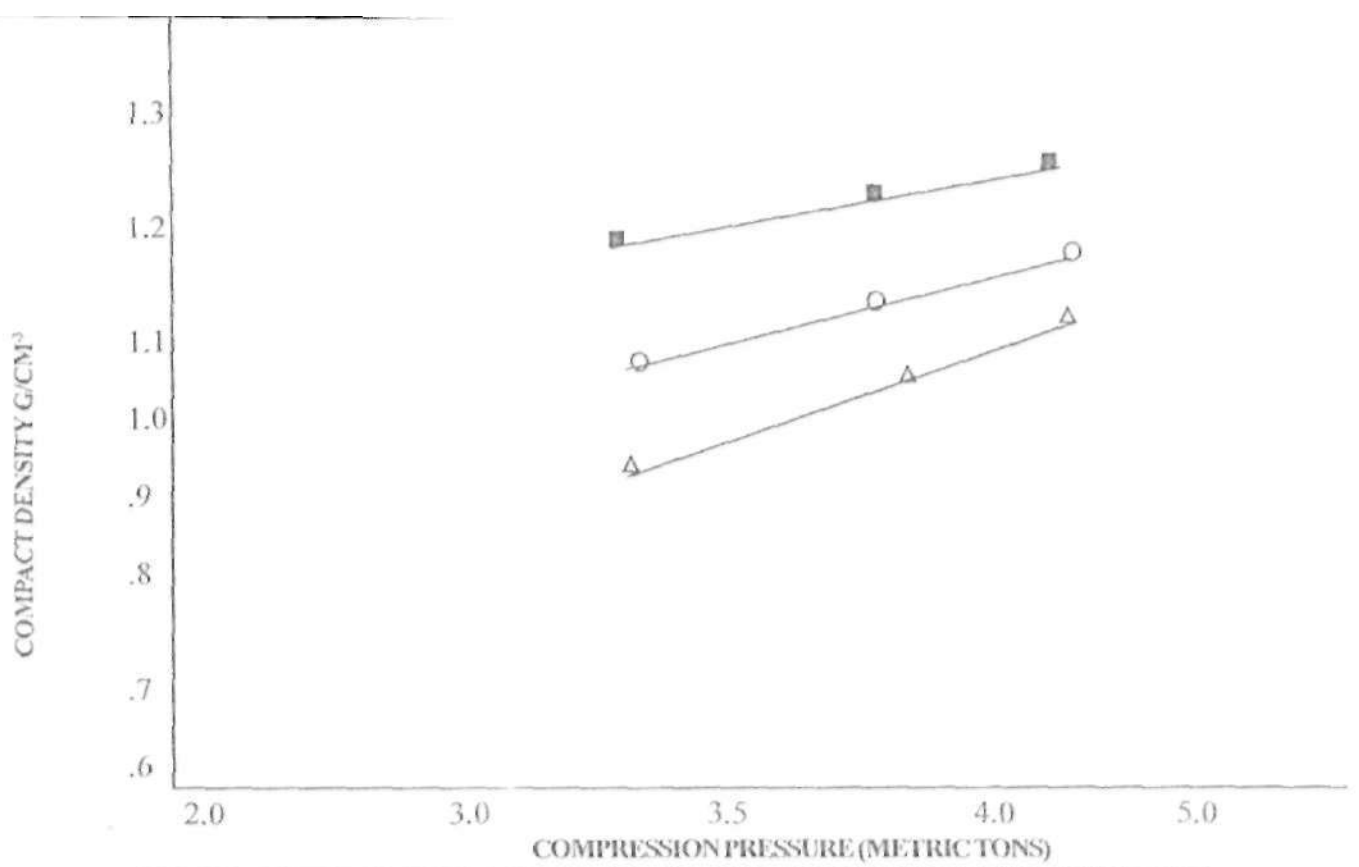


FIGURE 29: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL®

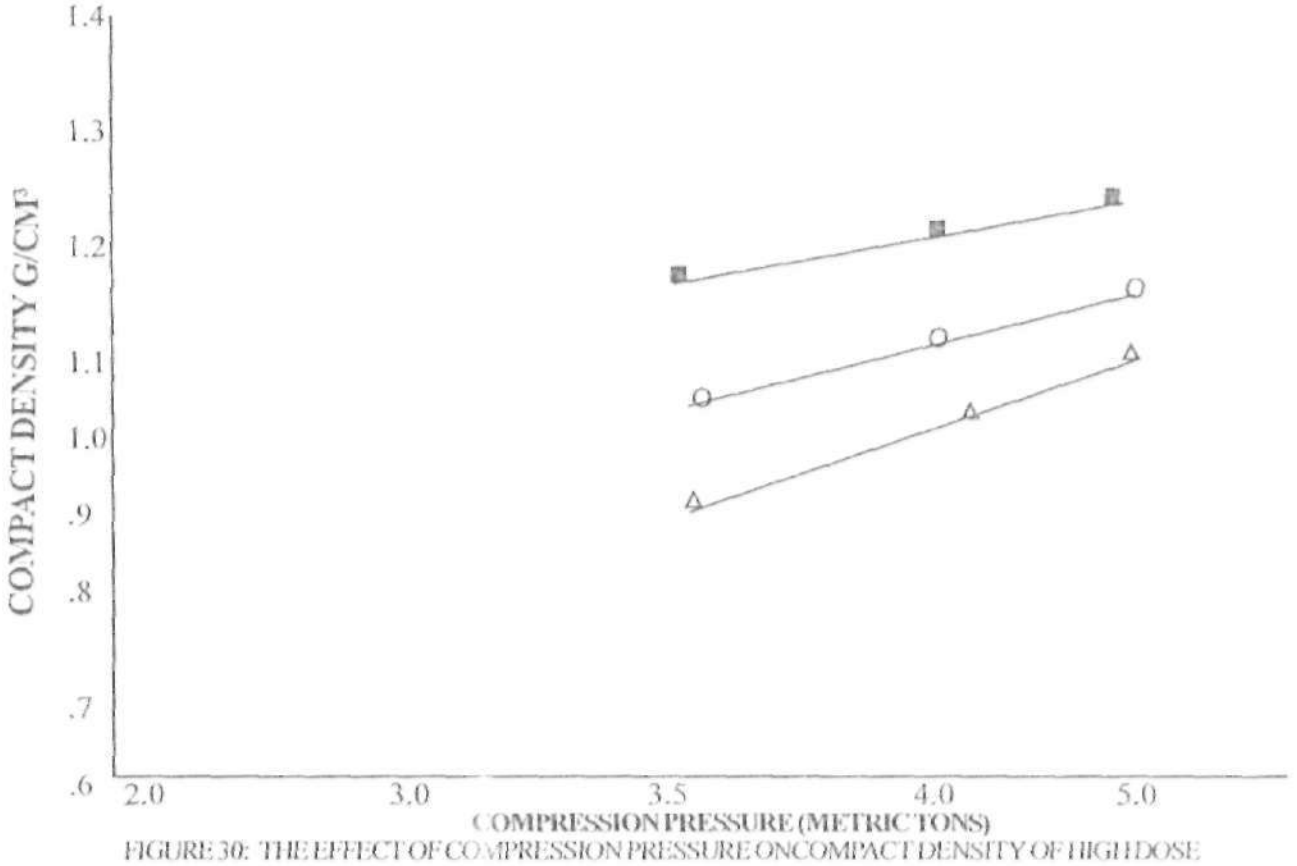


FIGURE 30: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 20% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL®

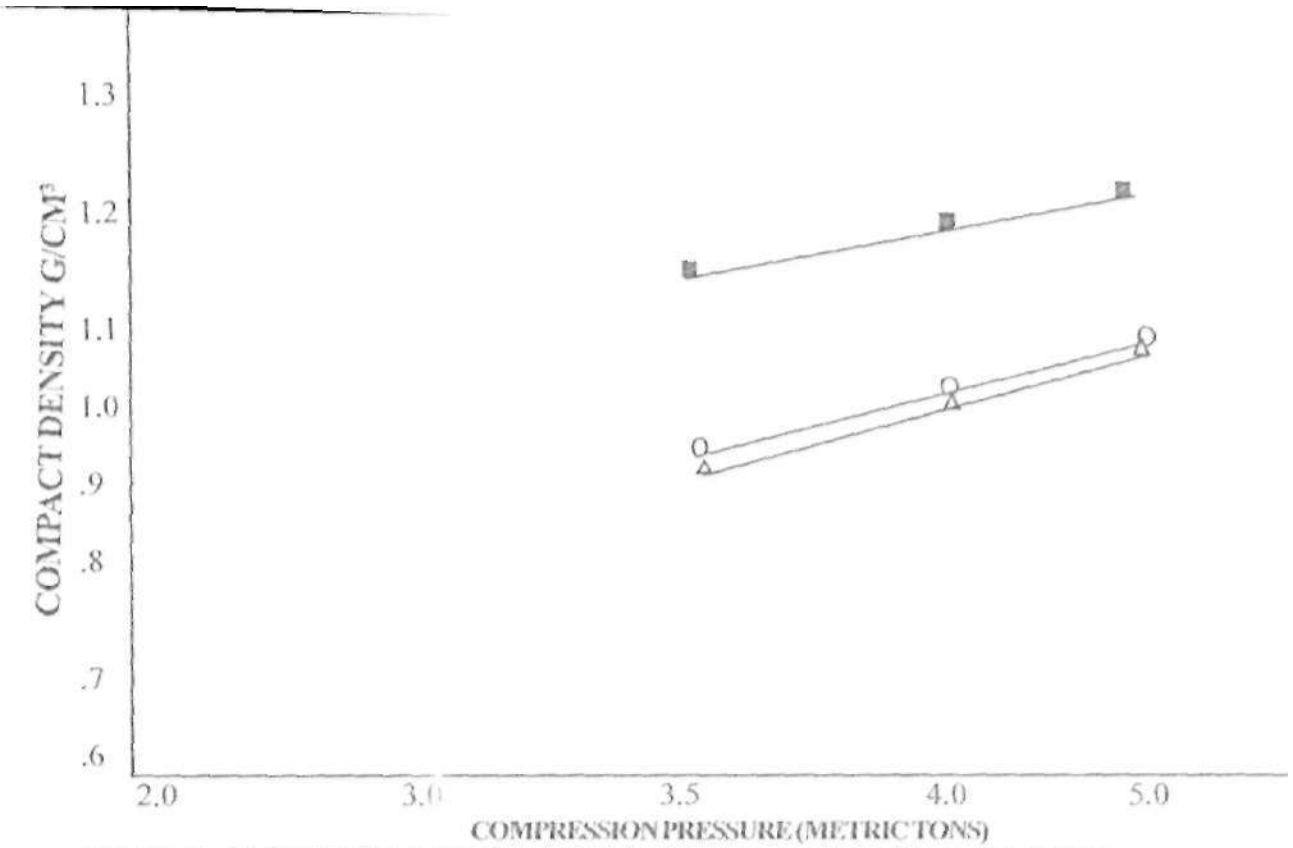
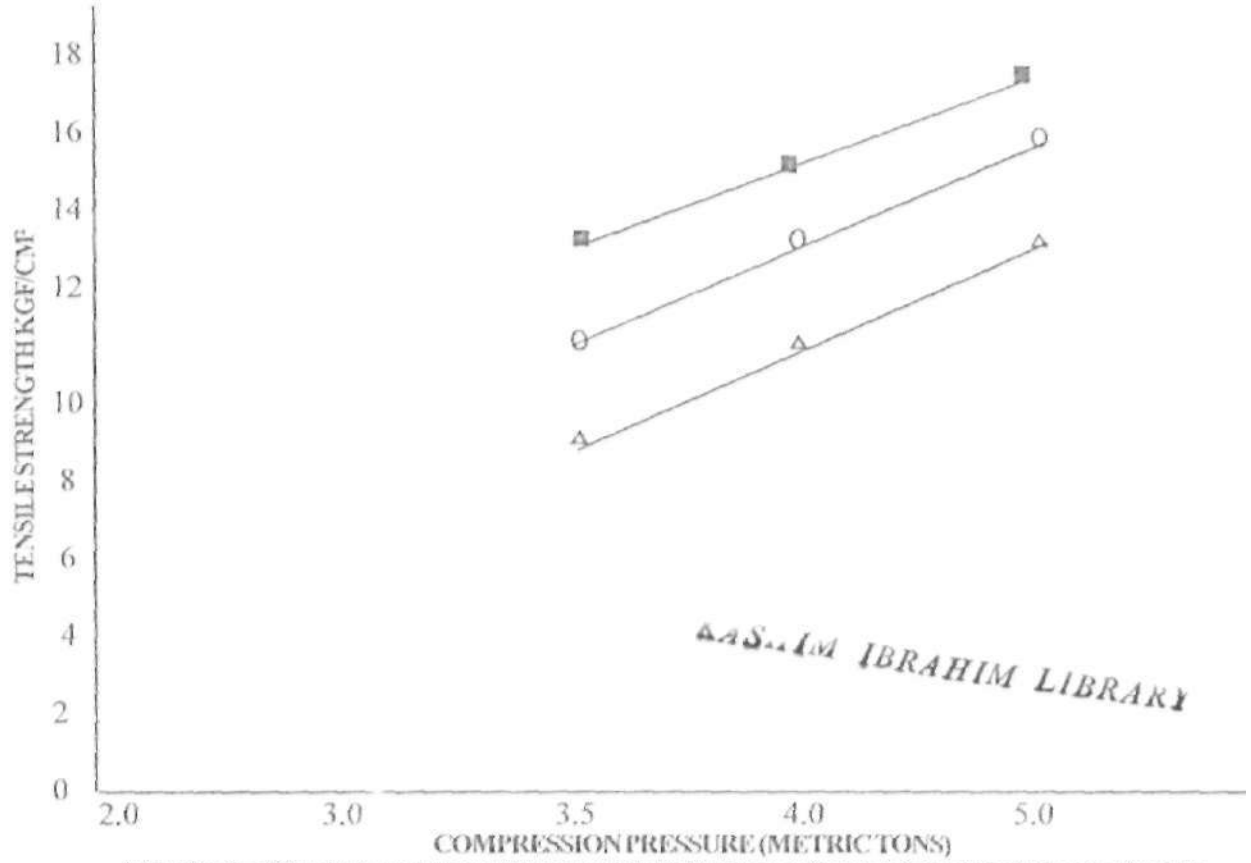


FIGURE 31: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 30% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]



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FIGURE 32: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]

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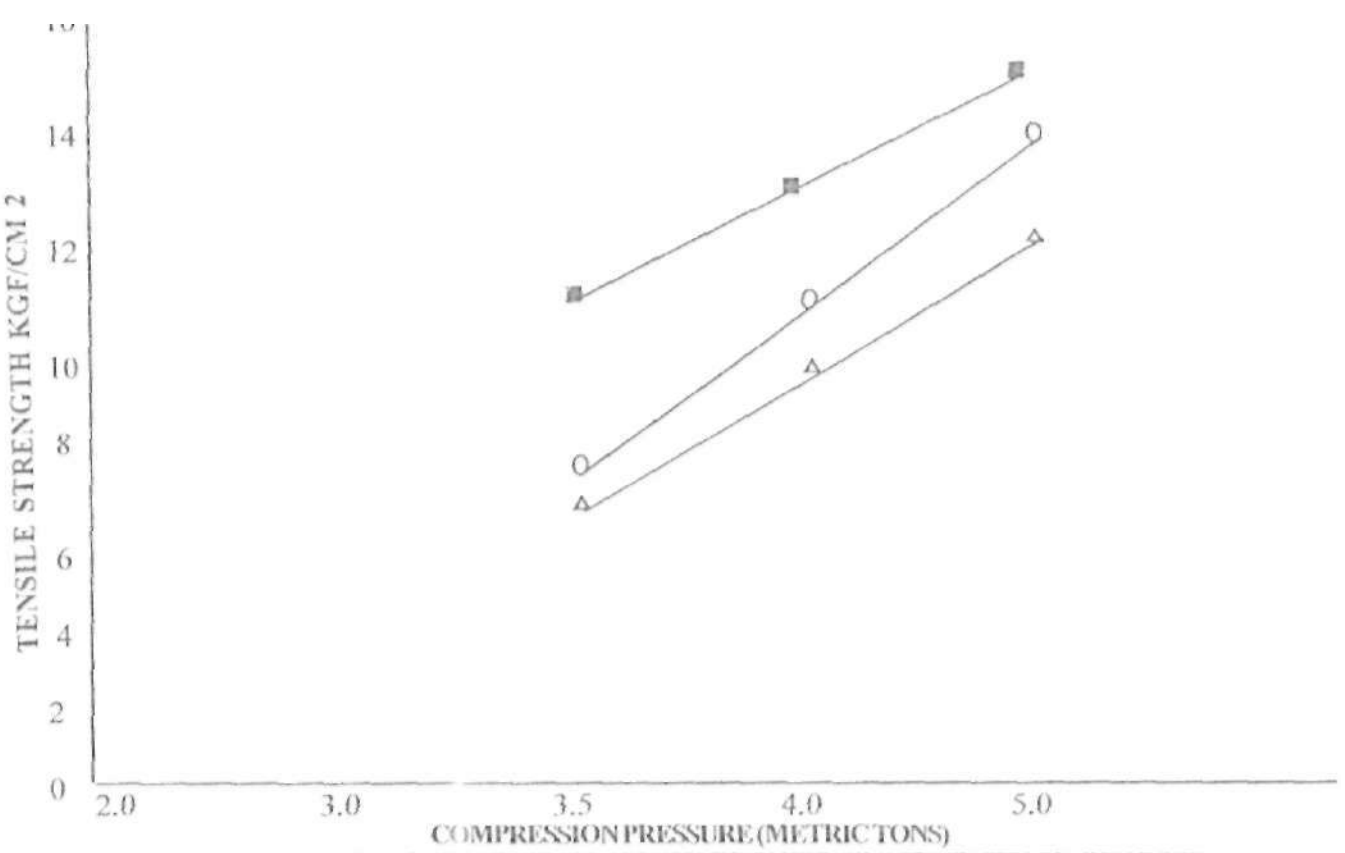


FIGURE 33: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 20% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]

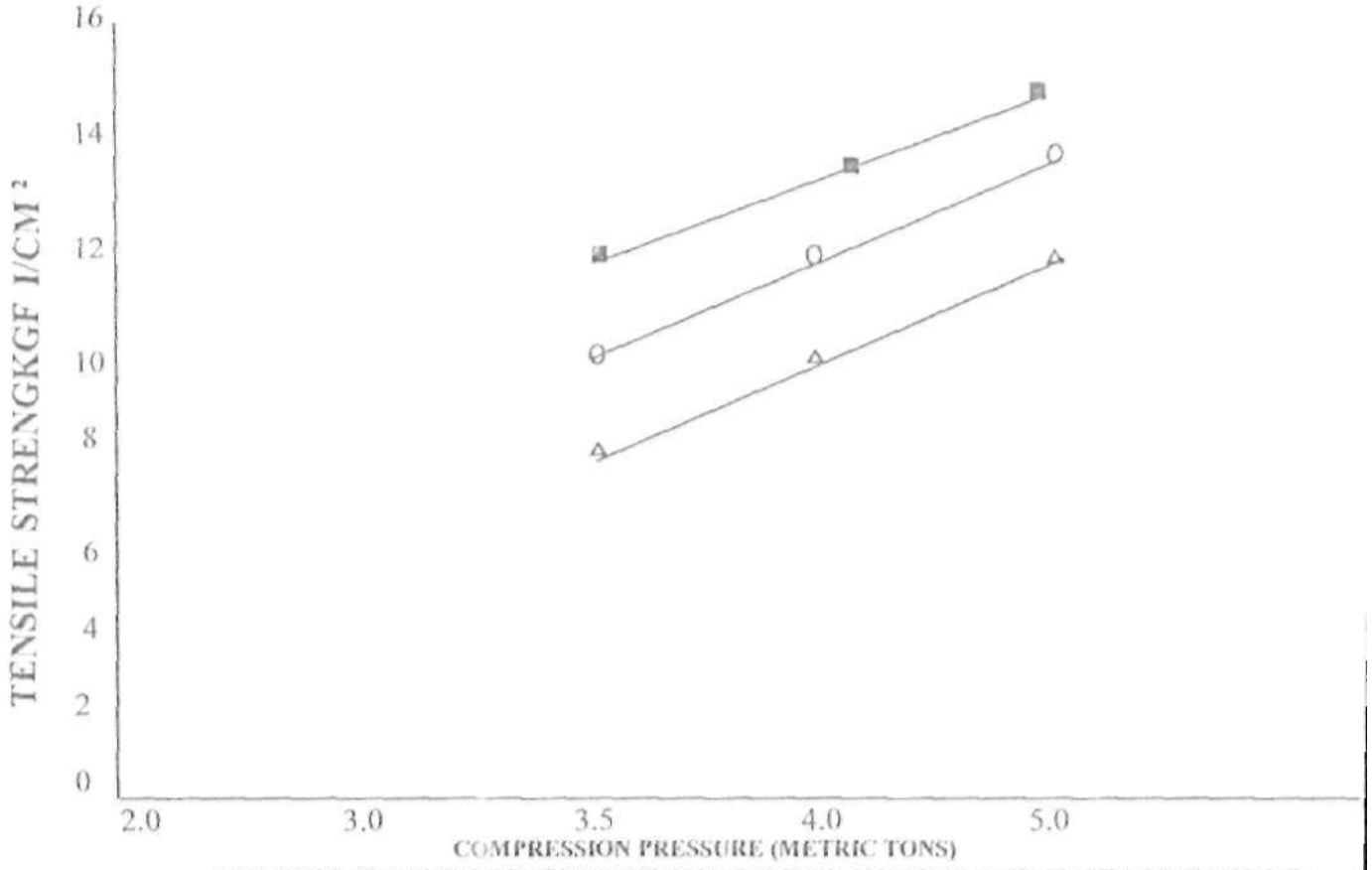


FIGURE 34: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 30% CONCETRATION OF SOLE EXCIPIENTS.

KEY: △ PGS ○ MDX ■ AVICEL[R]

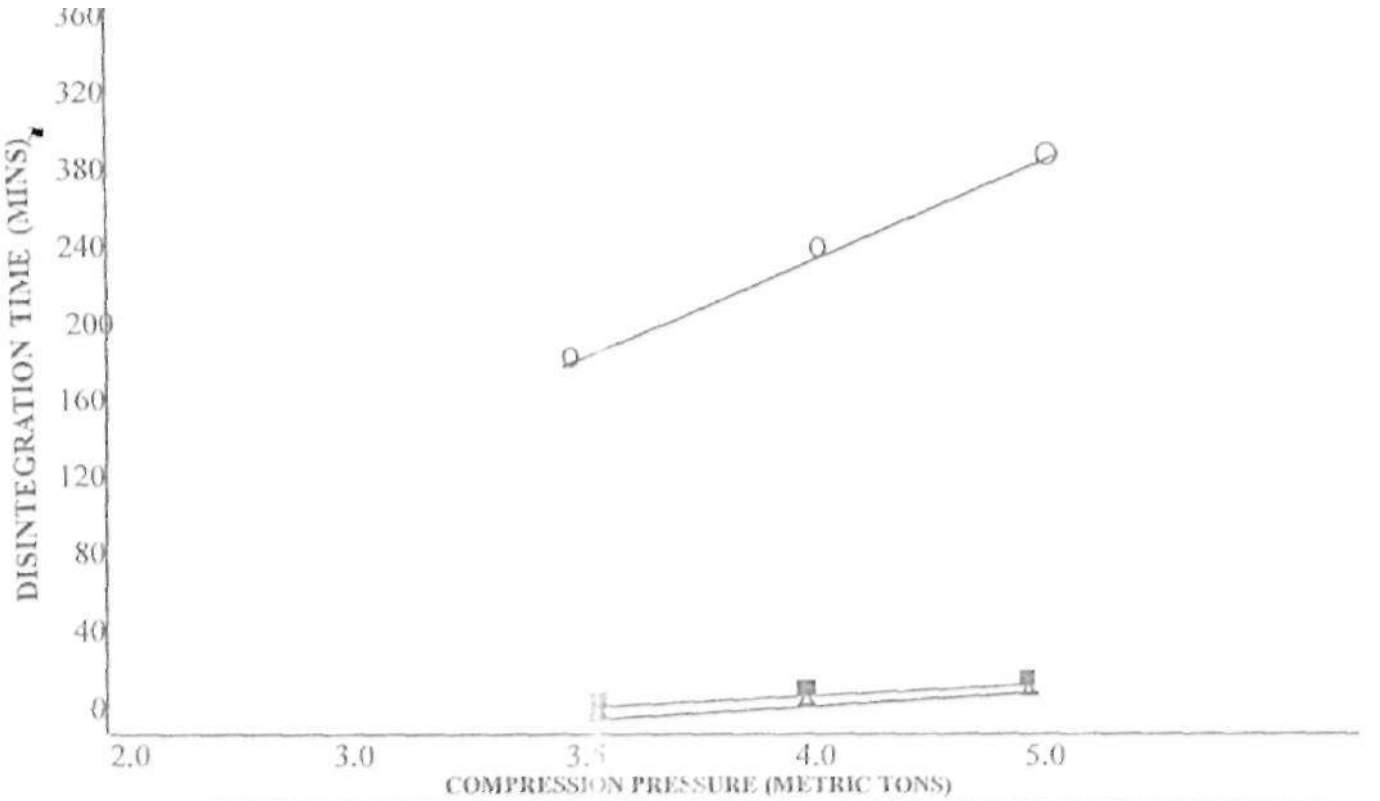


FIGURE 35: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 10% CONCETRATION OF SOLE EXCIPIENTS.

KEY: Δ PGS O MDX ▩ AVICEL®

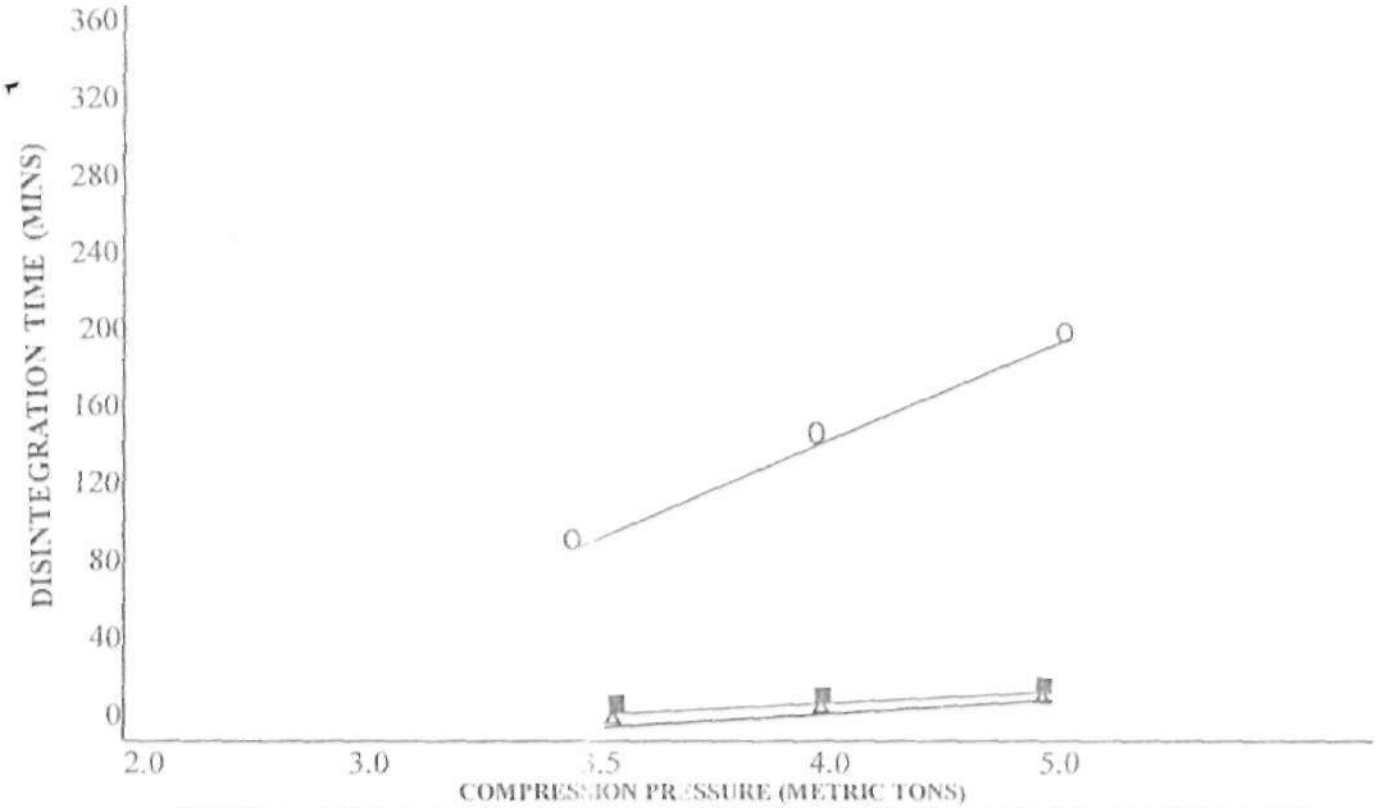


FIGURE 36: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 20% CONCETRATION OF SOLE EXCIPIENTS.

KEY: Δ PGS O MDX ▩ AVICEL®

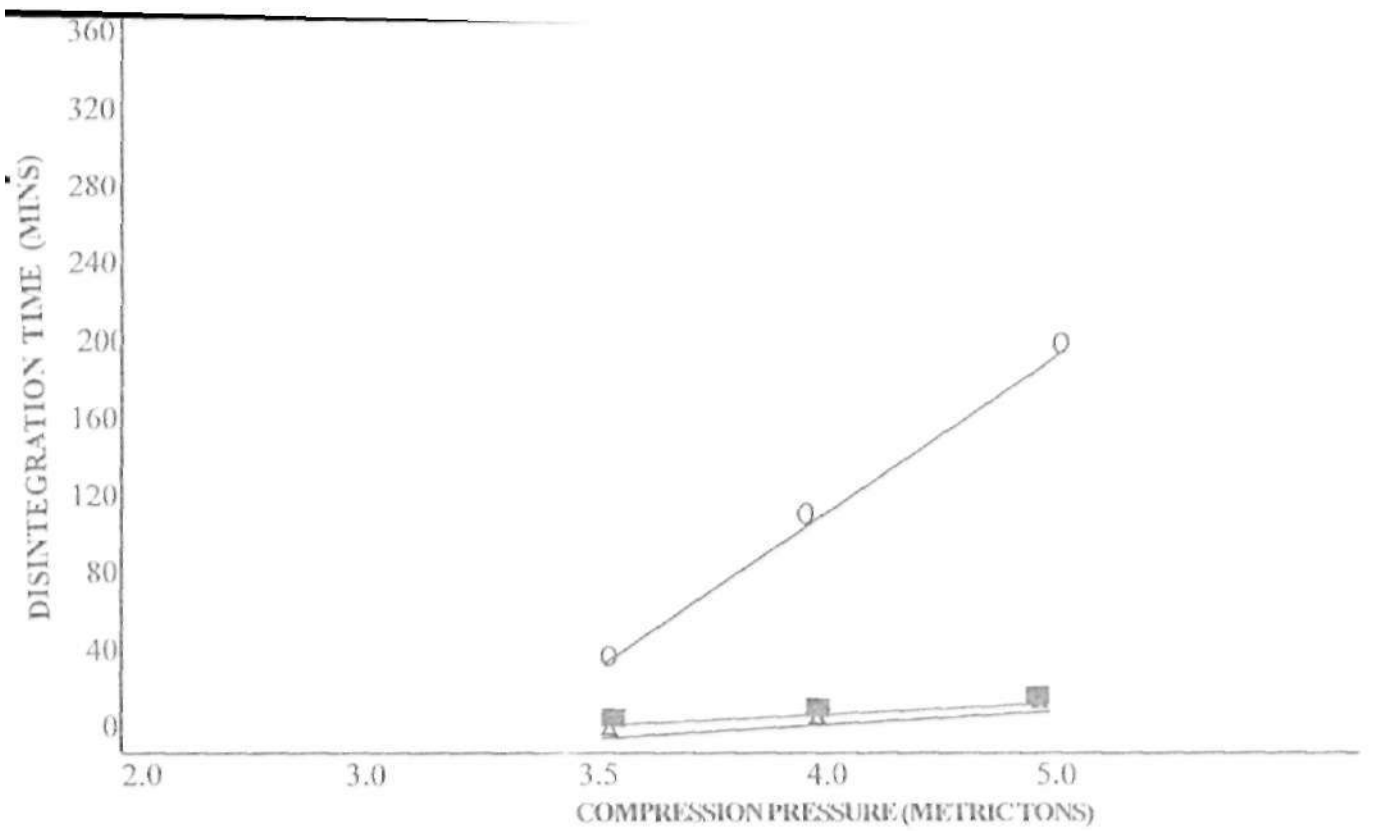


FIGURE 37: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM 30% CONCETRATION OF SOLE EXCIPIENTS.

KEY: Δ PGS O MDX ■ AVICEL[R]

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3.4 THE EFFECT OF COMPRESSION PRESSURE ON PROPERTIES OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET METHOD

TABLE 9: THE EFFECT OF COMPRESSION PRESSURE ON PROPERTIES OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET METHOD

ablet oper-ies	Weight and variations mg ±%			Thickness mm			Crushing strenght Kgl			Friability % Loss			Compact Density g/cm³			Tensile Strength KGF/cm²			Disintegration time (mins)		
	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0
tato ch	75.0 ±5%	75.0 ±5%	75.0 ±5%	3.2	3.0	2.85	2.5	4.5	7.0	1.3	0.7	0.2	.99	1.05	1.11	9.1	17.1	28.40	1.0	2.0	3.4
gela-sed	75.0 ±5%	75.0 ±5%	75.0 ±5%	3.0	2.9	2.8	2.8	5.0	8.0	1.0	0.4	.04	1.05	1.08	1.13	10.8	19.90	33.0	2.5	7.0	11
llo-tin	75.0 ±5%	75.0 ±5%	75.0 ±5%	2.7	2.6	2.5	3.2	6.0	10	0.8	0.5	0.0	1.17	1.21	1.26	13.7	26.7	46.3	7.0	10	25

3.4.1 Weight and Weight Variation

There were no significant differences in weight ($P \leq 0.05$). All were within ±0.9%.(As shown in Table 9).

3.4.2 Thickness and Friability

Increased in compression pressure decreased the thickness and also decreased the friability i.e they are inversely related to the compression pressure (Figures 40, & 41).

3.4.3 Crushing strenght, Compact Density, Tensile Strength and Disintegration Time

In all the formulation, the compression pressure was directly related to the tablet Crushing strenght, compact density, tensile strength and the disintegration time (Figures 41, 42, 43,and 44).

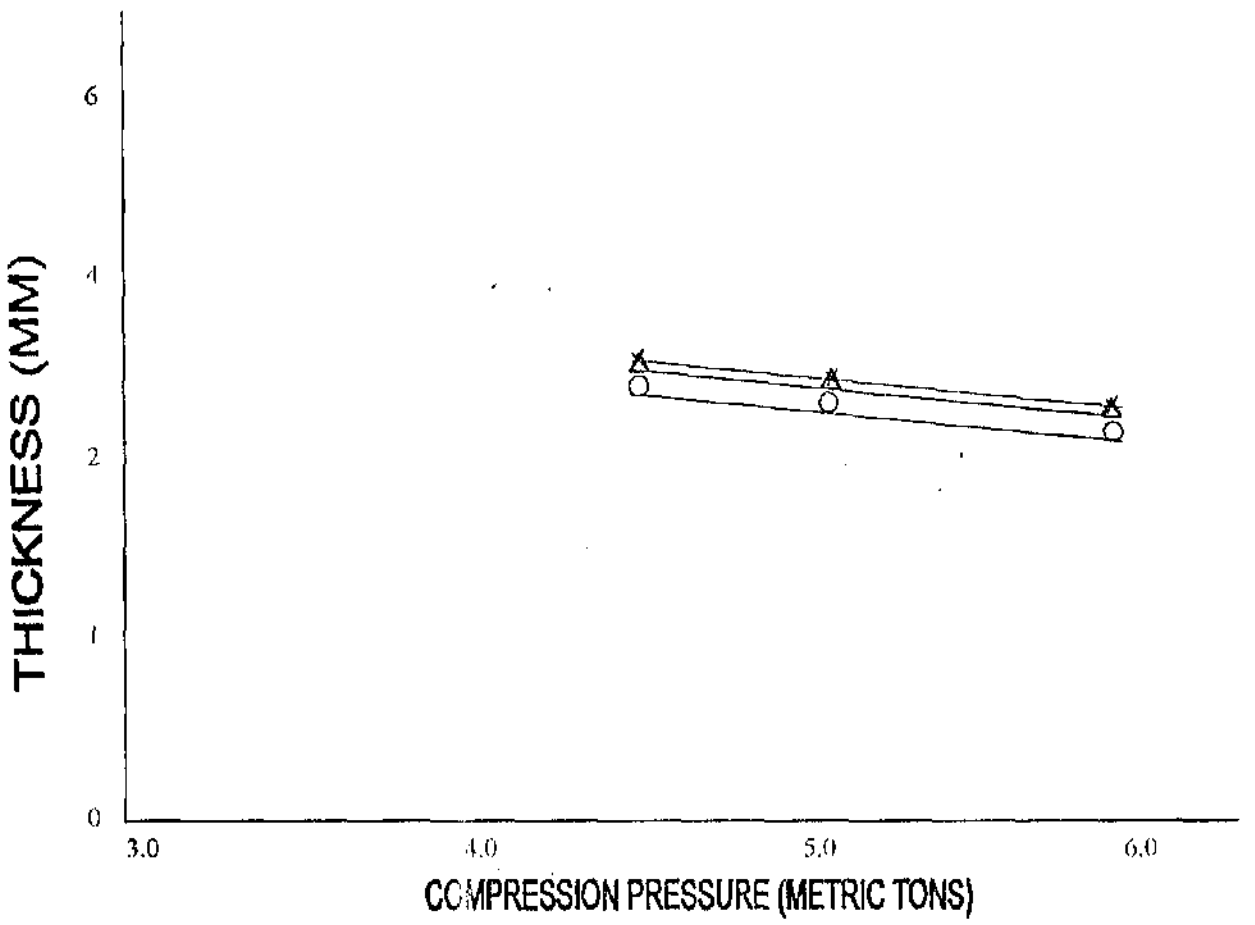


FIGURE 40: THE EFFECT OF COMPRESSION PRESSURE ON THICKNESS OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD.

KEY:

X PTS

△ PGS

○ MDX

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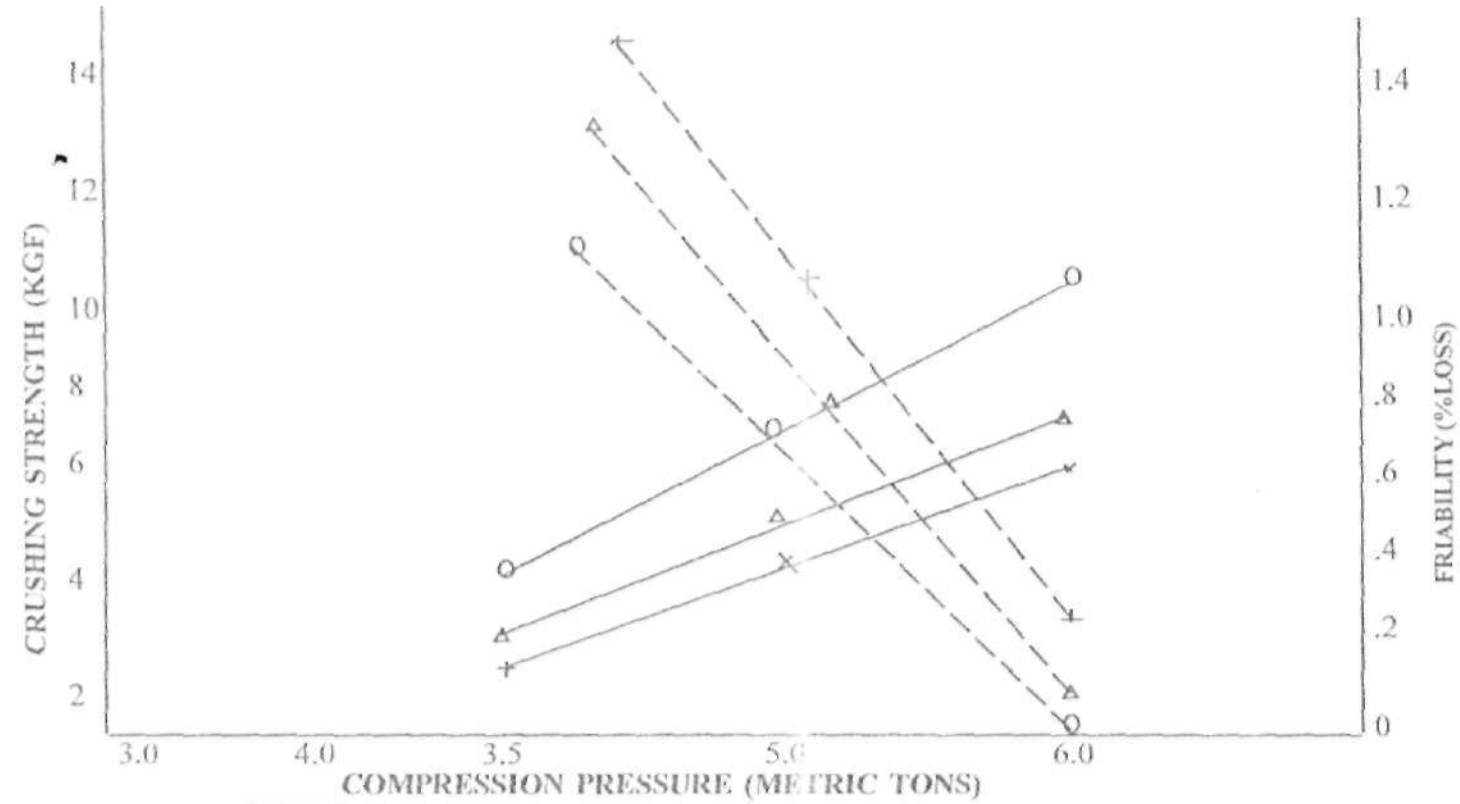


FIGURE 41: THE EFFECT OF COMPRESSION PRESSURE ON CRUSHING STENGTH AND FRIABILITY OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX _____CRUSHING/ST – – – –FRIABILITY

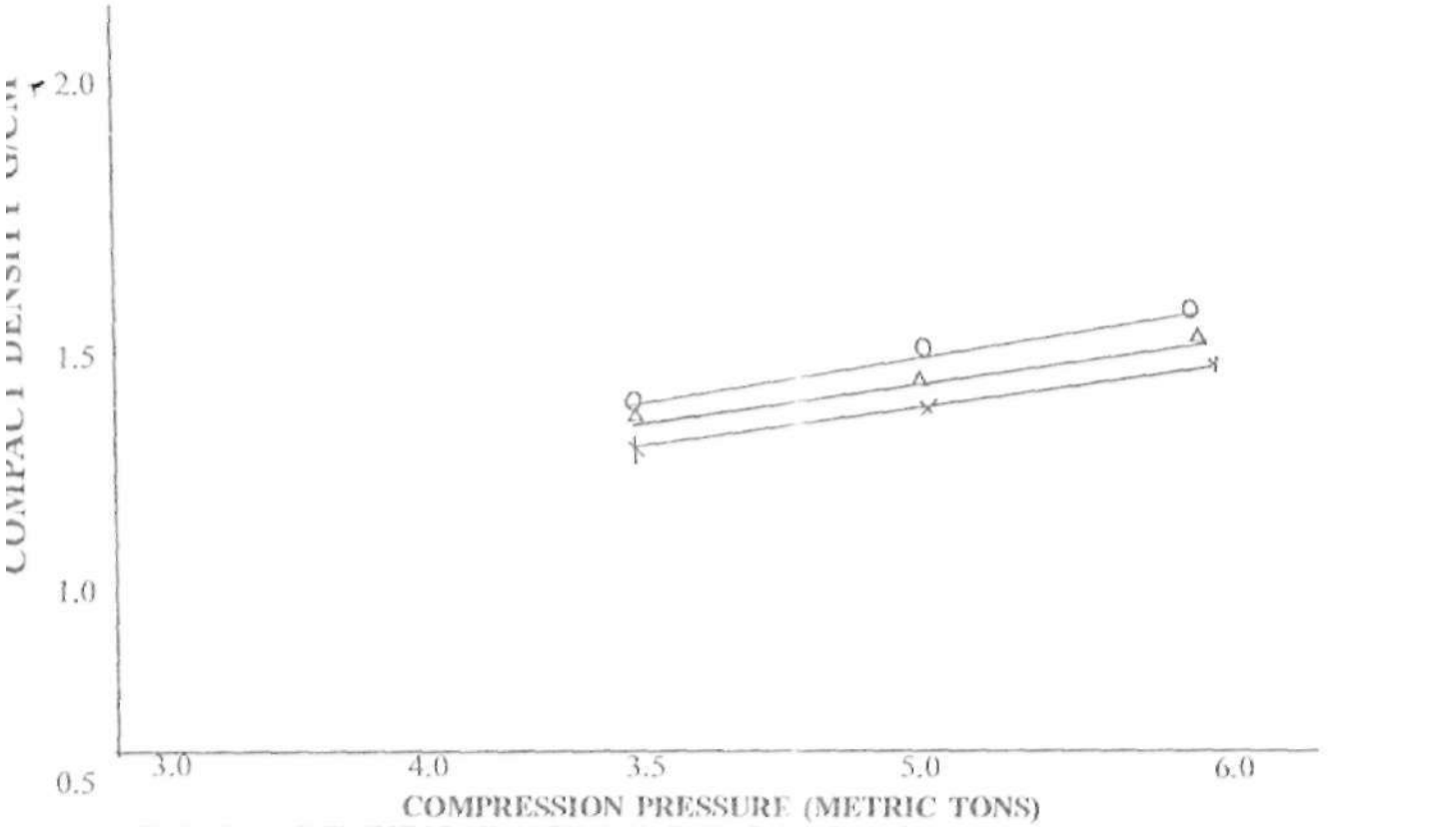


FIGURE 42: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX

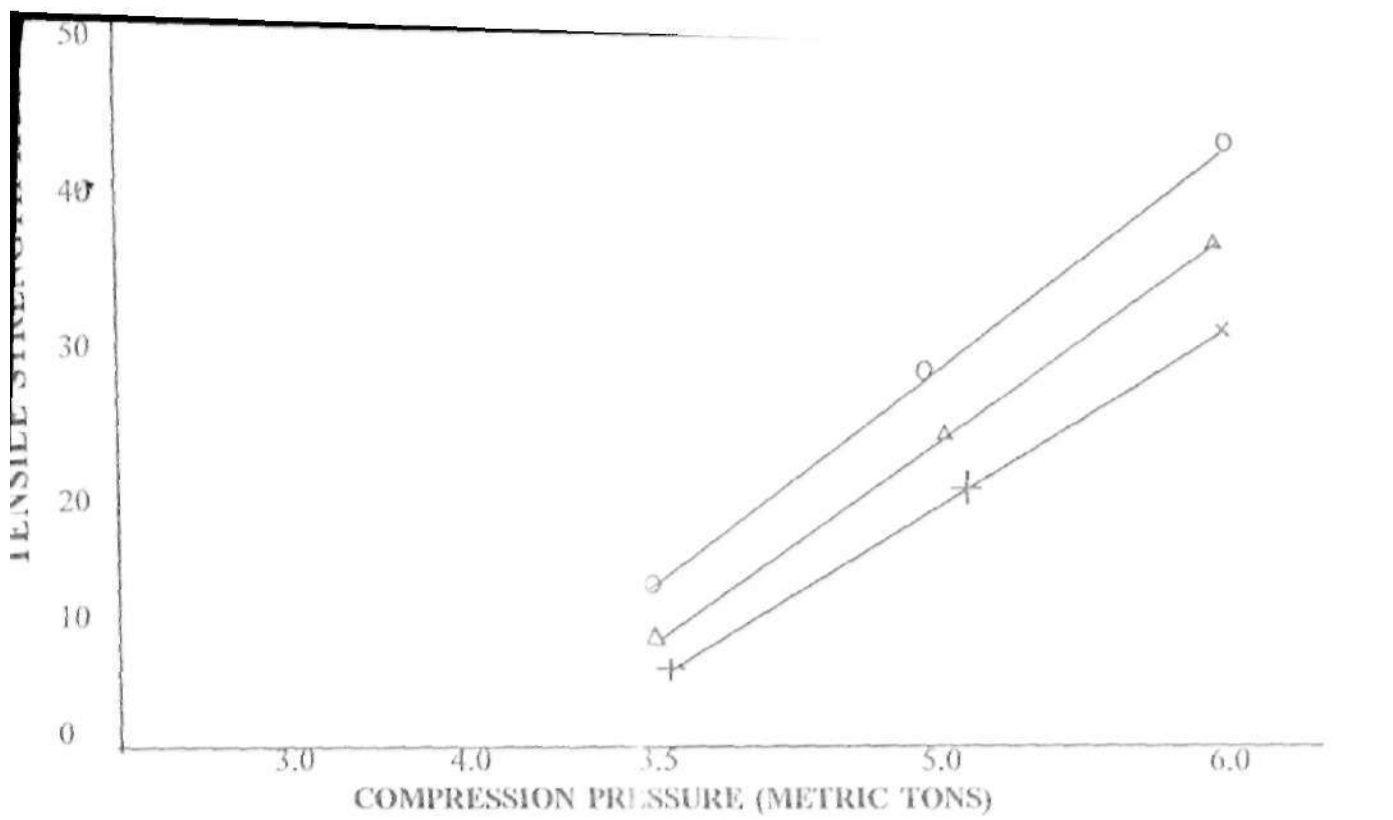


FIGURE 43: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX

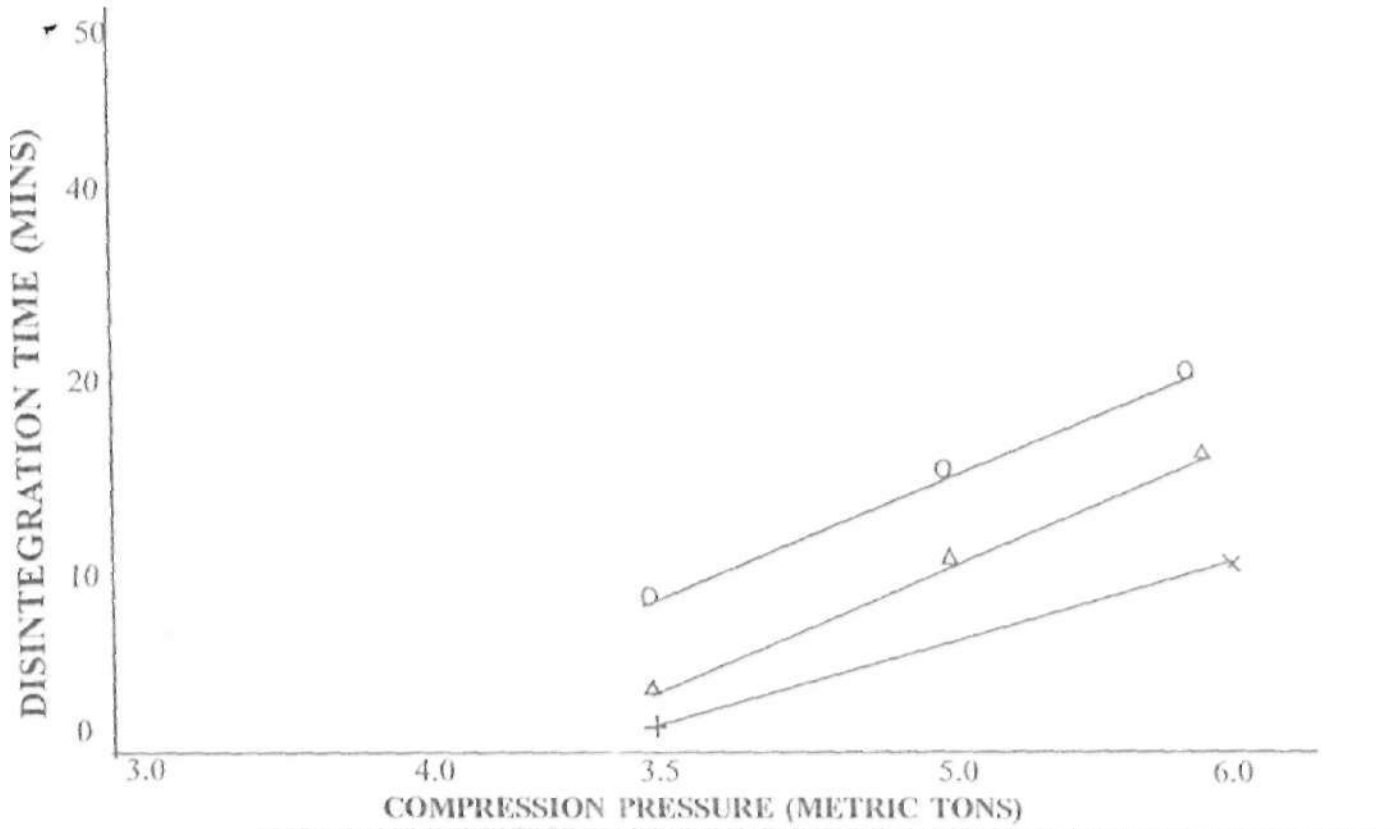


FIGURE 44: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF LOW DOSE FOLIC ACID TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX

3.5 THE EXCIPIENT PROPERTES OF POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN IN SULPHAMETHOXAZOLE TABLETS BY WET METHOD.

TABLE 10: THE EFFECT OF COMPRESSION PRESSURE ON PROPERTIES OF HIGH DOSE SULPHAMETHOXAZOLE TABLETS PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET METHOD

Tablet Properties	Weight and variations mg 1%			Specific Thickness mm			Hardness KgF			Friability % Loss			Compact Density g/cm3			Tensile Strength KGF/cm^2			Disintegration time (mins)		
	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0	4.5	5.0	6.0
Potato	614	614	614 10.5%	.81	.80	.70	3.5	8.3	13	1.0	0.5	0.1	.99	1.02	1.17	3.6	9.0	17.0	2.0	8.0	10.0
Pregelatinised starch	614	614	614 10.4%	0.8	.72	.65	5.5	11	14	0.9	0.3	0.1	1.0 6	1.14	1.25	5.1	12.9	18	4.0	20	28
Maltodextrin	614	614	614 10.7%%	.78	0.65	.62	9	14	14.	0.4	0.0	0	1.1 4	1.26	1.32	9.6	18	>18	40	14.0	100

3.5.1 Weight and Weight Variation

There were no significant differences in weight ($P \leq 0.05$). All were within ± 0.9%.(see Table 10).

3.5.2 Specific Thickness and Friability

Increase in compression pressure decreased the specific thickness and also decreased the friability. That is, they are inversely related to the compression pressure (Figures 45, and 46).

3.5.3 *Crushing strenght, Compact Density, Tensile Strength and Disintegration Time*

In all the formulation, the compression pressure was directly related to the tablet crushing strenght, compact density, tensile strength and the disintegration time (Figures 46, 47, 48 and 49).

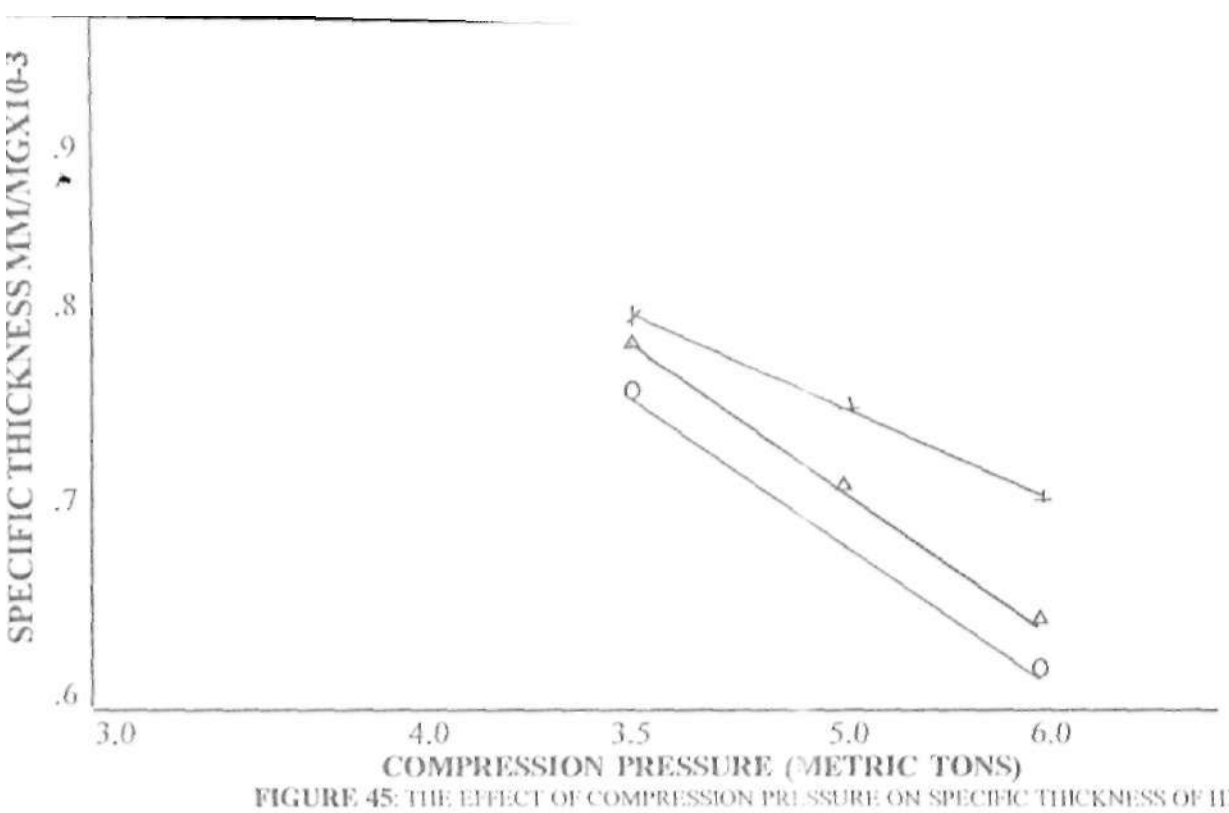


FIGURE 45: THE EFFECT OF COMPRESSION PRESSURE ON SPECIFIC THICKNESS OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX

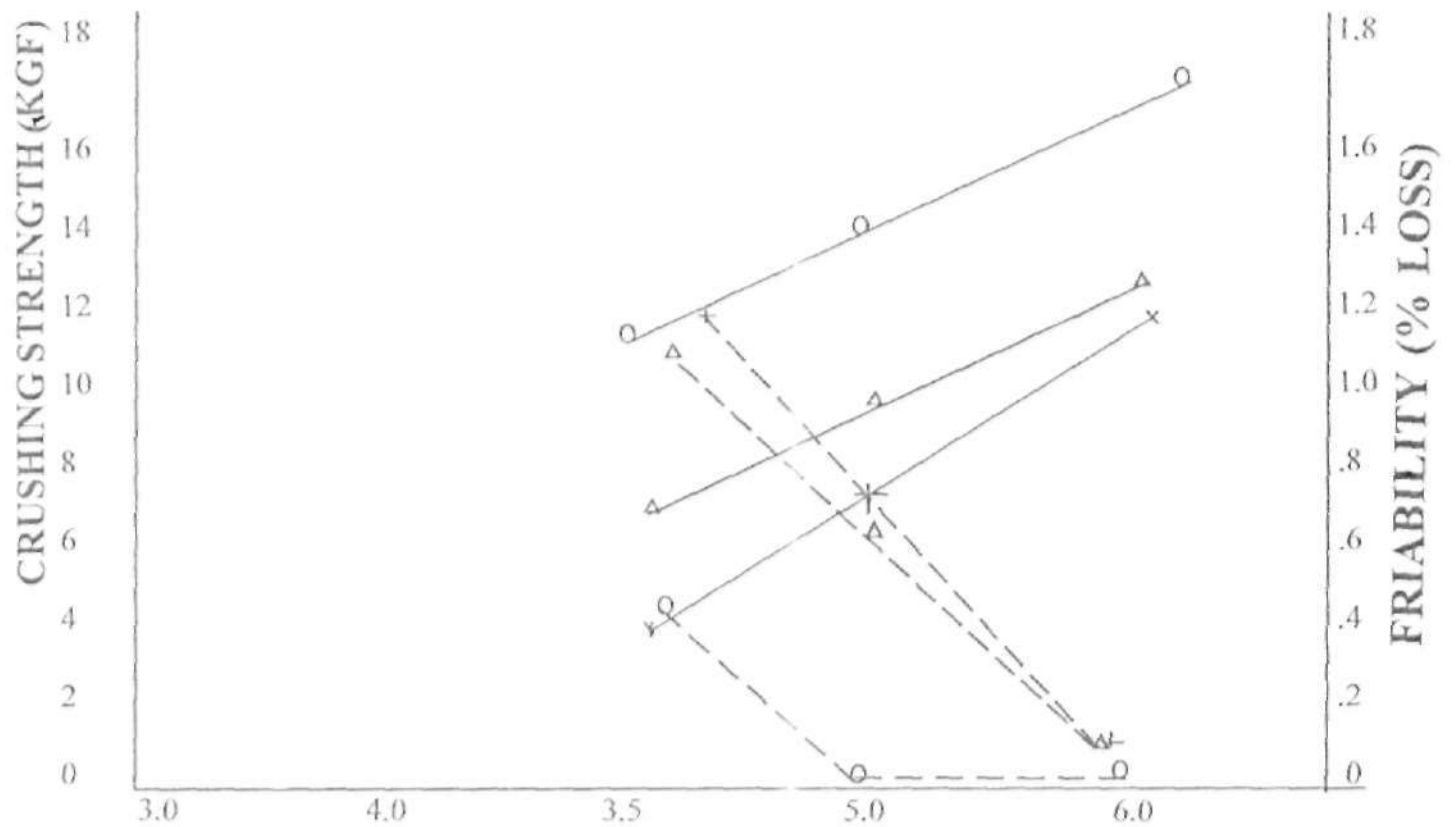


FIGURE 46: THE EFFECT OF COMPRESSION PRESSURE ON CRUSHING STRENGTH AND FRIABILITY OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS o MDX _____CRUSHING/ST — — — —FRIABILITY

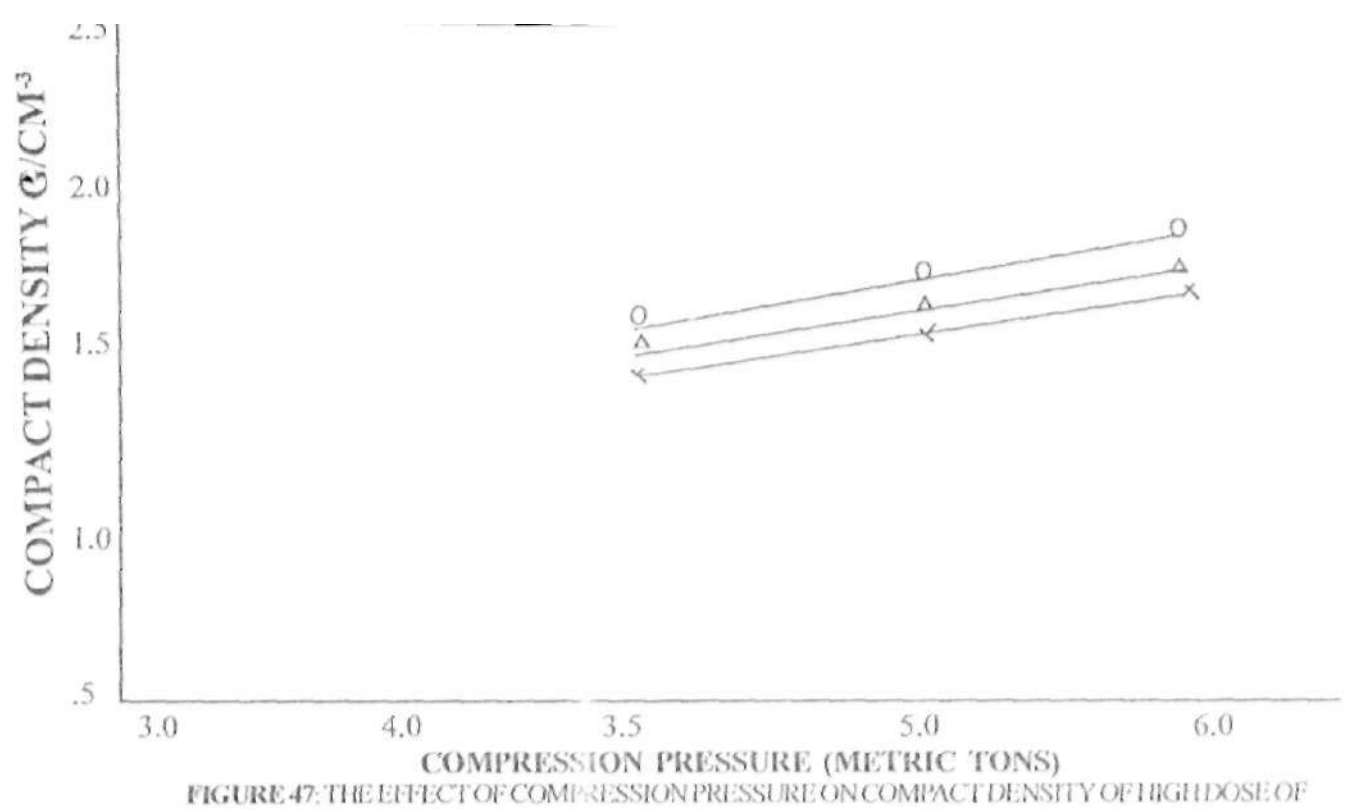


FIGURE 47: THE EFFECT OF COMPRESSION PRESSURE ON COMPACT DENSITY OF HIGH DOSE OF SULPHAMETHOXAZOLE TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS ○ MDX

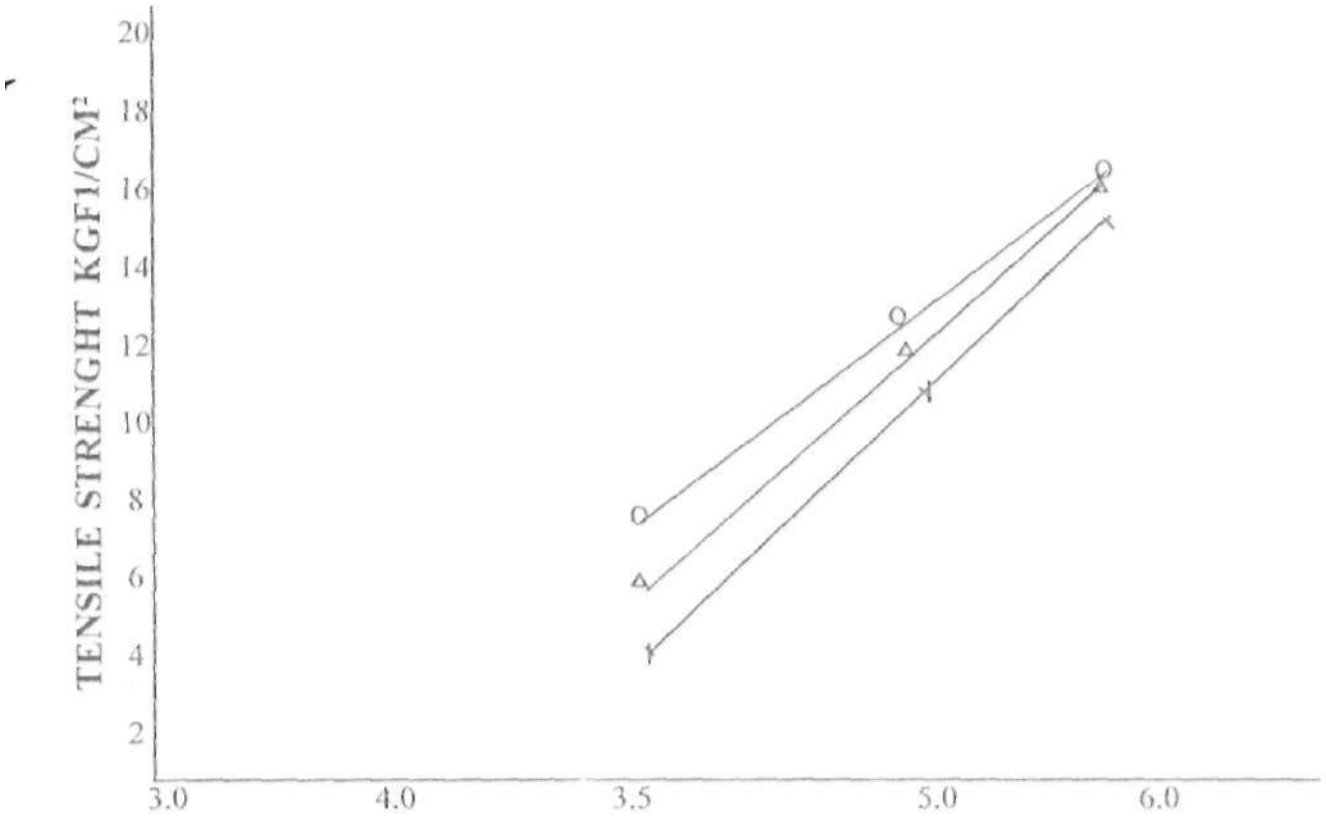


FIGURE 48: THE EFFECT OF COMPRESSION PRESSURE ON TENSILE STRENGTH OF HIGH DOSE SULPHAMETOXAZOLE TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH A MALTODEXTRIN BY WET GRANULATION METHOD

KEY: X PTS △ PGS ○ MDX

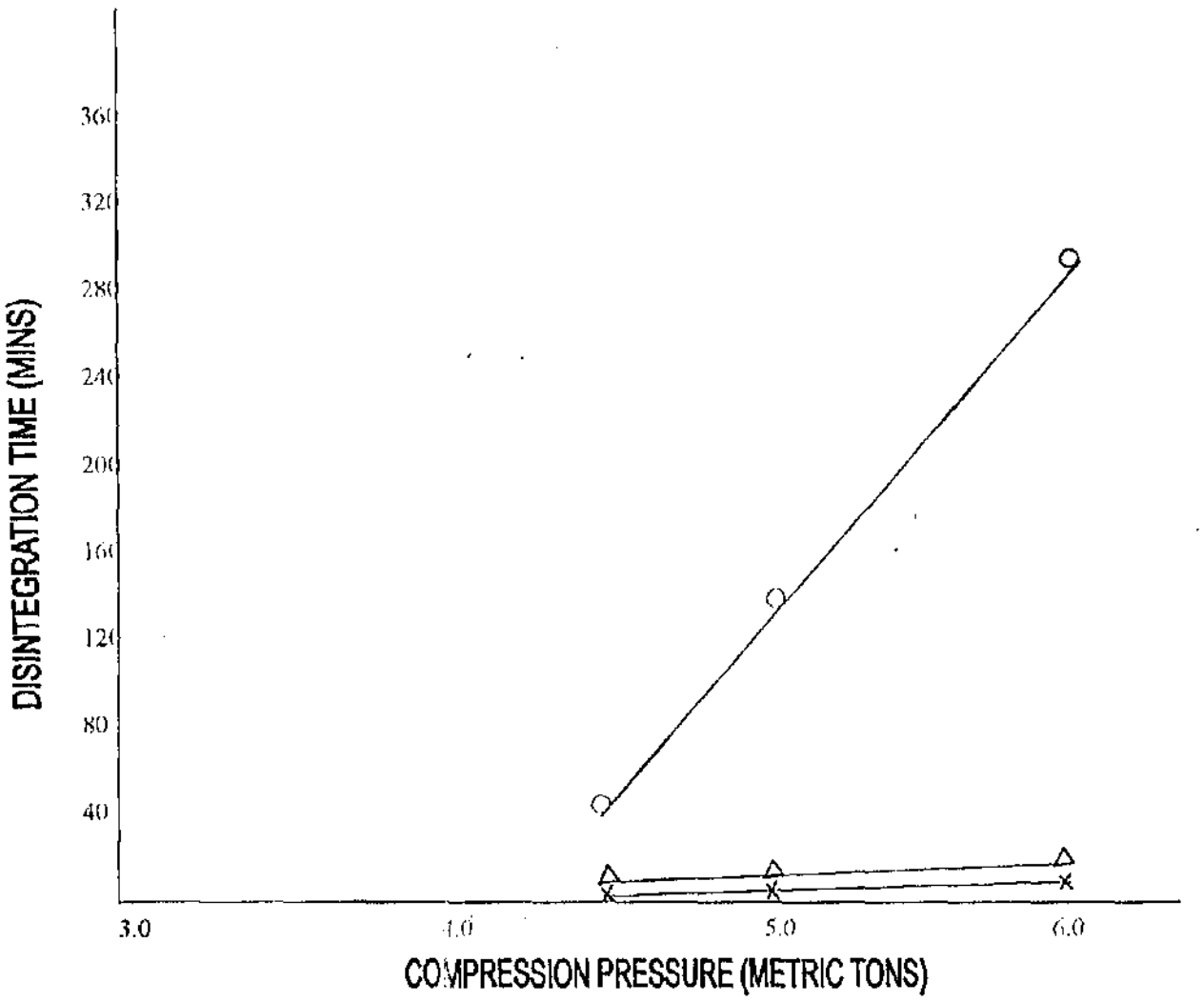


FIGURE 49: THE EFFECT OF COMPRESSION PRESSURE ON DISINTEGRATION TIME OF HIGH DOSE SULPHAMETHOXAZOLE TABLET PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET GRANULATION METHOD

KEY:

X PTS

△ PGS

○ MDX

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CHAPTER FOUR

4.0 DISCUSSIONS

4.1 PHYSIOCHEMICAL CHARACTERISTICS OF THE EXCIPIENTS

It was observed that the action of heat and acid had modified both the physical and chemical properties of the starch and it is actually a controlled hydrolysis. The physical properties of the modified products are mainly determined by the degree of starch hydrolysis. The degree of hydrolysis is affected by the duration of hot acid treatment. More uniform shapes and size reduced particles are produced upon hydrolysis.

Acid hydrolysis of the starch generally improve the flow rate. Increased duration of modification gave products with reduced friability value and increased hardness.

The degree of starch hydrolysis should be such that average particle size do not get to such a level to allow for excessive cohessive forces between particles which tend to retard flow rate.

Compressibility of the product depend on the degree of hydrolysis. The higher the deploymeration the better the cohesiveness of the tablet produced.

4.1.1 Gelatinization Temperature

Gelatinization is defined as the loss of the interference cross, visible within the granule under polarised light. Gelatinization temperature is that point at which this transition occurs, while each individual granule gelatinizes quite sharply, not all granules in a starch sample gelatinise at the same temperature but rather over a temperature range of 8 - 10 °C; Okafor et al, (1991).

This reflects the difference in the internal binding forces within the individual granules. The temperature of gelatinization indicates the strength of hydrogen bond formation within the starch granule or the amylose content of the starch. The stronger

the hydrogen bond or the amylose content, the higher will be the gelatinisation temperature. The gelatinization temperature of the potato starch is as shown in Figure 2.

The gelatinization temperature of potato starch was between 60 - 72 °C when subjected to the action of heat. When the aqueous suspension of starch is subjected to the influence of heat, it weakens the micellar network within the granules by disrupting the hydrogen bonds. The more the resistance to the influence of this heat, the higher the hydrogen bond (Blanshard; 1987). The higher the amylose content, the higher will be the gelatinization temperature (Sterling, 1978).

The differences in the proportion of gelatinized starch granules may be indicative of the differences in the physiochemical properties of the starch sample. For example, that of maize is between 63 - 68 °C and cocoyam between 75 - 83 °C (Okafor et al, 1991).

4.1.2 *Qualitative Analysis of Maltodextrin and Pregelatinised Starch by Paper* Chromatography

Chromatography which is defined as the techniques used for the separation and analysing the components of a mixture by a continuing distribution of the component between two phases, one which is moving past the other, the latter is called stationary phase and the former is called the mobile phase. The stationary and mobile phases were so chosen in a way that the solvents movement have a differential preference for another. The Reference Point (R_f) which is defined as the distance moved by the solutes to that moved by the solvent. The R_f values obtained were 0.18, 0.16 and 0.11 at 30 °C which were compared with the values in the literature which gave D-glucose, D-galactose and Maltose respectively.

These had shown that starch which is a polysaccharide can be broken down into their respective monosacharide units. The values obtained from both the prepared sample and the standard were compared and were found to be the same and this confirmed that the prepared sample was as pure as the standard. The R_F value depends on the composition of the developing solvent, types of paper used, direction of the paper (ascending, descending or circular), length of paper and the distance of the starting point from the solvent, concentration of the solvent, presence of other substances and the temperature at which it was developed.

4.1.3 Flow Properties

Modification of the potato starch yielded products with better flow properties compared to their unmodified form (Table 5). This was because more spherical shape of fine materials were produced. The ability of granules to flow properly is of immense importance during the tableting process.

Neuman, (1967) reported that the quality of a compressed tablet depended largely on a uniform flow of the material from hopper to the feed shoe and then into the die cavity. *Poor flowing powders could lead to variations in weight, hardness and* contents' uniformity of the tablets. The flow properties is dependent on particle size, shape, porosity, density and surface texture. Poor flow could result from the presence of moisture in which case drying the particles will reduce the cohesiveness. The flow order was MDX > PGS > PTS, possibily as a consequence of higher densification and smoother shape as the result on Table 5 shows.

4.1.4 Carr's Index

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

Compressibility is a measure of the ability of the material to reduce in volume under pressure and it is affected by the type of the material. Carr's index is affected by the characteristics of the individual particles and particle shape, size and size distribution and the packing configuration. Low Carr's index could therefore equally imply a good initial packing arrangement with less voids.

The bulk density value depended on the method adopted for the measurement and the reproducibility of the method. Therefore bulk density is not sensitive enough for the determination of powder properties. When the bulk density of the modified products were compared, the bulk density increased with hydrolysis and this could be ascribed to more uniform size obtained with hydrolysis and also to the more spherical nature of the granules. This correlated with the work of Ridgway and Pupp (1969) who investigated the effect of particle shape on powder properties. They found that the bulk density and flowability decreased with increasing departure from spherical shape due to greater resistance to shear of flow of an assembly of irregular particles compared to an assembly of spherical particles of the same size. The order of flow were MDX > PGS > PTS.

4.1.5 Moisture Content

The result of the moisture content was in the following order: MDX > PGS > PTS (Table 5). It must be noted that the level of moisture content affect the quality of the tablet produced. High moisture content level in the granule affect the flow property of the granules which could affect some parameters of the tablets such as uniformity of weight and the content uniformity. Formulation scientists generally considered that 3% moisture content as the maximum if chemical stability of hydrolysable drug content in a solid dosage form is to be assured. However it is agreed that it is only the free (mobile) water fraction rather than the total water content of excipient that is important in chemical stability. These bound fractions do not induce hydrolysis (Okhamafe et al, 1991).

Since potato starch and the modified products are chemically stable with most drugs, it then means that most of the water are bound and not available for chemical reactions. However, the cohesiveness of the granules and hardness of the tablets are brought about by the hydrogen bonds and solid bridges formed by the moisture content. When the moisture content is very low, it results into excess fines which will increase the flow time of the powder due to smaller sizes. Where the cohesive forces between the particles become significant. This can also affect the hardness of the tablet, (Esezobo et al, 1976).

4.2 DIRECT COMPRESSION

Properties of binary mixtures from maltodextrin, pregelatinised starch and Avicel® and the effect of compression pressure on properties of low dose folic acid tablets are considered hereunder.

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4.2.1 Effect of Compression Pressure on (Sole) Excipients and 50:50 Binary Mixtures on Tablet Properties

The results have shown that tablets of desirable qualities could be made from the various binary mixtures depending on the compression pressure and the proportion of the mixtures used (Table 7A & B).

(a) **Weight and Weight Variation**

There were no significant differences within the tablet weight ($P \leq 0.05$). Table 7A & B).

Multistation rotary press machine is used for industrial production with large batch sizes which means the hopper is large. Vibrations of the machine causes the vibration of the hopper which leads to segregation of the granules according to their sizes. Here, a vortex could be formed which allows larger sized granules to roll in preferentially by gravitational action if not attended to, thereby leading to lower tablet weight. At the tail end of the production, the smaller sizes left, if there is no adjustment made to the volumetric fill in the die, would allow higher tablet weights. These granular size segregative effects are the major cause of tablet weight variations which affect the dosage distribution.

In this work, the single punch machine was used and the batch size was low, meaning that the thickness of the layer of granules in the hopper was correspondingly low. Therefore there was very little chance for segregation of the granules to take place. This may account for the negligible weight variation that was obtained (Table 6).

(b) **Thickness**

Figure 3 shsows the effect of compression pressure on the tablet thickness. The thickness is a measure of the compressibility of the excipients, the highest compressible

excipients are expected to produce the thinnest tablets. Thickness is inversely related to the compression pressure.

The order for the thickness was: Avicel® < MDX < PGS.

This appears to show that Avicel® has a higher compressible or plastic characteristics, folowed by maltodextriin and then the pregelatinized starch.

(c) **Crushing strenght, Compact Density, and Tensile Strength**

Figures 4, 6 and 7 show that the crushing strenght, compact density and tensile strength are directly related to the compression pressure. As the compression pressure was increased, the excipients formed a stronger and more coherent tablets. This could have been caused by the formation of interparticulate bonding within the particles and/or excipients (Okafor 1991, Okhamafe, et al 1992).

At higher compression pressure, the particles are forced to become more intimate contact allowing more cohesive forces, such as vander Waal's forces to hold the particles together. This leads to densification of the compact appears to be reflected in the higher hardness, compact density and tensile strength that were obtained in Figures 4, 6 and 7. The order was Avicel® > MDX > PGS.

(d) **Friability**

As shown in Figure 5, friability was inversely related to the compression pressure. There was a decrease of friability from 0.1% to 0% for Avicel® and from 1.5 to 0.2% for pregelatinised starch and 0.15 to 0% for maltodextrin. The decrease in friability due to higher force of compression could be consequential to the cohesiveness of the tablets which would be more resistant to abrasive and chipping tendencies which were the nature of friability.

The order of increased friability was PGS > MDX > Avicel®. This was a reverse order for the hardness shown earlier.

(e) **Disintegration Time**

Table 7 and Figure 8 show the disintegration time at different compression pressures. There was an increase in disintegration time as the compression pressure was increased, but the magnitude of the increase depended on the nature of the excipients which are related to both the binding and/or disintegrant properties of the excipients.

The increase in compression pressure is a consequence of densification which may obliterate the capillaries or pores. Excipients with more capillaries have more tendency to allow water into the matrix thereby enhancing disintegration.

Fibrous materials form some gels around the tablet which may increase the disintegration time. Thus, there was increase in disintegration time in maltodextrin than in pregelatinised starch and Avicel®. This was due to their inherent disintegrant properties (Berry and Ridout; 1950, Jaminet et al; 1964).

The order of increased disintegration time was PGS < Avicel® < MDX.

With 50:50 Binary Mixtures The followings were obtained

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(a) **Thickness**

The thickness decreased with increased compression pressure. Since the excipients had the same ratio in the mixture the decrease in thickness depended on the extent of the compressibility of the excipients as shown in Figure 9.

The order was: MDX: Avicel® < Avicel®: PGS < MDX: PGS.

(b) **Crushing strenght**

As shown in Figure 10, there was a general increase in crushing strenght with the binary mixtures as the compression pressure was increased. The increase in crushing strenght was because more particles are forced closer allowing some cohesive forces such as van der Waals forces to hold them together. This leads to densification of the compact, thereby producing harder tablets.

There was increase in hardness in Avicel® and maltodextrin than in pregelatinised starch which was due to their inherent binding properties. This produces a more cohseive bond leading to harder tablets.

The order was:MDX: Avicel® > Avicel®: PGS > MDX: PGS

(c) **Friability**

Figure 11 shows that as the compression pressure was increased from 6.5 to 8.0 metric tons, the maltodextrin/Avicel® mixtures (MDX:: Avicel®) had a decrease in friability from 0.4 to 0% while Avicel®/pregelatinised mixtures (Avicel®:PGS) produced a friability value from 0.6 to 0% and maltodextrin/pregelatinised starch mixtures (MDX: PGS) had a value from 0.6 to 0%. The friability values therefore depend on the properties of the two components in the tablet with tablets that are more cohesive having lesser values. Pregelatinised starch was more friable and therefore higher fribility values. This was because of its poor binding properties and therefore less cohesive forces are exerted within the particles leading to more abrasive and chipping tendencies.

The order of decreased friability was MDX: Avicel® < Avicel®: PGS < MDX: PGS.

(e) **Compact Density**

Figure 13 shows that compact density increased with increased compression pressure. The most compressible excipients produced the highest compact density, since compact density depends on the weight and volume of the compact but since the ratio of the binary mixtures were the same 50:50, the pattern followed that of the pure component; with the most compressible binary mixtures producing the highest compact density.

The order was: MDX: Avicel® > Avicel®: PGS > MDX: PGS.

(f) **Packing Fraction**

As shown in Figure 14, the packing fraction was directly related to the compression pressure. The higher the compression pressure, the higher the reduction in the porosity of the tablet leading to a higher value of packing fraction and higher tablet hardness (Okhamafe et al, 1992). The compression characteristics of the binary mixtures are related to the proportion of the two excipients in the mixtures.

The order was MDX: Avicel® (0.92) > Avicel®: PGS 0.89 > MDX: PGS 0.83.

(g) **Disintegration Time**

As shown in Figure 15, the disintegration time generally increased with *increased compression pressure. The extent of the increase depended on the* characteristics of the excipients that made up the mixtures as follows:-

Avicel®: pregelatinised starch (Avicel®: PGS) 50:50 produced disintegration time of 10 minutes.

Maltodextrin: pregelatinised starch (MDX: PGS) produced 15 minutes

Maltodextrin: Avicel® (MDX: Avicel®) produced 20 minutes. This could be summaised as follows:-

AVICEL®: PGS (10 mins.) < MDX : PGS (15 mins.) < MDX: AVICEL® (20 mins).

Here, Avicel® and pregelatinised starch are good disintegrants and because of these inherent disintegrant characteristics, the tablet disintegrated within 10 mins. for all the mixtures at all the compression pressure of 6.5 to 8.0 metric tons.

4.2.2 The Effect of Binary Components of Dry Binder on Tablet Properties at Optimum Compression Pressure of 8.0 Metric Tons

(a) **Friability**

As shown in Figure 16, the friability generally depended on the component of the binary mixtures.

Maltodextrin: Avicel® (MDX: AVICEL®)

The binary mixture of 0:100 to 100:0 produced the lowest friability value of 0%.

This was attributed to the ability of the two components to compress well and to form more cohesive (harder) tablets.

Maltodextrin: Pregelatinisied Starch (MDX: PGS)

The friability values depended on the characteristics of the component that dominated the mixtures. When the mixture had pregelatinised starch (100%) the friability value was 0.2% and this value decreased to 0% as the maltodextrin was increased to 100%.

Avicel®: pregelatinised starch (AVICEL®: PGS)

The value decreased from 0.2 to 0% as the Avicel component was increased in the mixtures. The decreased friablity with increased Avicel® was due to more cohesive forces existing between particles in maltodextrin and Avicel® leading to the production of harder tablets. Pregelatinised starch was more friable due to its poor binding properties which produced lesser cohesive forces leading to softer tablets.

(b) **Crushing strenght**

As shown in Figure 17, maltodextrin: Avicel® (MDX: AVICEL®) binary mixtures gave a constant value for the crushing strenght i.e. 9 KgF, for all the binary mixtures either from 0:100 or 100:0. This was because the binary mixtures contained either maltodextrin or Avicel, both of which are very compressible (as shown in table 6 and figure 17) since they are very cohesive, very hard tablets are produced.

Maltodextrin: pregelatinised starch (MDX: PGS)

When the binary mixtures was 0:100 that is pregelatinised starch was 100%, the hardness value was 6 KgF but as maltodextrin component increased to 100% the hardness value also increased from 6 KgF to 9 KgF due to the formation of more cohesive forces among the particles thereby giving rise to harder tablets.

Avicel: pregelatinised starch (AVICEL: PGS)

At 100% pregelatinised starch had a hardness value of 6 KgF which increased to 9 KgF as the Avicel content in the mixtures was increased to 100%. This was due to

the formation of more cohesive force among the particles which increased the interparticulate bonding that took place (Bangudu, 1993; Okhamafe et al, 1995).

(c) Packing Fraction

Figure 18 shows the packing fractions of the different components in the binary mixtures.

Maltodextrin: Avicel (MDX: Avicel) combination shows that when Avicel® was 100% and Maltodextrin 0%, the packing fraction of was 0.99. The PF continued to decrease as the concentration of the maltodextrin increased to 20% (0.93), thereafter the PF values remained constant to 80% concentration and later dropped to 0.85% when the maltodextrin concentration was 100%. This shows that Avicel® was more densely packed then maltodextrin ever though it is more of a binder than Avicel® as pointed out previously.

Maltodextrin: pregelatinised starch (MDX: PGS)

The combination shows that when pregelatinised starch was 100% and maltodextrin 0%, the packing fraction of pregelatinised starch was 0.83 and this increased to 0.85 as the concentration of maltodextrin increased to 100%.

Avicel: pregelatinised starch (Avicel: PGS)

At 100% pregelatinised starch, the packing fraction was 0.83 which increased to 0.99 as the concentration of Avicel was increased to 100%.

The explanation could be related to the fact that when Avicel components in the mixture was 100%, the packing fraction was 0.99 that is with little or no pores since there was cohesive force among the particles leading to hard tablets. The decreased packing fraction with the presence of pregelatinised starch could be attributed to

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increase in the number of voids due to the poor binding properties of the pregelatinised starch.

(d) ***Thickness***

As shown in figure 19, maltodextrin: pregelatinised starch (MDX: PGS) mix produced thickness of 2.5mm from the binary mixtures of 0:100 to 50:50 but from 60:40 to 100:0 the thickness was 2.4mm. This was obvious for the fact that between 0:100 to 50:50 pregelatinised starch content was higher in the binary mixture. It has been shown earlier where pregelatinised starch compressed poorly compared to maltodextrin.

When maltodextrin dominated from 60:40 to 100:0 the thickness decresed showing that maltodextrin is more plastically compressible.

Avicel: pregelatinised starch (Avicel: PGS)

The thickness from the binary mixture of 0:100 to 50:50 was 2.5mm while 60:40 to 100:0 was 2.4mm which means that 100% Avicel with a lower thickness value of 2.4mm is more compressible.

Maltodextrin: Avicel (MDX: Avicel)

This produced a lower thickness value of 2.4mm. Since each of the two components compressed to produce more plastic (thinner) tablets, the thickness value could be used as a measure of compressibility. This appears to show why the mixtures have almost the same value of thickness.

The order was:

MDX: AVICEL	<	AVICEL: PGS	<	MDX:PGS.
Most compressible		intermediately compressible		least compressible

(e) ***Compact Density***

Figure 20 shows the compact density for maltodextrin: Avicel (MDX: Avicel) which was almost the same but differs from that of the maltodextrin: pregelatinised starch (MDX: PGS) and Avicel: pregelatinised starch (Avicel: PGS) and this was because the compact density depended on the weight and thickness of the compact. Since the weights were almost the same, the difference in compact density was therefore due to the difference in thickness.

(f) **Tensile Strength**

Figure 21 shows the tensile strength for the binary mixtures at optimum compression pressue of 8.0 metric tons for all the mixtures of maltodextrin: pregelatinised starch, Avicel: pregelatinised starch and maltodextrin: Avicel. Increased maltodextrin or Avicel in the mixtures increased the tensile strength of the tablet. As any of these two components was increased in the binary mixture, the hardness was also increased. The interparticulate bonding was stronger and therefore higher tensile strength was obtained. Maltodextrin: Avicel (MDX: AVICEL) mixtures produced the highest tensile strength compared to maltodextrin: pregelatinised starch and Avicel: pregelatinised starch. This was because pregelatinised starch in the mixtures had a poorer binding effect compared to maltodextrin and Avicel as discussed previously.

The order of increased tensile strength was

MDX: AVICEL > AVICEL: PGS > MDX: PGS.

(g) **Disintegration Time**

Figure 22 shows the disintegration time of the tablets from various binary mixtures at 8.0 metric tons. Generally, there was an increase or decrease in

disintegration time with different components depending on the component and content in the binary mixture.

Maltodextrin: Avicel (MDX: Avicel)

At 100% of Avicel and 0% of maltodextrin, the disintegration time was 15 minutes but as the concentration of maltodextrin was increased to 100% in the component the disintegration time was increased to 25 minutes.

Avicel: Pregelatinised Starch (Avicel: PGS)

The disintegration time was 10 minutes at 100% pregelatinised starch and increased to 15 minutes as the Avicel concentration was increased to 100%.

The different component of the binary mixture produced different disintegration time depending on the composite characteristics of the tablet produced from the mixtures.

When maltodextrin dominated the binary mixture the disintegration time was longest since maltodextrin was a poor disintegrant but a good binder but when Avicel or pregelatinised starch contents were higher in the mixtures the disintegration times were shorter.

Therefore the more the proportion of the disintegrant properties of the excipients in the tablet the shorter the disintegration time. Conversely, the more the binding properties of the excipients, the longer the disintegrtion time. This could be explained thus. Pregelatinised starch and Avicel are good disintegrants since the particles are porous. Therefore they exerted their disintegrant properties by enhancing water penetration by capillary forces into the porous tablets to cause the swelling of some components in the tablet to break apart.

This is in agreement with the work of Mital and Ocran (1968), Nasipuri (1978) and Garr (1988). Since maltodextrin did not have disintegrant properties, it resisted the

entry of water into the tablet possibly by forming a film (gel) around the tablet which served as a barrier between the tablet and water. Disintegration will only take place when the gel is diluted with continuous contact with the disintegrating medium thereby causing a longer disintegration time.

Another possible mechanism might be due to the formation of very strong interparticulate bonds between particles and/or between the excipients. The more compact a tablet is, the less the porosity or the voids between the particles. Therefore less penetation of water into the tablet would tend to cause a longer disintegration time. This is consistent with the work reported by Sagar (1947), Chuwaikowska and Krowozinsk (1968) and Iwuagwu et al (1986).

4.3 PROPERTIES OF HIGH DOSE POORLY COMPRESSIBLE SULPHAMETHOXAZOLE TABLETS CONTAINING 10%, 20% AND 30% EXCIPIENTS]

(a) Weight and Weight Variation

There were no significant differences in weight ($P \leq 0.05$) – Table 8. All were within ±0.9%. the reason for no weight variation could be this. The batch size used was so small that segregation action could not establish to cause any tablet weight variation. Besides, it was due to a longer compressble cycle resident time for enough granuules to fill the die. Therefore, no tablet weight variation was obtained.

With this low batch size, the granules thickness in the hopper is so negligible that granules size segregation is virtually non-existent.

(b) Crushing strenght and Friability

These are shown in Figures 23, 24 and 25. Increased compression pressure from 3.5 to 5 metric tons gave an increase in crushing strenght and decreased friability inall the concentration but those of 10% and 20% were harder. Therefore friability was

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highest in 30%, for pregelatinised starch (PGiS), the friability decreased from 1.8 to 0.4% and hardness increased from 4.0 to 10 KgF at 10% excipient (PGiS) content.

At 20%, the friability decreased from 1.6 to 0.2% and crushing strenght increased from 5.0 to 13.0 KgF. At 30%, the friability decreased from 2.0 to 0.1% and crushing strenght increased from 2.5 to 10 KgF.

For maltodextrin (Mdx), the friability decreased from 1.4 to 0% and hardness increased from 6.5 to 12.8 KgF at 10% of the excipient content.

At 20% friability decreased from 0.6 to 0% and hardness increased from 8.0 to 16.0 KgF. At 30%, friability decreased from 1.1 to 0.0% and hardness increased from 4.8 to 14.0 KgF.

For Avicel at 10%, the friability decresed from 1.1 to 0% and hardness increased from 7.5 to 13.0 KgF At 20%, the friability decreased from 0.8 to 0% and hardness increased from 5.5 to 15.0 KgF.

At 30% concentration, the friability was highest and hardness lowest. (Tables 8a/b and 25 Figure) Pregelatinised starch produced the highest friability and least hardness. These could be explained thus; At 30% concentration the tablet weight was 714mg. The friability was highest and hardness was the lowest (compared with 10% and 20% contents) due to the presence of higher percentage of fines.

At higher concentration of 30%, the content of the excipients are high enough that much higher compression pressures are needed to consolidate the particles to become so closely packed for cohesive forces like vander Waals' forces and hydrogen bonding to take place in forming stronger tablets. When the content of the fines is high the exposed surface area of the fines will be larger. A higher compression pressure will be needed to consolidate the particles for the van der Waals' forces to act for interparticulate bonding to take place. This appeared to be the reason why the tablet is

softer and more friable at a higher content of the dry binder excipients which paradoxically would have been expected to produce harder and less friable tablets(Ojile, et al, 1999, Ezezobo et al 1976).

The high friability value and low hardness value of pregelatinised starch compared to maltodextrin and Avicel® could be explained as due to their binding properties. Since Avicel® and maltodextrin have higher binding properties, a more cohesive interparticulate bonding could have taken place in Avicel® and maltodextrin than in pregelatinised starch (Parrot, 1989, Bangudu; 1993 and Okhamafe et al 1995).

(c) **Specific Thickness**

In the low dose tablet, the tablet weight was constantly maintained at 75mg which contains 5mg of the active ingredient (folic acid). For high dose tablets each tablet must contain 500mg of sulphamethoxazole. The weight of the sole excipients were varied from 10 to 30% w/w. This means that the tablet weight must be increased from the 10 to 30% w/w in order to maintain the drug content in each tablet at 500mg. The thickness measurement would be better equitably compared using the same tablet weight, that is, for every milligram weight of the tablet. This thickness value is called the specific thickness. The thickness of a tablet is a measure of how plastically compressible the tablets is. The higher the compressibility, the thinner is the tablet.

As shown in Table 7 and Figures 26, 27 and 28, the specific thickness decreased with increased compression pressure. The order was Avicel® < MDX < PGS. In this instance, Avicel® ws the most compressible, followed by MDX while PGS was the least compressible.

(d) **Compact Density**

As shown in Figures 29, 30 and 31, the compact density synchronised with lower values of thickness of the tablets dervied form their respective excipient and is a function of the diameter of the tablet which was set constant by the size of the die and of the weight which was also constant. Thus a change in compact density synchronises with the change in the thickness of the compacts. The lower the value, the more compressible the excipients resulting in denser and stronger compacts. The compact followed the same order in all the concentrations. The order was Avicel > MDX > PGS.

(e) **Tensile Strength**

As shown in Figures 32, 33 and 34, the tensile strength increased with increased compression pressure. This was closely related to the hardness. This was expected since there was a direct relationship between hardness and tensile strength of compacts (Okhamafe et al 1991). Avicel® > MDX > PGS

$$T_s = \frac{2H}{\Pi\, d\, t\, (1-e)}$$

where T_s in the tensile strength, H the hardness, d the diameter, t the thickness and e the porosity.

The tensile strength followed the same concentrations as in those in hardness. And the order was Avicel > Mdx > PGS.

(f) **Disintegration Time**

Generally, as shown in Figures 35, 36 and 37, disintegration time increased with increased compression pressure. The harder the tablet, the longer the time needed for the forces binding them to be broken apart. Therefore, the disintegration time depends on the nature of the excipients. The disintegration time of pregelatinised starch was the shortest among the excipients used followed by Avicel® and lastly by maltodextrin. This was because of the inherent disintegrant properties of pregelatinised starch and Avicel® both of which are being composed of porous particles that are amenable to shorter disintegration time.

This could be explained by any or all of the following mechanisms exhibited by a disintegrant which pregelatinised starch posseses viz: enhancing water penetration into the porous tablets where pressure was exerted which forced the tablet apart. Another possible mechanism was by capillary action thereby allowing the entry of aqueous fluid into the tablet where hydrostatic pressure was exerted to cause the swelling of some components in the tablet.

When maltodextrin was employed as a disintegrant, it resisted the entry of water into the tablet probably by forming a film (gel) around the tablets. The thickness of the film depends on the quantity of the excipients used in the tablet and these were responsible for different disintegration time at different concentrations.

Another possible mechanism could be by erosion of the tablet where the particles were gradually removed from the top layer by action of water until they were completely broken apart.

4.4 THE EFFECT OF COMPRESSION PRESSURE ON PROPERTIES OF LOW DOSE (FOLIC ACID) TABLETS PRODUCED FROM POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN BY WET METHOD.

The potato starch and its modified products were used as both binder and disintegrants. Figures 38 and 39 show their size distribution. The excipients that produced the highest amount of large sized granules might have formed the highest number of strong solid bridges by having the highest binder uptake,a process by which the granule sizes occur (Davis and Gloor 1972, Carstensen etal 1976).

The amount of starch and its modified products wetted depend on the amount of water that are available for the agglomeration process. In this case, the water is bound and not all was available for chemical reactions e.g. hydrolysis. So the high percentage of water content during granulation would not affect the stability of the products (Okhamafe, et al 1991).

Although the presence of fines can have glidant effect depending on their proportions, they were responsible for increase in flow time. Increase in the concentration of both starch and its modified products increase the tablet hardness.

The order is MDX > PGS > PTS.

The amount of bonding that occurred between particles due to asperitic melting, plastic and elastic deformation of the particles and consequently the hardness of the tablet depend on the compressing force that is applied and the amount of the binding agent present (York and Pilpel, 1973).

(a) Weight and Weight variation

There were no significant differences in weight $P \leq 0.05$ (Table 9). The reason was as discussed earlier.

(b) **Thickness**

As showed inTable 8 and Figure 40, the thickness of the excipients increased with increase in compression pressure. This is because the most compressible excipients produced the thinnest tablets.

Maltodextrin compressed to produce the lowest value of the thickness because of its binding properties compared to other excipients.

The order was MDX < PGS > PTS.

This indicates that MDX is most compressible followed by PGS and the least in PTS

(c) **Crushing strenght and Friability**

As shown in Figure 41. There was an increased crushing strenght and decreased friability as the compression pressure increased from 4.5 to 6.0 metric tons for all the excipients, but their values differ among the excipients. Maltodextrin having the highest binding properties had highest value of 10 KgF and friability from 0.8 to 0.0%.

Pregelatinised starch having intermediate intrinsic binding propeties had hardness value from 3.0 to 8.0 KgF and friability of 1.0 to 0.1% while potato starch had hardness value of 2.5 to 7.0 KgF and friability value of 1.2 to 0.2%.

The increased crushing strenght and decreased friability in maltodextrin were most prominent as compared with those in pregelatinised starch and potato starch.This was because the maltodextrin appears to produce higher binding properties thereby producing stronger interparticulate bonds leading to the formation of coherent hardest tablets. This could be due to more solid bridges being formed between particles since maltodextrin possess the most inherent binding properties compared with pregelatinised

starch and potato starch. Potato starch had the highest friability values because of its poor binding properties. It produced weak interparticulate bonding between particles and/or excipients. The order of increased hardness and decreased friability was:

MDX > PGS > PTS.

(d) **Tensile Strength**

Figure 42 shows the effect of compression pressure on the tensile strength and that increased compression pressure increased the tensile strength and this should be expected as tensile strength has a direct relationship with hardness. The order of *increased tensile strength was:*

MDX > PGS > PTS.

(e) **Compact Density**

As shown in Figure 43, the compact density increased with increase in compression pressure. Compact density followed the same increase pattern with the thickness of the excipients. The most compressible excipients formed the strongest compact. The order of compact density was:

MDX > PGS > PTS.

(f) **Disintegration time**

Figure 44 shows the relationship between the compression pressure and disintegration time. Generally, increased compression pressure increased disintegration time. However, potato starch and pregelatinised starch produced tablets that disintegrate within the official limit of 15 minutes. This was because of their inherent disintegration properties of higher porosity (Allagh, Ojile & Bangudu, 1994). When

compared with maltodextrin which has a strong binding effect, it produced the longest disintegration time due to a strong interparticulate bonding existing between particles and/or excipients which required a longer time to break apart.

4.5 THE EXCIPIENT PROPERTIES OF POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN ON SULPHAMETHONAZOLE TABLET BY WEIGHT METHOD

This project looked into the use of potato starch, pregelatinised starch and maltodextrin as sole excipients for producing high dose poorly compressible drug such as sulphamethoxazole tablet. Due to high dose one is limited to the content of the excipient as higher content more than 30% would make the tablet so bulky. Most patients do not normally accept and comply to larger sized tablets. So it was thought of using wet method to study whether the tablets would have better physical properties than those produced with the dry method.

(a) Weight and weight variation

As shown in Table 10,. there were no significant differences in the weight of the tablets ($P \leq 0.05$). All the tablets' weight variations were within $\pm 0.9\%$. The reasons were as discussed earlier.

(b) Specific Thickness

Table 10 and Figure 45 show the impact of compression pressure on the thickness. The thickness decreased with increased compression pressure. The most compressible excipient, maltodextrin, has the thinnest tablets. The order of specific thickness was as follows:-

MDX < PGS < PTS.

(c) ***Crushing strenght and friability***

As shown in Figure 46, there was increased crushing strenght and decreased friability as the compression pressure increased. The excipients that produced the hardest tablet had the lowest friability value.

Maltodextrin has hardness value of 9 to 18.5 KgF and friability of 0.4 to 0% as the compression pressure was increased from4.5 to 6.0 metric tons. The increased hardness and decreased friability was attributed to its highest binding properties. It formed a very cohesive bond leading to very hard tablets.

Pregelatinised starch had hardness value of 5.5 to 14 KgF and friability of 0.9 to 0.1% as the compression pressure was increased from 4.5 to 6.0 metric tons. These value, were intermediate having intrinsic intermediate binding properties while with the least intrinsic binding effects produced tablets with the least crushing strenght and the hightest value of friability. The reason can be due to poor binding properties of pregelatinised starch and potato starch which resulted to increased friability value.

The order of increased hardness and decreased friability was:

MDX > PGS > PTS.

(d) **Compact Density**

As shown in Figure 47, the compact density increased with increased compression pressure. The most compressible excipients formed a very strong compact. Compact density is direcly related to the weight of tablet and volume of the compact since the diameter is constant.

The order of increase compact density was:

MDX > PGS > PTS.

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(e) **Tensile Strength**

Figure 48 shows the effect of compression pressure on tensile strength. Increased compression pressure increase the tensile strength since tensile strength is directly related to the hardness. The stronger the compact, the more the tensile strength. The order of increase was:

MDX > PGS > PTS.

(f) **Disintegration Time**

As shown in Figure 49, disintegration time increased with increased compression pressure. Tablets containing potato starch and pregelatinised starch disintegrated faster than those from maltodextrin because of their inherent disintegrant properties.

Maltodextrn had disintegration time between 40 and 280 minutes as the compression pressure increased from 4.5 to 6.0 metric tons. Since a very cohesive interparticulate bond was formed between the particles and/or excipient, a longer time would be needed to break apart these particles which resulted in longer disintegration time.

In all, the formulations potato starch disintegrated within the official limit of 15 minutes. The order of disintegration time among the excipients was:

PTS < PGS < MDX.

CHAPTER FIVE

5.0 SUMMARY AND CONCLUSION

It was shown that the action of heat or acid hydrolysis broke down the polysaccharides starch to their various oligo and monosaccharide units, (D-glucose, D-galactose and maltose). The result obtained had shown that when starch and its modified products (pregelatinised starch and maltodextrin) were used as binders and/or disintegrants in tableting, the properties of the granules and tablets formed were affected by different methods of tablet formulations.

In general, increased concentration of starch and its modified products in mucilage form as a binder resulted in an increase in the hardness, tensile strength and disintegration time. Increase in compression pressure on the pure excipients have been shown to increase parameters such as tablet hardness, tensile strength, compact density disintegration time and decrease the friability, but the properties produced from the binary mixtures depended on the proportions of the excipients in the mix.

Thickness or specific thickness is a measure of the compressibility of the excipient. The less the thickness, the stronger the compact formed. Depending on the compression pressure and the proportion of the excipients used, tablets of desirable qualities can be produced.

Pregelatinised starch produced good disisntegrant properties for both low and high dose drugs and for all the methods of drug formulation.. Maltodextrin produced excellent binding properties for both wet and dry granulation and displayed a good excipient properties for direct compression like Avicel® but displayed poor disintegrant properties. But with better selection of maltodextrin and pregelatinised

starch from the binary mixed componets tablets with better disintegrant and binding properties could be produced.

Physiochemical properties of the individual ingredient such as particle size, fluidity and moisture content are most likely to be more critical in tablets prepared by direct compression than those prepared from both wet and dry granulations. Almost all low dose drugs can be formulated by direct compression but the only problem is centered towards uniform distribution of the active ingredients.

Drugs characterised by high dose, high bulk values, poor compressibility and poor fluidity are better prepared by wet and dry granulation method rather than by direct compression. However, moisture sensitive and thermolabile drugs can only be prepared by dry granulation. Therefore, formulation should be directed at optimizing tablet hardness without applying excessive compression force while at the same time assuring rapid disintegration and drug dissolution.

5.1 RECOMMENDATION

Maltodextrin displayed good binding properties and produced a very long disintegration time among the excipients used for this work. It is recommended that the use of this excipient as a sustained release excipient and coating of tablets could be feasible. Further work should be carried out in this area to ascertain its suitability compared to other materials currently in use.

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APPENDIX 1 SIZE DISTRIBUTION OF FOLIC ACID GRANULES USING POTATO STARCH AS A BINDER AND DISINTEGRANT

Sieve Size μ	Weight (g)	% Retained on sieve	Cumulative % over-size	Mean granular size μm
500	32.50	65.0	65.0	325.00
250	9.50	19.0	84.0	47.50
150	4.60	9.2	93.2	13.80
75	2.40	4.8	98.0	3.60
Collecting Pan	1.00	2.0	100.0	<3.60

APPENDIX 2 SIZE DISTRIBUTION OF FOLIC ACID GRANULES USING PREGELATINISED STARCH AS BOTH BINDER AND DISINTEGRANT

Sieve Size μ	Weight (g)	% Retained on sieve	Cumulative % over-size	Mean granular size μm
500	34.00	68.0	68.0	340.00
250	10.30	20.6	88.0	51.50
150	3.20	6.4	95.0	9.50
75	2.0	4.0	99.0	3.00
Collecting Pan	0.5	1.0	100.0	<3.00

APPENDIX 3 SIZE DISTRIBUTION OF FOLIC ACID GRANULES USING MALTODEXTRIN AS BOTH BINDER AND DISINTEGRANT

Sieve Size μ	Weight (g)	% Retained on sieve	Cumulative % over-size	Mean granular size μm
500	34.40	68.8	68.8	344.00
250	10.30	20.0	88.8	50.00
150	3.20	6.4	95.2	9.60
75	2.0	4.1	99.3	3.08
Collecting pan	0.5	0.7	100.0	<3.00

APPENDIX 4 SIZE DISTRIBUTION OF SULPHAMETHOXAZOLE GRANULES USING POTATO STARCH AS A BINDER AND DISINTEGRANT

Sieve size µm	Weight of granules (g)	% retained on sieve	cumulative % over-size	Mean granule size
500	29.12	58.24	58.24	291.20
250	9.95	19.9	78.14	49.25
150	5.08	10.16	88.3	15.22
75	3.85	7.70	96.0	5.78
Collecting pan	2.0	4.0	100.0	<5.75

APPENDIX 5 SIZE DISTRIBUTION OF SULPHAMETHOXAZOLE GRANULES USING PREGELATINISED STARCH TO REPLACE POTATO STARCH

Sieve size µm	Weight of granules (g)	% retained on sieve	cumulative % over-size	Mean granule size
500	29.50	59.00	59.00	295.90
250	10.18	20.34	79.36	50.90
150	5.24	10.48	89.84	15.72
75	4.08	8.16	98.00	6.12
Collecting pan	1.00	2.00	100.00	<6.12

APPENDIX 6 SIZE DISTRIBUTION OF SULPHAMETHOXAZOLE GRANULES USING MALTODEXTRIN TO REPLACE POTATO STARCH

Sieve size µm	Weight of granules (g)	% retained on sieve	cumulative % over-size	Mean granule size
500	32.00	64.00	64.00	320.00
250	9.35	18.70	82.70	40.75
150	4.65	9.30	92.00	13.95
75	3.60	7.20	99.20	5.40
Collecting pan	0.40	0.80	100.00	45.40

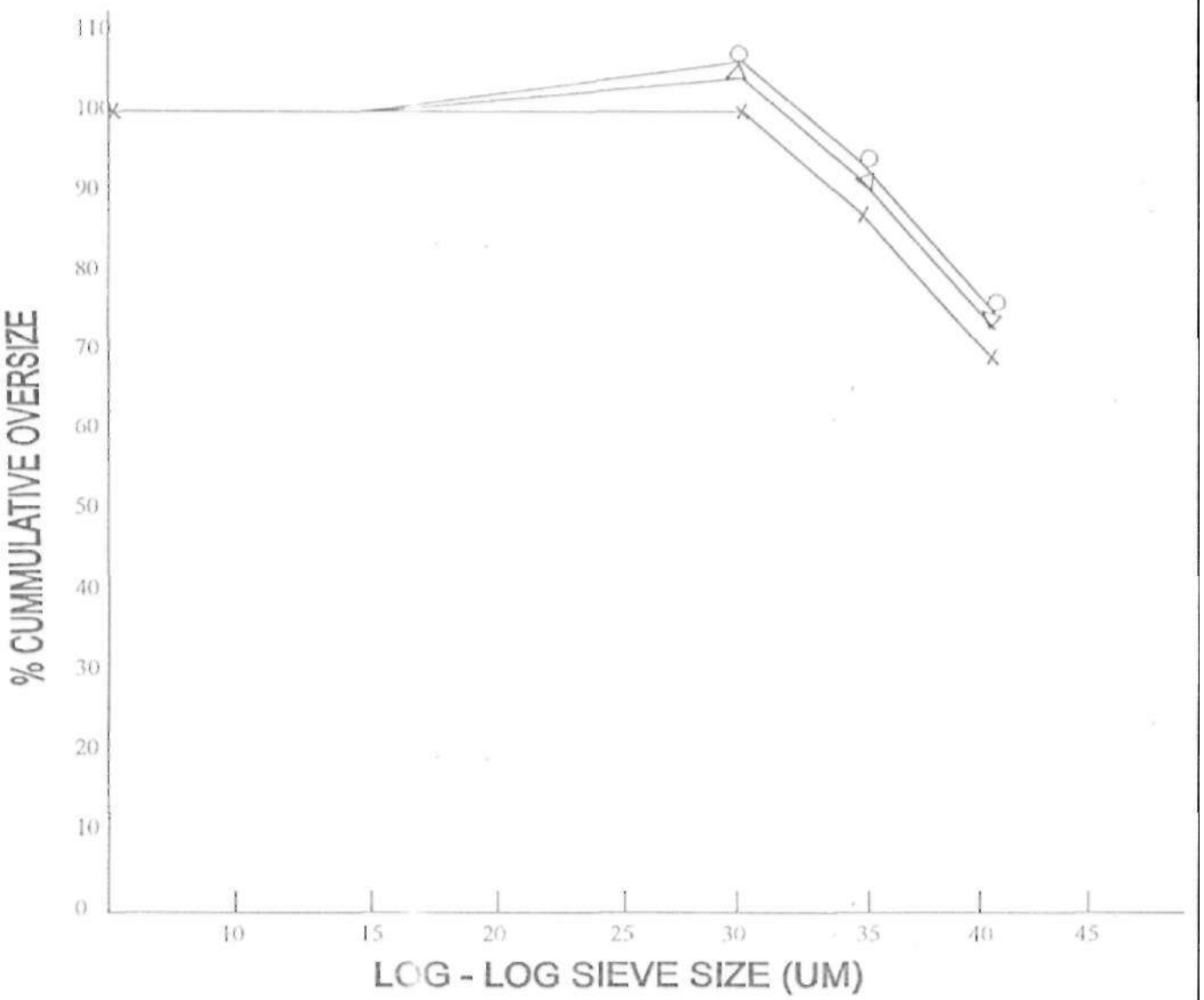


FIGURE 38: THE LOG – LOG SIEVE SIZE AGAINST CUMMULATIVE OVERSIZE OF POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN IN FOLIC ACID.

KEY:

X PTS

△ PGS

○ MDX

APPENDIX 8

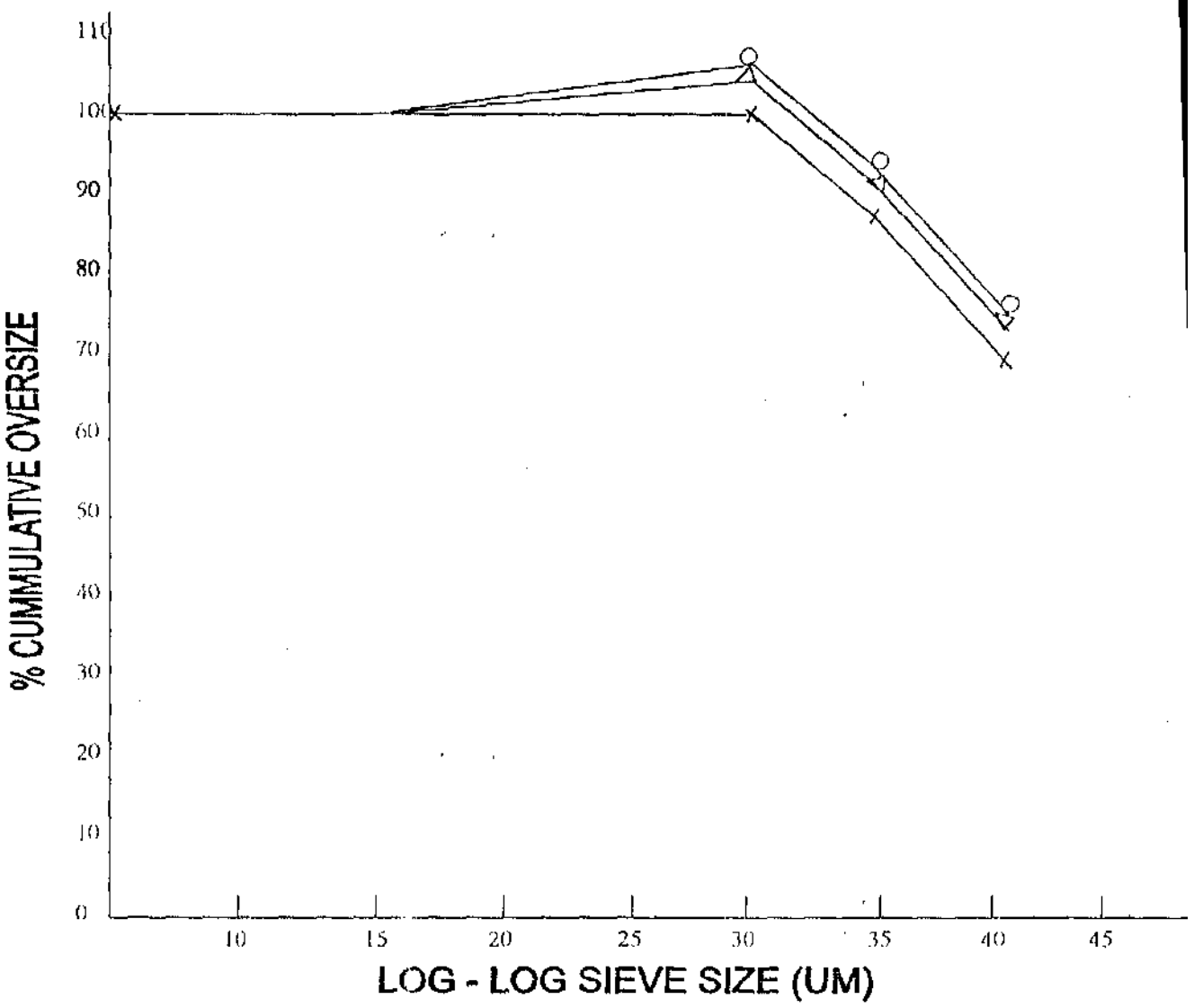


FIGURE 39: THE LOG – LOG SIEVE SIZE AGAINST CUMMULATIVE OVERSIZE OF POTATO STARCH, PREGELATINISED STARCH AND MALTODEXTRIN IN SULPHAMETHOXAZOLE.

KEY:

X PTS

△ PGS

O MDX

APPENDIX 9A

THICKNESS AT COMPRESSION PRESSURE OF 6.5.0 METRIC TONS.

MDX: PGS	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	4.0	+ 0.33	0.109
20:80	2	3.8	+ 0.13	0.017
40:60	3	3.7	+ 0.03	0.001
50:50	4	3.6	- 0.07	0.005
60:40	5	3.6	- 0.07	0.005
80:20	6	3.5	- 0.17	0.029
100:0	7	3.5	- 0.17	0.029
		25.7	0.01	0.195

$\overline{X} = \frac{25.7}{7} = 3.67$, where $\overline{X}$ = mean of the population.

$SD = \sqrt{\frac{E(X - \overline{X})}{n-1}} = \sqrt{\frac{0.195}{6}} = 0.18$

NOTE: $(X - \overline{X})$ is normally zero but because of approximation it might not be so in all cases.

AVICEL:PGS	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	4.0	+ 0.4	0.16
20:80	2	3.7	+ 0.1	0.01
40:60	3	3.5	+ 0.1	0.01
50:50	4	3.5	- 0.1	0.01
60:40	5	3.5	- 0.1	0.01
80:20	6	3.5	- 0.1	0.01
100:0	7	3.5	- 0.1	0.01
		25.2	0.0	0.22

$\overline{X} = \frac{25.2}{7} = 3.6$

$SD = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.22}{6}} = 0.19$

MDX:AVICEL	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	3.6	0.14	0.020
20:80	2	3.5	0.04	0.002
40:60	3	3.5	0.04	0.002
50:50	4	3.4	- 0.06	0.004
60:40	5	3.4	- 0.06	0.004
80:20	6	3.4	- 0.06	0.004
100:0	7	3.4	- 0.06	0.004
		24.2	-0.02	0.040

$\overline{X} = \frac{24.2}{7} = 3.46$

$SD = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.04}{6}} = 0.08$

NOTE: X – X is normally zero but because of approximation it might not be so in all case.

APPENDIX 9B

THICKNESS AT COMPRESSION OF 7.0 METRIC TONS.

MDX:PGS	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	3.00	0.18	0.032
20:80	2	2.9	0.08	0.006
40:60	3	2.8	- 0.02	0.004
50:50	4	2.8	- 0.02	0.004
60:40	5	2.8	- 0.02	0.004
80:20	6	2.75	- 0.07	0.005
100:0	7	2.7	- 0.12	0.014
		19.75	+ 0.01	0.069

$$\overline{X} = \frac{19.75}{7} = 2.82$$

$$SD = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.069}{6}} = 0.107$$

AVICEL:PGS	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	3.0	+ 0.20	0.04
20:80	2	2.9	+ 0.10	0.01
40:60	3	2.9	+ 0.10	0.01
50:50	4	2.7	- 0.10	0.01
60:40	5	2.7	- 0.10	0.01
80:20	6	2.7	- 0.10	0.01
100:0	7	2.7	- 0.10	0.01
		19.60	0.00	0.10

$$\overline{X} = \frac{19.6}{7} = 2.80$$

$$SD = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.10}{6}} = 0.13$$

MDX:AVICEL	NO.	X	$(X - \overline{X})$	$(X - \overline{X})^2$
0:100	1	2.7	- 0.01	0.000
20:80	2	2.7	- 0.01	0.000
40:60	3	2.8	+ 0.09	0.008
50:50	4	2.7	0.01	0.000
60:40	5	2.7	0.01	0.000
80:20	6	2.7	0.01	0.000
100:0	7	2.7	0.01	0.000
		19.0	+ 0.03	0.008

$$\overline{X} = \frac{19.0}{7} = 2.71$$

$$SD = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.008}{6}} = 0.04$$

APPENDIX 9C

Thickness at compression pressure of 8.0 metric tones.

MDX: PGS	NO.	X	(X-X)	(X-X)2
0: 100	1	2.5	0.04	0.002
20: 80	2	2.5	0.4	0.002
40: 60	3	2.5	0.04	0.002
50: 50	4	2.5	0.004	0.002
60: 40	5	2.4	0.06	0.004
80: 20	6	2.4	0.06	0.004
100: 0	7	2.4	0.06	0.004
		17.20	0.02	0.020

$\overline{X}$ = 17.2/7 =2.46 $\overline{X}$ = mean of the population

$$S.D = \sqrt{\frac{E(X - \overline{X})}{n-1}} = \sqrt{\frac{0.02}{6}} = 0.06$$

AVICEL:PGS	NO.	X	(X - $\overline{X}$)	(X - $\overline{X}$)2
0:100	1	2.5	0.06	0.004
20:80	2	2.5	0.06	0.004
40:60	3	2.5	0.06	0.004
50:50	4	2.4	0.04	0.002
60:40	5	2.4	0.04	0.002
80:20	6	2.4	0.004	0.002
100:0	7	2.4	0.004	0.002
		17.1	0 .02	0.020

$\overline{X}$ = 17.1/7 = 2.44

$$S.D = \sqrt{\frac{E(X-\overline{X}}{n-1}} = \sqrt{\frac{0.00}{6}} = 0.0$$

MDX:AVICEL	NO.	X	(X - $\overline{X}$)	(X - $\overline{X}$)2
0.100	1	2.4	0.0	0.0
20:80	2	2.4	0.0	0.0
40:60	3	2.4	0.0	0.0
50:50	4	2.4	0.0	0.0
60:40	5	2.4	0.0	0.0
80:20	6	2.4	0.0	0.0
100:0	7	2.40	0.0	0.0
		16.80	0.0	0.0

$\overline{X}$ = 16.8/7 = 2.4

$$S.D = \sqrt{\frac{E(X-\overline{X})}{n-1}} = \sqrt{\frac{0.02}{6}} = 0.06$$

APPENDIX 10A

CRUSHING STRENGTH AT COMPRESSION PRESSURE OF 6.5 METRIC TONES.

MDX: PGS	No	X	$(X-\bar{\bar{X}})$	$(X-\bar{\bar{X}})^2$
0:100	1	2.0	-1.43	2.0449
20:80	2	2.5	-0.93	0.8649
40:60	3	3.2	-0.23	0.0529
50:50	4	3.3	-0.13	0.0169
60.40	5	3.5	0.07	0.0049
80:20	6	4.5	1.07	1.1449
100:0	7	5.0	1.57	2.4649
		24.0	**-0.01**	**6.5943**

$\bar{\bar{X}} = \frac{24.0}{7} = 3.43$ $\bar{\bar{X}}$ = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{\bar{X}})^2}{n-1}} \quad \sqrt{\frac{6.5943}{6}} = 1.048$

AVICEL : PGS	No	X	$(X-\bar{X})$	$(X-\bar{X})^2$
0:100	1	2.0	-1.36	1.8496
20:80	2	2.5	-0.86	0.7396
40:60	3	3.0	-0.36	0.1296
50:50	4	3.5	+0.14	0.0196
60.40	5	3.7	+0.34	0.1156
80:20	6	3.7	+0.34	1.1156
100:0	7	5.1	+1.74	3.0276
		23.50	**-0.02**	**5.9972**

$\bar{X} = \frac{23.5}{7} = 3.36$ X = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{5.9972}{6}} = 0.999$

MDX: AVICEL	NO.	X	$(X-\bar{X})$	$(X-\bar{X})2$
0: 100	1	5.1	+0.29	0.0841
20: 80	2	4.5	-0.31	0.0961
40: 60	3	4.6	-0.21	0.0441
50: 50	4	4.8	-0.01	0.001
60: 40	5	4.8	-0.01	0.001
80: 20	6	4.9	0.09	0.0081
100: 0	7	5.0	0.19	0.0361
		33.7	+0.03	0.02687

$\bar{X} = \frac{33.7}{7} = 4.81,$

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.2687}{6}} = 0.212$

APPENDIX 10B

CRUSHING STRENGTH AT COMPRESSION PRESSURE OF 7.0 METRIC TONES.

MDX: PGS	No	X	$(X-\bar{\bar{X}})$	$(X-\bar{\bar{X}})^2$
0:100	1	4.0	-1.086	1.179
20:80	2	4.5	-0.586	0.343
40:60	3	4.6	-0.486	0.236
50:50	4	4.8	-0.286	0.081
60.40	5	5.0	0.086	0.007
80:20	6	5.7	+0.614	1.377
100:0	7	7.0	+1.914	3.663
		35.6	**0.00**	**5.886**

$\bar{X} = \frac{35.6}{7} - 5.086$

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{5.886}{6}} = 0.990$

AVICEL : PGS	No	X	$(X-\bar{\bar{X}})$	$(X-\bar{\bar{X}})^2$
0:100	1	4.0	-1.271	1.615
20:80	2	4.5	-0.771	0.594
40:60	3	4.6	-0.671	0.450
50:50	4	5.0	-0.271	0.073
60.40	5	5.9	+0.629	0.396
80:20	6	5.9	+0.629	0.396
100:0	7	7.0	+1.729	2.989
		36.90	**-0.003**	**6.513**

$\bar{\bar{X}} = \frac{36.9}{7} = 5.271$, $\bar{\bar{X}}$ = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{\bar{X}})^2}{n-1}} \quad \sqrt{\frac{6.513}{6}} = 1.042$

MDX: AVICEL	NO.	X	$(X-\bar{X})$	$(X-\bar{X})2$
0: 100	1	7.0	+0.086	0.007
20: 80	2	6.8	-0.014	0.013
40: 60	3	6.9	-0.014	0.000
50: 50	4	6.9	-0.014	0.000
60: 40	5	6.9	-0.014	0.000
80: 20	6	6.9	0.014	0.000
100: 0	7	7.0	+0.086	0.007
		48.40	+0.002	0.027

$\bar{X} = \frac{48.4}{7} = 6.914$, $SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.027}{6}} = 0.067$

APPENDIX 10C

CRUSHING STRENGTH AT COMPRESSION PRESSURE OF 8.0 METRIC TONES.

MDX: PGS	No	X	$(X-\bar{\bar{X}})$	$(X-\bar{\bar{X}})^2$
0:100	1	6.0	-0.80	0.64
20:80	2	6.2	-0.60	0.36
40:60	3	6.5	-0.30	0.09
50:50	4	6.6	-0.20	0.04
60.40	5	6.8	0.00	0.00
80:20	6	7.0	0.20	0.04
100:0	7	8.5	1.70	2.89
		47.60	**0.00**	**4.060**

$\bar{\bar{X}} = \frac{47.60}{7} = 6.8$, $\bar{\bar{X}}$ = Mean of the total population X = various value of the crushing strength at different concentration

$SD = \sqrt{\frac{\Sigma (X - \bar{\bar{X}})^2}{n-1}} \quad \sqrt{\frac{4.06}{6}} = 0.823$

AVICEL : PGS	No	X	$(X-\bar{X})$	$(X-\bar{X})^2$
0:100	1	6.0	-0.96	0.922
20:80	2	6.2	-0.76	0.578
40:60	3	6.6	-0.36	0.130
50:50	4	6.9	- 0.06	0.004
60.40	5	7.0	+0.04	0.001
80:20	6	7.4	+0.44	0.194
100:0	7	8.6	+1.64	2.690
		48.7	**-0.02**	**4.519**

$\bar{X} = \frac{48.7}{7} = 6.96$ $\bar{X}$ = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{\Sigma (X - \bar{\bar{X}})^2}{n-1}} \quad \sqrt{\frac{4.519}{6}} = 0.868$

MDX: AVICEL	NO.	X	$(X-\bar{X})$	$(X-\bar{X})2$
0: 100	1	8.6	+0.09	0.0081
20: 80	2	8.5	-0.01	0.0001
40: 60	3	8.5	-0.01	0.0001
50: 50	4	8.5	-0.01	0.0001
60: 40	5	8.5	-0.01	0.0001
80: 20	6	8.5	-0.01	0.0001
100: 0	7	8.5	-0.01	0.0001
		59.6	+0.03	0.0087

$\bar{X} = \frac{59.6}{7} = 8.51$ $SD = \sqrt{\frac{\Sigma(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.0087}{6}} = 0.038$

APPENDIX IIA

PACKING FRACTION AT COMPRESSION PRESSURE OF 6.5 METRIC TONES.

MDX: PGS	No	X	$(X-\overline{X})$	$(X-\overline{X})^2$
0:100	1	.52	-0.04	0.002
20:80	2	.54	-0.02	0.000
40:60	3	.56	0.00	0.000
50:50	4	.57	0.01	0.000
60.40	5	.57	0.01	0.000
80:20	6	.58	0.02	0.000
100:0	7	.59	0.03	0.001
		3.93	**0.01**	**0.003**

$\overline{X} = \frac{3.93}{7} = .56$, $\overline{X}$ = Mean of the total population X = various value of the packing fraction at different consentrations.

$SD = \sqrt{\frac{E(X-\overline{X})^2}{n-1}} \quad \sqrt{\frac{0.003}{6}} = 0.02$

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AVICEL : PGS	No	X	$(X-\overline{X})$	$(X-\overline{X})^2$
0:100	1	.52	- 0.11	0.012
20:80	2	.60	- 0.03	0.001
40:60	3	.67	+ 0.04	0.002
50:50	4	.67	+ 0.04	0.002
60.40	5	.62	-0.01	0.000
80:20	6	.63	0.00	0.000
100:0	7	.68	0.05	0.003
		4.39	**0.00**	**0.02**

$\overline{X} = \frac{4.39}{7} = 4.63$ $\overline{X}$ = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\overline{X})^2}{n-1}} \quad \sqrt{\frac{0.02}{6}} = 0.06$

MDX: AVICEL	NO.	X	(X-X)	(X-X)2
0: 100	1	.68	0.06	0.004
20: 80	2	.63	0.01	0.000
40: 60	3	.63	0.01	0.000
50: 50	4	.63	0.01	0.000
60: 40	5	.61	0.01	0.000
80: 20	6	.60	- 0.02	0.000
100: 0	7	.59	-0.03	0.001
		4.37	0.03	.005

$\overline{X} = \frac{4.37}{7} = 0.62$ $SD = \sqrt{\frac{E(X-X)^2}{n-1}} = \sqrt{\frac{0.005}{6}} = 0.03$

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APPENDIX IIB

PACKING FRACTION AT COMPRESSION PRESSURE OF 7.0 METRIC TONES.

MDX: PGS	No	X	$(X-\bar{\bar{X}})$	$(X-\bar{\bar{X}})^2$
0:100	1	.69	-0.04	0.002
20:80	2	.71	-0.02	0.000
40:60	3	.74	0.01	0.000
50:50	4	.74	0.01	0.000
60.40	5	.74	0.01	0.000
80:20	6	.75	0.02	0.000
100:0	7	.76	0.03	0.001
		5.13	**0.00**	**0.003**

$\bar{X} = \frac{5.13}{7} = 0.73$

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{0.003}{6}} = 0.022$

AVICEL : PGS	No	X	$(X-\bar{X})$	$(X-\bar{X})^2$
0:100	1	.69	-0.1	0.000
20:80	2	.77	-0.02	0.000
40:60	3	.77	-0.02	0.000
50:50	4	.81	+0.02	0.000
60.40	5	.81	+0.02	0.000
80:20	6	.82	+0.03	0.001
100:0	7	.89	+0.01	0.01
		5.56	**0.03**	**0.011**

$\bar{X} = \frac{5.56}{7} = 0.79$ X = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{0.011}{6}} = 0.04$

MDX: AVICEL	NO.	X	(X-X)	(X-X)2
0: 100	1	.89	+0.086	0.005
20: 80	2	.82	-0.014	0.000
40: 60	3	.79	-0.014	0.001
50: 50	4	.82	-0.014	0.000
60: 40	5	.82	-0.014	0.000
80: 20	6	.82	0.014	0.000
100: 0	7	.76	+0.086	0.004
		5.72	0.02	0.01

$\bar{X} = \frac{5.72}{7} = 0.82$ $SD = \sqrt{\frac{E(X-X)^2}{n-1}} = \sqrt{\frac{0.01}{6}} = 0.04$

APPENDIX 11C

PACKING FRACTION AT COMPRESSION PRESSURE OF 8.0 METRIC TONES.

MDX: PGS	No	X	$(X-\bar{X})$	$(X-\bar{X})^2$
0:100	1	.83	-0.01	0.0001
20:80	2	.83	-0.01	0.0001
40:60	3	.83	-0.01	0.0001
50:50	4	.83	-0.01	0.0001
60.40	5	.86	+0.02	0.0004
80:20	6	.86	+ 0.02	0.0004
100:0	7	.86	+ 0.02	0.0004
		5.9	**0.02**	**0.0008**

$\bar{X} = \frac{5.9}{7} = .84$ X = Mean of the total population X = various value of the packing fraction at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{0.0008}{6}} = 0.012$

AVICEL : PGS	No	X	$(X-\bar{X})$	$(X-\bar{X})^2$
0:100	1	.83	- 0.02	0.0049
20:80	2	.89	- 0.01	0.0001
40:60	3	.89	- 0.01	0.0001
50:50	4	.89	-0.01	0.0001
60.40	5	.89	-0.01	0.0001
80:20	6	.92	+0.02	0.0004
100:0	7	.99	0.09	0.0081
		6.3	**0.00**	**0.014**

$\bar{X} = \frac{6.3}{7} = 0.09$, $\bar{X}$ = Mean of the total population X = various value of the crushing strength at different consentrations.

$SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} \quad \sqrt{\frac{0.014}{6}} = 0.048$

MDX: AVICEL	NO.	X	$(X-\bar{X})$	$(X-\bar{X})2$
0: 100	1	.99	0.07	0.0049
20: 80	2	.92	0.00	0.0000
40: 60	3	.92	0.00	0.0000
50: 50	4	.92	0.00	0.0000
60: 40	5	.92	0.00	0.0000
80: 20	6	.92	0.00	0.0000
100: 0	7	.86	0.06	0.0036
		6.45	0.01	0.009

$\bar{X} = \frac{6.45}{7} = 0.92$, $SD = \sqrt{\frac{E(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.009}{6}} = 0.039$

Note: The standard error (deviation) of an estimate among other considerations depend on the size of the sample i e as the size increases, the standard error decreases with resultant effect of it getting closer to the population parameter .

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APPENDIX 12.

ANNUAL PRODUCTION OF SWEET POTATO, CASSAVA AND YAM BETWEEN 1991/1996.

CROPS	ANNUAL PRODUCTION				
	1991	1994	1995	1996	KG/HECTRES
Yam	10485	11400	10984	10984	
Cassava	10820	10593	10682	10678	
Sweet Potato	7667	8000	8100	8200	

Adapted from FAO 1996