PROPERTIES OF DIRECTLY COMPRESSED PARACETAMOL TABLETS CONTAINING ALPHA - AND MICROCRYSTALLINE - CELLULOSE DERIVED FROM MAIZE COBS

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DECLARATION.

I hereby declare that the work reported in this thesis was carried out by me under the supervision of Drs. J. E. Ojile and P. G. Bhatia, both of the Department of Pharmaceutics and Pharmaceutical Microbiology. This work is original and has not been reported elsewhere for a higher degree. The work of other investigators have been properly acknowledged and referred to accordingly.

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CERTIFICATION

This thesis entitled, "Properties of Directly Compressed Paracetamol Tables Containing Alpha - and Microcrystalline - Cellulose Derived from Maize Cobs", meets the regulation governing the award of the degree of Master of Science, Ahmadu Bello University Zaria, and it is approved for its contribution to knowledge and literary presentation.

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DEDICATION.

This work is dedicated to the glory of God and my Lord and Saviour Jesus Christ. Maranatha!.

ABSTRACT

Cob alpha-cellulose (CAC) was extracted from maize cobs by standard extraction procedures with a yield of 21%. Part of the CAC was partially depolymerised into cob microcrystalline-cellulose (CMCC) by hot acid treatment, yielding 90%. The CAC and CMCC were compared with Aviccl[1R] PI 1101 which is also microcrystalline cellulose.

The mean particle sizes of CAC, CMCC and Avicel[k] were 58.4, 38.9, and 39.2 Dm respectively.

The moisture content and sorption capacity for CAC were 3.1% and 23.4%; for CMCC were 2.9% and 22.1% and for Avicel[R] were 2.9% and 11.4% respectively.

The significance of these could be reflected in the disintegration of tablets and storage conditions of the products.

Their perticulate and packing properties show comparable values with Avicel[R], indicating comparable direct compression properties with it.

A non-self compressible high dose drug as exemplified by paracetamol, (500mg dose per tablet) was employed in the tablet formulation using five dry mixed concentrations from and including 10 to 30% of CAC, CMCC and Aviccl as sole excipient dry binder. Half of the excipient was dry mixed with the drug before pelletization and comminution processes while the other half was admixed extra granularly and compared in the single station tablet. Although the tablet weight varied according to the excipient content, each tablet contained 500mg of the drug.

The percent weight variation were all within 2.4% with upper limits mostly within the higher excipient concentrations most probably due to higher content of exragranular fines which is amenable to higher segregative tendencies.

The specific thickness in mm per mg tablet weight was generally lowest with the highest (25 and 30%) dry binder content due to higher compressibility of the tablet containing higher compressible excipient. It also followed that the hardness and the friability of the tablets were highest and lowest respectively with the highest dry binder content.

The shortest disintegration time was obtained at 20% and 30% dry binder content for both CAC and CMCC while Avicel[R] produced exceptionally longer disintegration time at both extreme contents.

CAC and CMCC at both extreme contents appear to produce better bioavailability properties than the Avicel possibly due to its lowest hardness effect observed at lowest concentration and highest hardness effect at highest binder content. The formulation was most successful at 25% excipient content with CAC and CMCC which were found superior to Aviccl , possibly consequential upon the two different plant sources.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 General Introduction

Following the successful moulding of solid drug substances into tablets over a thousand years ago, tablets still remain the most popular dosage form among other dosage forms for administration of medicines. This is obvious from prescription trends of which more than 50% are tablets. The popularity of tablet as dosage form is as a result of its ease of administration and therefore convenience to the patients. It offers precision of dosage as well. It can be economically produced at high production rate which can be extrapolated to less cost to the patient (Burlinson, 1968, Remington, 1970, Lachman *et al* 1976).

The United States Pharmacopoeia defines compressed tablets as "... solid dosage form containing medicinal substances with or without suitable diluents, and they may be prepared by compression or by molding".

Thus, in its manufacture, certain pharmaceutical compounds of diverse origin and chemical activities are usually incorporated with the active ingredient(s) to aid the processing in one way or the other. These compounds are generally referred to as tablet excipients, additives or adjuncts, and they include diluents, disintegrants, binders, lubricants, etc. These excipients form an important component in tablet formulations and they represent the framework of the design for tablet formulations. The classification of the excipients are based on their principal function in the tablet. Therefore, "diluents" are those substances that usually make up the major portion of the tablet especially microdose drugs. Substances that bind powders together and

make them cohesive are called "binders". They are the adhesives in the formulation. Materials that help tablet to break up and dissolve to release the medicament are called "disintegrants".

In order for granules to flow from a hopper on the tablet press to the dies and for consistent and uniform fill, "glidants" are added to the formulation. Once the tablet has been compressed, it will not be released from the die unless a "lubricant" is present in sufficient amount. Sometimes, the compressed tablets leave a film on the punches and "anti adhesives" are needed to prevent this. Other ingredients are usually added, but not essential for tabletting are dyes, flavours, sweetners, absorbents, and buffers.

It is however obvious that some of the excipients oppose the function of each other and there is the need for careful choice of concentrations at optimal level to bring out their usefulness. The realization of the fact that tablet additives can interfer with or modify in one way or the other the performance of tablets and the activities of incorporated drugs has contributed to the catalogue of investigations of the influence of tablet formulation factors on tablet characteristics. Suffice it to indicate here however, that not only should each excipient contribute a necessary attribute to the essential processing requirements, but should also support the therapeutic objective of the drug substance and permit compliance with pharmacopoieal or manufacturers' quality standards; i.e. it should enhance the production of tablets which will not only meet the pharmacopoieal specifications but will be pharmaceutically and clinically acceptable.

For tablets in which the drug itself constitues a major portion of the total

tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed especially if direct compression method is to be used. Paracetamol is an example of such high dose drug, and being the most widely and frequently prescribed analgesic, (Fletcher *et al* 1998) yet its production is most often difficult and expensive due to its lack of compressibility and cohesion (Ojile, 1994; Ojile *et al* 1995). Due to its lack of compressibility, on application of compaction forces, capping and lamination often occur. To overcome these problems, other diluents, binders and disintegrants are added. The most popular method of production is by wet granulation method; which is too costly due to the many processes involved.

Paracetamol is a high dose drug which is not compressible on its own. There is therefore a need to incorporate an excipient which should have a high capacity for compressibility bearing in mind that only as little amount as possible is added to the formulation to avoid too bulky tablet that is already a high dose. Such excipient should have adequate compressible characteristics with high dilution capacity and yet make a satsifactorily firm tablet which is capable of releasing the drug rapidly in the gastrointestinal tract. It will therefore be beneficial if tablets can be made with as few excipients as possible using direct compression method which unarguably is the less expensive method of tablet production.

Microcyrstalline Cellulose, MCC, (Avicel ^{R}) is one material that has the desirable properties of a tablet vehicle necessary for compression of paracetamol into a tablet because it has the ability to produce very hard tablets which rapidly

use of Avicel [R] as a single vehicle excipient is its high cost and other associated problems with importation difficulties. The ability to locally produce a pharmaceutical grade of MCC at lower cost will therefore be a major feat.

1.2 The Dire Need and Commitment to Local Production of Pharmaceutical Grade of Raw Materials

The ready availitility of raw materials is vital to the existence and survival of any industry the world over. Pharmaceutical industries in Nigeria are more than ever before faced with the challenges of procuring these raw materials locally.

Before now, like in most developing countries, these industries rely mostly on imported raw materials (or the outright importation of finished and semi-finished goods) from the developed countries for their continued operations. A study carried out by Kio (1987) showed that while more than 73% of drugs consumed in Nigeria are imported, the raw materials for the remaining 27% of the drugs produced locally were imported. The changes observed in world economy in the nineties have necessitated various governments including that of Nigeria to pursue economic policies that will ensure their survival and relevance in the new world order. Following these worldwide changes and their concomitant effect on the economy of Nigeria, in particular, certain policies had to be put in place to rise to the challange. One of such policies is the restriction on the importation of certain goods which brought about difficulties in obtaining import licenses, delays in clearance of imported goods at the ports, high import duties on goods and the high devaluation of the Naira. These have made the importation of raw materials or the finished goods very costly, culminating in high production cost hence high prices for drug

products. This invariably translates to inability of most consumers to purchase these drugs leading to the manufacturers housing large precentage of finished drugs in their ware houses.

The Nigerian government has tried to encourage the local enterpreneur to source for their raw materials locally by putting in place incentives like tax waiver, access roads, electricity, etc.

However, because most of the pharmaceutical industries were owned and managed by foreigners, there were no appreciable response to these overtures of the government, but rather, they started de-investing from the Nigerian economy and going elsewhere. This can be seen in the recent phenomena of big pharmaceutical companies being bought over by some Nigerian enterprencurs. The challenge for funding research into these raw materials is now in the hands of these Nigerian enterpreneurs. It is worthy to note that a research may take time and resources, but the final outcome is less expensive and will be a boom for the economy of the nation.

Some researchers anticipated these problems and are pioneers in finding the solutions. Nasipuri (1979, 1979a, 1979b) developed a pharmaceutical grade starch from yam, cassava, and cocoyam, while Akande (1988) and Giari (1988) developed pharmaceutical grade starch from millet and sorghum respectively. The use of food crops for these raw materials for the pharmaceutical industries is now threatened by the recent decrease in food production as a result of climatic changes necessary for crop production. Other factors include poor crop yield, increasing population competing with industries for the food crops and also competing demands for the food crops by industries like textile, packaging and pharmaceutical.

Now, interests have shifted to agricultural wastes especially after the success of the work done by Okhamafe et al (1991, 1995) on the pharmaceutical qualities of cellulose from groundnut shells, rice husks, maize cobs and bagasse.

1.3 Cellulose

Cellulose (with its derivatives like hydroxyethylcellulose, hydroxyprophylcellulose, methyl cellulose, sodium carboxymethylcellulose, cellulose acetatephthallate and microcrystalline-cellulose) is one of the frequently used but imported excipients in the pharmaceutical industry in Nigeria. Unfortunately, because of the high tariff on imported goods and the high rate of exchange rate of the Naira against international currencies, it has become a very expensive, but vital excipient for the local industries. With the pioneering work by Okhamafe *et al* (1991, 1995) interest is now into research in these possible sources of cellulose and its derivatives from agricultural waste materials.

1.3.1 Sources of Cellulose

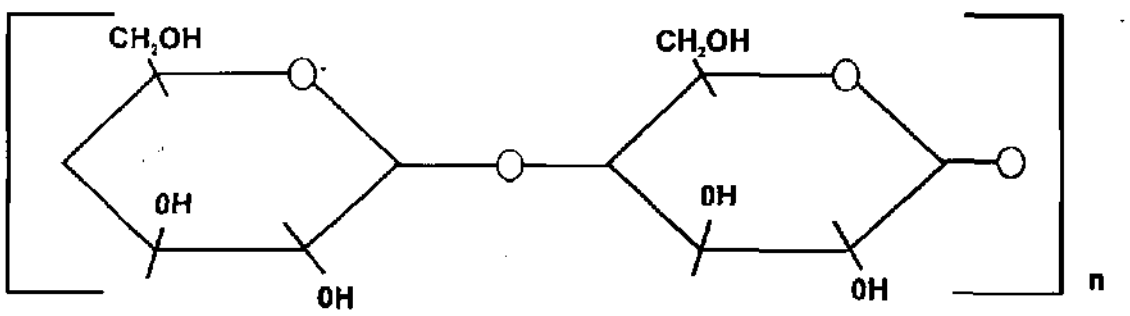
Cellulose is abundantly available in all higher plants. Avicel ^{R}, a brand of microcrystalline cellulose, is obtained from a special grade of purified alpha wood cellulose by acid hydrolysis to remove amorphous cellulose portion. This yield particles that are made up of bundles of needle-like microcyrstals (Bolhium and Lerk, 1973).

Cellulose is present in high quantity in maize (Zea mays) cobs. The work done by Okhamafe *et al* (1995) has shown that cellulose is present in the maize cob, and it was also said to exhibit some tabletting properties.

1.3.2 Chemistry of Cellulose

Cellulose is the chief polysaccharide of plant cell walls. It is made up of linear chains of ß-1, 4-linked glucose residues.

Structure of Cellulose (Tyler et al 1986)



Powdered cellulose is the purified, mechanically distintegrated cellulose prepared by processing α-cellulose obtained as a pulp from fibrous plant cell materials. It exists in various grades and exhibit degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy non-flowing material. Microcrystalline cellulose is a purified, partially depolymerised cellulose prepared by treating α-cellulose obtained as a pulp from fibrous plant material with hot mineral acid.

1.3.3 Cellulose Derivatives

1.3.3.1 Methyl Cellulose

This is a methyl ether of cellulose containing not less than 27.5% and not more than 31.5% of methoxy groups. It is prepared by dissolving α-cellulose in NaOH and then reacting with methyl chloride or dimethyl-sulfate (Swinyard and Lowenthal, 1990). Melthyl cellulose consists of a white, fibrous powder or granules which swell in water to produce clear, to opalescent viscous colloidal suspension.

Its uses include as a synthetic substitute for natural gum, as a dispersing, thickening, emulsifying, sizing and coating agent especailly in enteric coating of granules or tablets.

Pharmaceutical preparations that may contain it include nose drops, eye preparations, burn medications, cosmetics, toothpastes, creams and lotions. It functions as a protective colloid for many types of disperse substances and it is another stabilizer for oil-in-water emulsions. Methyl cellulose is also used therapautically as bulk laxative in chronic constipation.

1.3.3.2 Hydroxyethyl cellulose (also called ethyl cellulose)

This is an ethyl ether of cellulose containing not less than 44% and not more than 51% of ethoxy groups. It is obtained from α-cellulose by treating it with NaOH and then reacting with ethylene oxide (Swinyard and Lowenthal 1990).

Ethyl cellulose is used as a thickener, protective colloid, binder, stabilizer and suspending agent in emulsions, jellies and ointments, lotions, suppositories and tablets.

1.3.3.3 Hydroxypropyl Cellulose

This is prepared by treating α-cellulose with NaOH, then reacting it with propylene oxide at elevated temperatures and pressures. (Swinyard and Lowerthal, 1990). It is used as binder, granulation agent, film coater in the manufacture of tablets, stabilizer for emulsion alcohol-soluble thickner and suspension agent for elixirs and lotions.

1.3.3.4 Carboxymethyl cellulose sodium

This is another α-cellulose derivative which is used as a pharmaceutical aid (as suspending agent, as tablet excipient and as a viscosity increasing agent). In tablet form, it is used as hydrophilic colloid laxative.It has been produced and used as a cathartic bulk laxative by Ojile *et al* (1999).

1.3.3.5 Hydoxypropylmethyl cellulose

This is prepared from methyl cellulose by dissolving it in NaOH and then reacting with propylene oxide at elevated temperature and pressure for a reaction time sufficient to produce desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to hydroglucose rings of cellulose. It is used as a protective colloid and therefore useful as a dispensing and thickening agent in opthalmic solutions to provide demulcent action and viscous properties essential for contact lenses, and in "artificial-tear" formulations (Swinyard and Lowenthal, 1990).

1.3.3.6. Microcrystalline cellulose

This is a synthetic derivative of α-cellulose which is obtained by the partial hydrolysis of cellulose with hydrochloric acid (Swinyard and Lowerthal 1990). Of recent, this cellulose derivative has proved to be highly indispensable in tablet formulations in which it is used as a binder and a disintegrant.

Microcrystalline cellulose has good compressibility (Swinyard and Lowerthal, 1990). Hence it is widely used in direct compression method of tablet production as a dry binder, gum, disintegrant as well as a diluent. It can be compressed into self-binding tablet which disintegratres rapidly when placed in water.

1.4 Extraction of Cellulose

There are three basic steps used for the extraction of cellulose from plant materials; defibering, delignification and bleaching.

The earliest recorded extraction of cellulose from plant material was by Fremy and Turrel (1886). They obtained crude cellulose by treating wood with chlorine and then with aqueous potassium hydroxide. Cross and Bevan (1895) also used chlorination as the first step, but then extracted the chlorinated lignin with hot aqueous sodium sulphite solution.

Defibering was achieved by Asplund (1939) by subjecting cellulose material to heating in a closed vessel to above 100°C without digestion. This was done without adding extra water besides the natural moisture present in the material. Ralph and Lew (1940) were able to isolate a high quality α-cellulose when they treated comminuted hardwood with nitric acid of 50% or less strength for about 24-30 hrs at a temperature of between 60-80°C. Thereafter it was steamed for about 15 minutes, rinsed and to it was added 2% sodium hydroxide and boiled for about 2 hrs. The pulp so obtained was first bleached with chlorine (0.6-2% of the weight of the air dried pulp). Further treatment of the pulp was done with NaOH solution (9-10 times its dry weight) for about 10-20 minutes at room temperature and then finally bleached for approximately 2 hrs with 0.15-0.3% NaOCl (sodium hypochlorite).

Foster and Joachin (1940) adapted a different approach by liberating cellulose from bagasse by the digestion of sugar cane bagasse with sodium hydroxide solution after a preliminary treatment with a solvent or emulsifying agent to remove cane wax from the fibre bundles of the bagasse.

Okhamafe *et al* (1991) extracted cellulose from groundnut shells and rice

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husks and later from bagasse and maize cobs (1995) by treating the materials with 3.5% nitric acid and sodium nitrite to remove lignin; defibering by using 2% NaOH; and finally bleaching with a 1 in 2 dilution of NaOCl at pH between 5-8.

1.4.1 Types of Cellulose

According to their solubilities in 17.5% NaOH solution, crude cellulose can be fractionated into α, β and γ - cellulose (Cross, Bevan and Beadle 1895). The treatment with 17.5% NaOH solution removes xylose and variable amount of other non-cellulosic cellwall constituents.

1.4.1.1 α-Cellulose

This is also referred to as true cellulose. It is insoluble in 17.5% NaOH solution and it represents a much higher average degree of polymerization and approximates pure cellulose.

1.4.1.2 β-Cellulose

This is the fraction of cellulose that is soluble in 17.5% NaOH solution but can be precipitated out by acidification.

1.4.1.3 γ-Cellulose

This fraction is soluble in 17.5% NaOH solution, but unlike β-cellulose, it cannot be precipitated by acidification.

β and γ-cellulose represent non-complex polysaccharides removed during treatment and preparation of α-cellulose (true-cellulose).

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1.5 Maize (Zea mays) Family Graminea

1.5.1 The Maize Plant

Maize is a strong annual grass, usually producing one stem and growing to 1.5-3.0 m in height. Older varieties of the crop mature after 100-120 days but more rapidly maturing varieties are now available. The male inflorescence, called tassel is produced after 50-60 days as a continuation of the main stem. The female inflorescence called the ear or cob is a modified spike formed on a short branch in the axil of one of the largest foliage leaves, about half way up the stem. The silky filaments, which are the stigma of the female flowers emerge shortly after the male flowers have begun to produce pollen. About 5% of flowers on a maize plant will be self pollinated and the rest will be by cross pollination. The seed develop on the cob which is a condenser spike of pairs of spikelets arranged in a spiral.

1.5.2 Origin and Importance.

Maize does not exist in wild state as it has no seed dispersal mechanism. It was widely spread through the Americas before 1500 AD and it is now thought to have originated by at least 7000 BC in Central America (Gibbon and Pain 1985). After 1500 AD, it spread rapidly into Europe, Asia and Africa following early movement of explorers and traders. Maize has since become the dominant food crop in many sub-humid areas of Africa.

The crop has become important because it has several advantages over the other cereals viz:

a) It produces a high output per unit of labour input

b) It is easy to establish and cultivate

c) Birds do not usually eat the grain in the field.

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d) It is easy to harvest, store, transport and process

e) Time of harvest is not critical.

f) It has a wide adaptation to latitude, (50°N to 40°S) and altitude (from sea level to 3300m) (Gibbon and Pain, 1985)

1.5.3. Uses of Maize

Apart from rice and wheat, maize is the world's third most important cereal crop and it has the widest distribution of all the cereals. It is primarily grown for its grain which is consumed as human food. Only a small proportion of total production enters world trade. In some developed countries, maize is also grown for animal feed and as a base for industrial products such as oils, syrup, and starch. The grain may be fermented to produce beverages and then distilled to provide whisky or industrial alcohols, acids, acetaldehyde, acetone and glycerol. The cob residues can be used as fodder, bedding, building material, fuel, and more recently a source of cellulose for pharmaceutical industries (Okhamafe et al 1995).

1.5.4 Ecology

Maize is adapted to warm, moisture conditions and will not tolerate frost or arid conditions unless grown under irrigation. Soil moisture and temperature at planting and during first four weeks of growth have an important influence on subsequent development but the most critical growth period is during the 30 days of rapid growth before male flowers appear. Drought at this stage can seriously impair fertilization and this ultimately reduce yield. The ability of the crop to overcome these stress periods is closely related to the early development of the root system. Unlike sorghum, the maize roots do not develop to exploit the full volume of wetted soil so under similar conditions of stress maize may wilt or die while sorghum will be

able to survive because of its better developed root system.

Though maize has a wide latitude and altitude tolerance, individual varieties only perform well within a relatively narrow latitude and altitude range. Maturation periods in the tropics vary between 6-8 months at 2500 m to 3 - 4 months at sea level. Maize can be grown on a wide variety of soil types provided drainage is adequate and the pH is above 5.0. In almost any part of the dry tropics and under rainfall conditions a substantial soil moisture holding capacity is necessary to carry the crops through dry periods during the rainy season.

When the crop is mature, the leaves dry and the husks surrounding the cob become dry and papery. The grain becomes hard as it looses moisture and the crop is often left in the field until the grain moisture content has dropped to 15-20%. In Nigeria and other dry tropical areas, the crop is harvested by hand by the removal of the cob and husks from the plant. The cobs may be dried further by tying together the husks and hanging them up or putting them in a well ventilated store or crib. Most of the crop is left stored on the cob until needed. Shelling (removal of grain from cob) is mostly by hand or by other locally fabricated mechanical shellers.

1.6 Tablets

Tablets are solid dosage forms of medicinal substances usually prepared with the aid of suitable pharmaceutical adjuncts (Howard, 1981). Depending upon the intended use, and their mode of manufacture, tablets vary in size, shape, weight, hardness, thickness and disintegration characteristics. Majority of tablets are intended for oral administration and many of these tablets are prepared in addition to active medicament with colourants, flavourants and coatings of various types to enhance their taste, acceptability and to give various differentiating characteristics to

the tables. Other tablets such as those intended for buccal administration or sublingual or vaginal may not contain the same adjunct or be prepared to possess the same type of feature as tablets for oral administration.

Tablets are popular due to convenience, ease of administration, precision of dosage, durability and stability of the preparation. The total composition of a tabletting formulation generally represents the selection of a number of ingredients and their concentrations based upon a compromise which will uniformly provide a product with optimal biological properties under the conditions of routine but standardized processing conditions.

Considerable attention must be given to inherent properties of all substances introduced into the formula. Each ingredient should contribute a necessary attribute to the essential requirement and also support the therapeutic objective of the drug substance, permitting compliance with pharmacopoeial or the manufacturers quality standards. Although excipients can indirectly influence the pharmacological activity of a drug substance they should by themselves possess no significant biological potency in the concentration used in tablet compositions.

Materials intended for compression into a tablet must possess two essential characterictics fluidity and compressibility. Fluidity is necessary for the easy transport of the materials through the hopper into the feedframe. Compressibility is the property of forming a stable compact mass when pressure is applied.

The techniques for preparing tablets should confer on the granulation or powders fluidity and compressibility by possessing these properties, viz:

- They should contain particles which approach spherical shapes so as to minimize interparticulate friction and to be relatively free from static charges.

- They should present a range of particle sizes that resembles a normal distribution curve, with a suitable percentage of coarse and fine particles and with the rest in a rather narrow range between.
- They should have a uniform distribution of all the ingredients in the formulation.
- They should possess compressible components that will confer physical strength and form to the tablet. These components may be the active ingredients themselves or more likely, added diluents.

1.6.1 Methods of Tablet Production

The techniques for preparing tablets may follow one or a combination of several established methods which are

1. Dry methods
   a. Direct compression
   b. Granulation by pre-compression and comminution
2. Wet Methods
   a. Massing and Screening
   b. Special procedures
      i) Fluidized granulation
      ii) Spray dried granulation
      iii) Selective crystallization.

Compressed tablets are made by compressing with a force of up to 10 metric tonnes (Audu-Peter, *et al* 1999) fine crystals, free flowing powders or granules in a die between punches. Materials to be tabletted must have certain physical properties including

a) "Cohesiveness" that is, the tendency of individual particles in the powder to bind to one another.

b) Lubrication

c) Ability to flow freely.

Very few pharmaceutical materials possess these characteristics and the methods of tablet production are developed to impart these properties to the material being compressed.

Wet Methods.

i) Massing and Screening:

This is the traditional and most popular method of tablet production. The steps involved in this method include:

- Weighing and mixing of drug powders
- Moistening of powder mix with granulating solution which is usually a solution of a binding agent.
- Screening of the moist mass through a predetermined sieve size to produce granules
- Drying of the wet granules in hot air oven or in fluidized bed drier.
- Seiving of dried granules to breakdown aggregates and to remove excess fines.
- Any remaining excipient like extragranular binder, lubricant and extragranular disintegrant are added.
- Compression of granules into tablets.

ii) **Special Procedures.**

a) **Spray dried granulation.**

The active medicament and tablet excipients are suspended or made into thin paste or slurries in a suitable vehicle. The fluid is dispersed as fine droplets into a moving stream of hot gas where they evaporate rapidly before reaching the wall of the drying chamber. The product dries into μm micrometer fine spherical granules ranging from as low as 10μm to as high as 250 in diameter. The size of the granule depends on the speed and flow rate of the slurry.

b) **Fludized granulation.**

Dry ingredients are placed in a chamber and fluidized by air stream while the granulating liquid is sprayed into the bed, causing the particles to agglomerate into granules. In this processes the agglomeration and drying are almost simultaneous.

c) **Selective crystallization.**

Depending on the temperature of the crystallizing solution, large or small crystals, which are free-flowing, are formed, filtered and dried.

ii) **Dry Methods.**

It is generally agreed among most manufacturers that when possible, the dry methods are superior to those employing liquids since these dry processes do not require as many equipment and handling expenses required in wetting and drying procedures of wet methods. In addition, dry methods may over-come the problem encountered with moisture and heat sensitive drugs.

a) **Direct compression method.**

Only few crystalline substances like inorganic salts (e.g. sodium chloride, sodium bromides, potassium chloride) and aspirin form suitable direct compression materials. The steps involve breaking down the crystals and passing them through sieves to select required size. They are then mixed with diluents or disintegrants if necessay in the dry state and the mix is compressed into tablets.

The direct compression of a single substance may produce tablets that may not disintegrate e.g aspirin. A disintergrant needs to be added to counter the problem. Most materials possess weak intermolecular attraction or are covered with films or absorbed gases that tend to circumvent the effects of compaction. With most drugs the effective dose is very small and its direct compression is impractical and uneconomical without the additin of a suitable diluent. A directly compressible diluent is an inert substance which may be compacted with no difficulty and which do so even when larger quantities of drugs are mixed with it. It will still retain its capacity to compact when blended with other tablet materials necessary for flow, compaction, extrusion and disintegration. Compressible diluents include spray-dried lactose, mannitol, sorbitol, and microcrystalline cellulose.

Microcrystalline cellulose (Avicel ^{R}) is one of the few materials used in tabletting that combines two desirable properties for tablet vehicle in direct compression. These properties are binding and disintegration properties. Thus it is able to produce very hard tablets, yet disintegrate rapidly in water due to swelling of the crystalline particles and destruction of the bonding

forces holding them together (Gunsel and Kanig, 1976)

Compression studies carried out with microcrystalline cellulose and mixtures of it with other directly compressible vehicles indicate that it acts as an auxilliary dry binder and increases the compressibility of the other substances (Fox et al, 1963). The addition of 5 - 10% microcrystalline cellulose is often very useful in improving tabletting characteristics of other diluents.

b. Granulation by compression (slugging)

The steps in this method involve mixing drug and diluents as powder, feeding the mix into a heavy-duty compressing machine to form large tablets called slugs with sizes depending on die and punch size. The slugs are then comminuted through desirable mesh screen by hand or mechanical mills. Alternatively, mixture of powder are passed between high pressure rollers to compress powder and remove air to produce sheets which are then comminuted in a mill and then tableted. This method is valuable for materials which cannot be compressed directly and are at the same time thermolabile and/or moisture sensitive. Examples of such materials are aspirin, ascorbic acid and acetophenetidine (King, 1970)

1.6.2. Forms of Compressed Tablets

Tablets are made with specific end use and mode of administration in mind and they are administered as chewable, effervescent, sublingual or soluble tablets. Due to problems of stability, or to achieve prolonged action, others have been made into multi layer and compression-coated tablets.

a **Chewable tablets.**

Most available chewable tablets are antacids. They are preferred by patients

who have not yet learnt to wash down with water e.g. children. The form also makes it possible to take medication at any time or place, when water is not available. Chewing speeds up disintegration and begins the wetting of the metallic salts used in antacid tablet production. Many of these salts are hydrophobic and are slowly soluble. The production of chewable tablets mostly involve wet granulation techniques. The choices of binder and other auxiliary materials depend heavily on the anticipated effect or taste in the mouth. Satisfactory mannitol granulations are usually made with adhesive solutions by methyl cellulose, gelatin and starch pastes. Gums are avoided with these substances that produce hard granules. The use of disintegrants is unnecessary since the mastification by the teeth performs the function. When possible, the lubricant should be chosen on the basis of their contribution to the taste of the tablet.

b. Soluble tablet

The early methods of production is the moulding of lactose and active ingredient with aqueous alcoholic solution. The damp mass is forced into moulds and dried. With advent of antibiotics, soluble tablets made from them become more popular, particularly for administering to infants in formulae or other suitable liquids e.g. soluble cyanocobalamine tablet. The problem with the production of soluble tablet is in finding a suitable soluble lubricating and mould releasing agent. The criteria in selecting excipient for soluble tablet base include that all of them be completely soluble, inert, non-toxic and contribute no significant taste of their own. Examples of such lubricant was developed by Sperandio and Dekay (1952) which include a

mixture of 4% sodium benzoate and 1% sodium acetate as 60 - mesh powder with powdered polyethyleneglycol 4000 which they said made satisfactory tablets with lactose granulated with a 2% solution of glucose.

c. **Effervescent Tablets**

The production of carbon dioxide by alkali metal carbonate or bicarbonate with tartaric or citric acid in water has been employed in conjunction with medicaments to hasten their dissolution and increase palatability (Gunsel and Kanig, 1976). Two methods are used for production of effervescent tablets;

i **Wet Fusion**

Sodium bicarbonate is added to moist citric acid. Partial fusion occurs and granules are formed by kneading then together in a suitable mixer. The granules are tableted while still damp as the moist citric acid act as the lubricant. The tablets are dried at 70 - 73^{0}C and drying hardens the tablets. They are then packaged in aluminum foil lined with polyethylene. Alternatively, the alkali and acidic materials are granulated separately and then mixed together after drying for tableting.

ii. **Heat fusion**

All components including 15 - 25% of citric acid monohydrate are blended. The batch is heated while it is mixed until the molecule of water in the citric acid is released and becomes the granulating agent

The choice of auxiliary excipient in effervescent tablets should be such that it should be water soluble, not hygroscopic and should not react with each other.

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d. **Buccal and sublingual tablets**

These are tablets meant to dissolve under the tongue or in the buccal cavity. They are designed to release their active ingredients slowly because absorption is slow. Buccal products are often small, oval or flat and are formulated like chewable or sucking tablets. They contain large proportion of mannitol and /or sucrose to impart sweetness and binding action to retard disintegration.

e. **Implantation pellets or tablets**

These consists of small tablets of compressed drug usually without excipient. They must be asceptically prepared and sterile. They are designed for insertion into body tissues by surgical procedures, where as an result of their hardness and low solubility, they are slowly absorbed into body to exert their action. Implants are used largely for administration of hormones like testosterone and stilboestrol.

f. **Multi layer Tablets**

These are made by compressing several different granulations fed into a die in succession, one on top of the other, in layers. Each layer is from a separate feedframe with individual weight control. Multilayered tablets have the advantages of:

- Keep separately two or more incompatible drugs in a single tablet;
- separate layer of each drug can be made with different colour for easy identification;
- accurate control of the delayed or prolonged action portion of a tablet is feasible; and

- the multi layer presses having greater out put than the compression coaters and therefore cheaper to produce.

g. **Other types of tablets include:-**

- compression coated tablets
- enteric coated tablets
- film coated tablets
- sugar coated tablets
- lozenges.

1.6.3. Tablet excipient

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials, known as additives, excipients or adjuncts. They may be classified according to the part they play in the finished tablet. The first group are those which help to impact satisfactory compression characteristics to tablet formulation and they include diluents, binders and lubricants. The second group are those that give additional desirable physical characteristic to the finished tablet and included in this group are colours, flavours, disintegrants and sweetening agents.

1.6.3.1. Diluents (also called fillers).

Diluents are pharmacologically and chemically inert materials added to tablet formulae in order to reach the minimal bulk volume required to compress a tablet to convenient size. They are especially useful in very potent and microdose drug tableting. Ideally, diluent should be cheap, non-toxic and inert with respect to the drug and its particle sizes should be approximately equal to that of the drug to facilitate mixing.

Examples of diluents include sucrose, lactose, spray-dried lactose, powdered

starch and dibasic calcium phosphate. (HPE, 1994) The choice of diluent in direct compression technique is especially critical as such diluent apart from increasing bulk volume of the mass of power should have good flow, and compression characteristics as observed with spray-dried lactose. The choice of diluent will also depend on the type of tablet. (Thus mannitol is used extensively as diluent in chewable tablets due to its pleasant taste). Chemical stability and lack of hygroscopicity were demonstrated by Brownley and Lachman (1964) who also showed the difference in colour stability between tablets prepared using spray-dried and conventional lactose in otherwise identical formulations. The selection of diluent for use is also influenced by experience and cost factors. However, in the formulation of a new therapeutic agent the compatibility of the diluent with the new drug substance must be considered. For instance the use of calcium salts as diluents for tetracycline has been shown to interfere with the drug absorption from the gastro intestinal tract. (Boger and Garvin 1959).

1.6.3.2. Binders

These are cohesion agents added to tablet formulations in order to impact structural strength required during processing, packaging and handling of the tablets. Examples of such agent are gums like veegum, cellulose like methylcellulose, carboxy methylcellulose, sugars like glucose, polymers like polyvinyl pyrrolidoine and copolymers like polyvinyl pyrrolidone - vinylacetate.

Cohesiveness in powdered materials is desirable because it improves free flow of granules made from such materials. Free flow is desirable in granules so that tablets compressed will have desired hardness and weight. This is because the uniform flow of the granules from hopper to die ensures uniform filling throughout

compression cycles and hence tablets of uniform sizes and hardness ensue.

The concentration of binder used has a considerable influence on the disintegration characteristics of the compressed tablets. The choice of a binder will depend on the type of other excipient in the formulation. Materials which do not possess cohesive property of their own will require a stronger concentration of binder than those with cohesive properties. Binders in solution usually possess more cohesive power and therefore more effective than dry binders. Some important drug binders are microcrystalline cellulose (Avicel^{R}), amylose and polyethyleneglycol (PEG).

Binders act by forming the necessary bonds between particles to form granules which under compaction pressure form a cohesive mass or compact known as the tablet.

The nature, concentration and mode of incorporating the binder will influence the compression characteristics of given tablet. Therefore, these factors must be evaluated empirically for each formulation to prevent adverse effects. Thus workers like Jacob and Plein (1968) have shown that increasing the binder (gelatin solution) concentration caused an increase in the mechanical strength of phenobarbital tablets but at the same time resulted in a decrease in the dissolution rate of the tablets.

Others like Sakr *et al* (1972) reported that as the concentration of gelatin binder increases in lactose tablets, the friability decreases but disintegration and dissolution times increased.

Apart from retarding disintegration and dissolution rates of tablets, excessive binder can also wear out prematurely punches and dies with regular compression of

such formulations. In rare cases, tablet capping can occur with high binder concentration in formulation. On the other hand, inadequate binding agent will cause inadequate binding and formulation of extremely soft tablets. Of interest and increasing importance is the use of dry binders for direct compression of tablets. The main objectives of direct compression is to produce a pharmaceutically elegant tablet within minimum processing time and cost. But most drugs cannot be compressed directly. Therefore, one or more agents have to added to be impart suitable compression properties. A major set back of this development is the fact that most of these additives are either too costly like microcrystalline cellulose (Avicel^{R}) or react with the active ingredients to decrease stability eg. Lactose, dicaluim PO_4 or drug bioavailability. Moreover, the ratio of these additives to the drug necessary to effect compression characteristics may preclude use with macrodose drugs.

1.6.3.3. Lubricants

Three main difficulties are usually encountered in tablet compression. They include the ease of flow of granules, adhesion or sticking of granules or powders to punches and dies and the ejection of tablet from the die after compression. They are ameliorated by a group of substances collectively referred to as "lubricants". Cooper and Pasquale (1958) defined lubricants in tablet technology as substances which facilitate the passage of a granule or powder through the various orifices of a tableting machine based on their ability to carry out certain functions Munzel classified lubricants into three groups:-

a. Glidants

These act as flow regulators and improve the flow properties of the granule

in the feed hopper, thereby eliminating the problem associated with flow of materials from larger through smaller apertures in the tablet press. They are not generally deformed significantly under the pressure of compression forces. Jones and Pilpel (1966) investigated the mechanism by which glidant improve flow and classified them into two categories based on their findings:-

i those that reduce vander Waal's type of interparticle cohesive forces;

ii those that reduce surface rigosity and hence coefficient of interparticle friction e.g. talc.

Another mechanism of action of glidants was proposed by Gold *et al* (1966) who said glidants act by filling void spaces between large particles with fine particles which may be chemically similar or dissimilar to the materials with which they are admixed. There is a limit however to the concentration of fines and other glidant to be added to a specific tablet formulation in order to improve flow properties and above this concentration, granule flow rate decreases and becomes erractic. This was explained by the theory of "Cohesive bridging" of the fine particles by Trevor (1968).

Examples of glidants are talc, starch, magnesium stearate, sugar and sodium chloride.

b. Anti-adhesives and Anti-sticking agents

These prevent the adhesion of tablet surfaces to dies and punches during compression. They are easily deformed under compression pressure. Examples are paraffin, stearic acid, cocoa butter and soaps.

c. **Proper lubricants**

These act by reducing interparticle friction during compression and also reduce friction between tablet and die wall during ejection cycle and therefore facilitate tablet ejection. Example of the proper lubricants include talc., calcium stearate and magnesium stearate. Most commonly used tablet lubricants are hydrophobic substances. This is because the most efficient lubricants are materials that are water insoluble due to the relationship that exists between degree of lipophilic properties and general effectiveness as tablet lubricants. Since hydrophobic lubricants by their water-repellant properties can markedly interface with disintegration and dissolution of tablets, it is practical that a sufficient quantity of a lubricant should be used to optimise tablet manufacture but its concentration in compressed tablet should be as low as practical to prevent a marked slowing of dissolution and therefore absorption. An example of hydrophobic lubricant is magnesium stearate whose mechanism of retarding dissoluting of tablet is attributed to its inhibition of penetration of solvent into tablet (Levy and Gumtow, 1963). Others, Lachman *et al* (1976) attributed the mechanism to a complex reaction in which the magnesium stearate modifies the mechanism of bonding during compression and therefore break up of the tablet in water. Hqwever, inhibition of penetration of solvent remains the major mechanism and Ganderton (1969) has shown that inhibition of penetration by liquids is approximately proportional to the concentration of magnesium stearate. The inhibition of penetration is due to the high contact angle with water; and contact angle of water with magnesium stearate is greater than 90° so that

water will not penetrate a tablet composed of this material only. When magnesium stearate is incorporated in a tablet formulation, capillaries composed of some proportion of magnesium stearate will not transmit water and the proportion of capillaries so affected will depend mainly on its concentration. Higher concentration yield an increase in the non-wetting surface and the number of capillaries not contributing to the transport of water, hence the slower rate of dissolution.

In the light of these disadvantages with use of hydrophobic lubricants, investigations were carried out (Lachman *et al* (1976) on the potential use of hydrophilic lubricants like sodium benzoate, sodium lauryl sulphate, polyoxyethylene monostearate and sodium acetate. Sodium lauryl sulphate, a surfactant and with high lubricating activity was found to enhance dissolution rate of salicylic acid tablets and granules as a result of the lowering of interfacial tension by virtue of its surfactant action.

The method of incorporating lubricants into tablet formulation are by two principal ways:-

(I) internal lubricant e.g stearic acid and hydrogenerated oil are dissolved in appropriate solvents like chloroform and isopropanol and added to the moist powder mix before granulation process;

(ii) external lubricants eg. magnesium stearate and calcium stearate are usually added in form of fine powder (passed through 60-85 mesh sieve) to the dried granules prior to compression.

They are thought to function by coating the surface of the granules with a film which reduces interfacial friction between the granules

and the compression surface.

1.6.3.4 Disintegrants

These are substance added to the tablet formulation to facilitate its break up by overcoming the cohesiveness of the compact and release the drug particle for solubilization in the gastrointestinal fluid within a limited period of time. For a drug to elicit its pharmacological action, it must be present at the site of action at a therapeutic concentration level. Being a solid dosage form however, the medicament present in the tablet must find a way of escape into the surrounding fluids of the body which will take it to the site of action. Disintegrants function to break open the tablet into granules which subsequently dissolves in the gastro intestinal fluids and are absorbed. Thus the function of the disintegrant cannot be over emphasised and the rate of disintegration is critical to the overall therapeutic level of the drug at the site of action.

Disintegrants can be classified according to their natural sources and they include starches, celluloses, algins, gums and clays (Feinstenward, 1966). Fakhouhi et al (1963) based their classification on the mechanism of action of the disintegrant and they include:

- agents that react with moisture to constitute a foam
- effervescent substances that react with moisture to produce a gas.
- substances that react with moisture to swell

Those disintegrant that "absorb moisture and swell" are the most commonly used and they include starches like corn starch, potato starch, wheat starch and rice starch. Other disintegrating agents include gums like veegum, magnesium and aluminium silicate, alginic acid, cellulose derivatives like carboxymethyl cellulose,

ethyl cellulose, microcrystalline cellulose, polymers, cation exchange resins and synthetic polymers like cross-linked polyvinylpyrrolidone

Methods of incorporating disintegrants into tablet formulations.

Opinion differ on the best method for adding disintegrants. Some formulators add the total amount to granules just prior to compression (extra granularly) because they insist the disintegrant must be dry and the state can best be controlled at this stage. Another way is to add the disintegrant to the total mass of powered materials before the wet granulation process take place. The drying cycle of process, they argue will dry the agent sufficiently to permit it to function adequately and in addition the method places the disintegrant at the site where it can exert maximum effect i.e. within the granules where the binding agent is present. This argument however do not hold true for disintegrants that are gums, since on wetting, they become binders.

A third approach utilises the important features of both to the best advantage. The total disintegrant is divided so that one portion (usually half) is added to the powderedcomponents before the wet granulation process and the remaining portion is added to the finished granulation just prior to compression. This method thus is able to place the disintegrant between the granules as well as within them so that the disintegrating action will not only force the tablet apart into the original granules but will also break down the granules themselves (Ojile, 1995)

Theories of Disintegration

The mechanisms by which disintegrants in use elicit their action had generated controversy which has led to the development of new and more effective disintegrating agents. Some of the theories put forward to explain their mechanism

of action are as follows:-

i. **Evolution of Gas**

Bicarbonates are usually incorporated into the tablet so that when the tablet comes into contact with water, carbon dioxide is released, disintegrating the tablet in the process. Disintegration occurs because there is a build up of internal pressure within the tablet when the bicarbonate reacts with water to produce carbon dioxide gas. This results in the generation of pressure within the tablet causing the tablet to expand and eventually burst open to release the pressure. This bursting of the tablets is what is know as its disintegration.

ii **Heat of wetting**

Heat is produced when a tablet is immersed in water and this causes the entrapped air in the tablet to expand and exert sufficient pressure to disintegrate the tablet.

iii **Effect of water**

When a tablet comes into contact with water, the disintegrant incorporated in the tablet absorbs the water and other ingredients of the tablet that is water soluble are dissolved. This leads to the breakdown of existing bonds between the ingredients and the disintegrant and hence the collapse and disintegration of the tablet.

iv **Swelling**

Grains of disintegrants, particularly starch swell in the presence of water. The swelling causes an increase in the size of the starch grains, making them large and exacting pressure on the granule to create more space. This causes

the tablet to expand and when the bonds are totally destroyed by the force of expansion, the tablet disintegrates.

v **Capillary action**

The spherical shape of the starch grains increase the porosity of the tablet, promoting capillary action (wicking action). Water is absorbed by this capillary action and this disturbs the internal bonds formerly existing in the tablet. Other water soluble ingredients dissolve in the water and contribute to the disruption of the internal bonds, causing disintegration of the tablet.

Properties of disintegrants

Results of studies carried out by Odusote *et al* (1987) show that there is a correlation between hydration capacity as well as the swelling power of starches with the disintegration time of tablets. Increasing hydration capacity or swelling capacity of starches decreased disintegration time. This means a substance must have high hydration or swelling capacity for it to be a good disintegrant.

Chemical substances may also be used as disintegrant due to their ability to react in presence of water to produce gas, which subsequently increases the internal pressure of the tablet causing disintegration. Therefore the ability to produce gases like carbon dioxide is also important and may be considered a good property of a disintegrant.

Because capillary network of disintegrant within tablet facilitates uptake of water in to the tablet, breaking it up, substances with high capillary network may be considered good disintegrants. Curlin (1955) has suggested that the disintegrating effect of starch is due to capillary action rather than swelling. Kornblum et al (1973) have also shown that disintegration property of polyvinylpyrrolidone (PVP) is due to

capillary action. It can therefore be said that high affinity for water is imperative for any good disintegrant.

1.6.3.5 Colouring Agent

Colours are incorporated in tablet formulation for the following reasons.

i. to make the tablet more elegant in appearance so as to appeal more to the user;

ii it helps the manufacturer to control the mixing of the drug and for identifying various drugs during processing and quality control in laboratories which manufacture different drugs at the same time;

iii it serve as a means of identification of various drugs by the user.

In general colours and dyes used in tableting must be safe for human consumption and should comply with the requirements of the legally controlling body in the particular country.

A major problem in the manufacture of coloured tablet is the phenomena of motling which is defined as "an unequal distribution of colour on the surface of tablet, with light or dark areas standing out in an otherwise uniform surface " (Gunsel and Kanig 1976). Motling has been attributed to the migrating dye with the granulation fluid during drying. Armstrong and March (1976) have outlined some suggestions on how to minimize motling as it cannot be eliminated completely as follows:-

- drying of granules should be by method that prevents intergranular migration of the dye e.g fluid bed drying as opposed to tray drying.
- granules should not be subjected to a comminution process after drying, otherwise the dye deficient interior of the granules will be exposed.

- and as far as commensurate with granular flow properties, the granular size should be as small as possible. In such granules, the amount of dye available for immigration is minimised and the colour contrast between the periphery and the interior reduced.

1.6.3.6. Flavouring and Sweetening Agents

These are often used in chewable tablets and lozenges to improve taste and flavour.

1.6.4 Tablet Properties

The way a tablet is made may have profound effects on the biological availability of the medication in it. The manufacturer must therefore, achieve a fine balance between those factors that are necessary to produce an elegant tablet with those that effect the utilization of the drug.

A good tablet should meet the following specifications:-

i they should contain the stated active agent within the permissible limit;

ii. they should be sufficiently robust and able to withstand the rigours of mechanical treatment involved in production, packaging, shipment or transportation and dispensing;

iii. the tablets should be reproducible at any time in their disintegration and dissolution properties in a predictable manner;

iv. they should be elegant in appearance and should not have any physical defects like chipping, cracks and discolouration; and

v. the tablet should have reasonable chemical and physical stability of the active medicament throughout its shelf life.

To ensure these properties of tablet from batch-to-batch during production,

appropriate tests and specifications have been developed which are capable of guaranteeing quality. These tests include:-

a. **Tablet weight variation test.**

The actual weight of tablet is determined by the geometry of the die and the weight adjustment cam on the tablet machine. Tablet weight is determined then by the amount of fill placed in the die. A tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. The weight of the tablet is routinely measured as tableting procedure proceeds at intervals of says 30 minutes to three hours. About 20 tablets are individually weighed and then they are weighed together and the mean determined. The deviation of each tablet weight from the mean must be within official limits. Since a more uniform weight means uniform amount of granules or powder in each tablet this test can be used to determine rough estimate of content uniformity of the tablet especially with high dose tablets.

Weight variation tolerance for uncoated tablet - USP

Average weight of tablet (mg)	Percentage difference (%)
130 or less	10.0
from 130 through 324	7.5
more than 324	5.0

Twenty tablets are individually weighed and then the average calculated. It is expected that not more then two of the tablets differ from the average weight by more than the percentages listed and no tablet differ by more than double the percentage.

b. **Drug content uniformity**

This is a test used to detect dose variation in the tablets which may arise from uneven distribution of the active ingredient throughout the tablet mass.

It is determined by grinding a large sample of the tablet and the aliquot is analysed.

U.S.P XVIII describes the content uniformity test. If the individual monograph requires testing for context uniformity, a representative sample of 30 tablets are selected and 10 are assayed individually. At least nine must comply within ± 15% of the declared potency and non may exceed ±25%. If not more than 2(two) exceed the ±15% limit, the other twenty are also assayed. None of these may fall outside the limits.

c. **Tablet thickness and diameter tests.**

The dimensional specification of tablet are important for reasons like:

- ensuring that tablets of given strength and weight are approximate size which would otherwise be frowned at by some patients and other users; and
- presenting no problem during packaging.

Micrometer calipers or veiner calipers are used to determine tablet thickness and diameter . Tablet thickness is directly related to tablet hardness and is therefore used as an in-process control of tablet hardness in routine manufacturing of tablets. A change in tablet thickness is often an indication of problem of flow through the feeder or a faulty deposition of granulation in the die.

Undue Thickness variations not only interfers in the tablet hardness, but packaging problems occur especially for packaging container holding more than 500

d. **Friability Test**

This is a measure of the surface hardness of a tablet. The test provides an indication of the likely edge damage that may occur when the tablet is handled during packaging, transportation and dispensing.

The test is determined by using a friabilator which drops tablets through a fixed distance during each revolution of a horizontally disposed plastic-drum.

The permissible loss in weight is usually set by production experience, but with the friabilator, a usual range of 1.0 to 5.0% for ten minutes treatment is allowed. (Rawlins, 1977) Friability is not a Pharmacopoieal standard but percentage change in weight in the range of 0.5 to 1.0% is mostly acceptable by most manufacturers.

e. **Tablet hardness test.**

A tablet requires certain amount of strength or hardness to be able to withstand mechanical forces of handling during manufacture, packaging and transportation. A relationship exist between tablet hardness and disintegration time and more significantly drug dissolution (Deshpande, 1984.)

Tablet hardness monitoring is important for drug products that possess real or potential bioavailability problems or are sensitive to altered dissolution release profiles as a function of the comprehensive forces employed. The commonect unit of measurement of the hardness is the kilogram force. It is the value at which, when sufficient force is applied, the tablet breaks. There is no official range of values for tablet hardness. It should therefore be controlled during production so that the product is firm enough to withstand handling without breaking, clipping or crumbling and yet not so hard that the disintegration time is unduly prolonged.

Hardness is measured by placing the tablet between the jaws of the Monsanto harness tester. The force is applied to the edge of the tablet gradually by turning the compression screw. The tablet breaks when its hardness is overcomed by the applied force.

f. **Tablet disintegration time test**

For the medicinal component of an oral tablet to be fully available for absorption from the gastro intestinal tract, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution and subsequent absorption. Complete tablet disintegration is defined by the NF XIII as "..... that state in which any residue of tablet, except fragments of insoluble coating, remaining on the screen is a soft mass having no palpable firm core". This makes tablet disintegration a necessary first step to achieve rapid availability of the active medicament. The importance of the test as a parameter in quality control to tablets cannot be overlooked.

The current emphasis on the bioavailability of drugs highlight the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behaviour. When the disintegration process is slower than the deaggregation, dissolution and absorption processes, then disintegration will be rate limiting. One might expect a reasonable correlation between disintegration measured in vitro and some in vivo parameters like physiological availability. A quantitative correlation exists between physiological availability of drug with its disintegration time with only few exceptions (Ojile *et al*, 1999).

The disintegration time test measures the time it will take a tablet to breakdown into small granules when placed in an aqueous medium. Several

equipment have been designed to determine this factor but the most commonly used is that based on the B.P specifications.

The apparatus consists of six perspex tubes of which the bottom are sealed with number 10 meshes perinch (1700cm). A tablet is placed in each tube attached to an arm. The tubes are then adjusted such that they are always immersed in the disintegrating medium. The up and down movement is set at 30 cycles per minute.

The disintegrating medium which is normally distilled water is placed in a water bath at 37°C ± 1°C. Complete disintegration occurs at the state in which any residue of the tablet, (except fragments of soluble coating remaining on the screen) is a soft mass having no palpable firm core.

All uncoated tablets should disintegrate within 15 minutes.

Factors affecting disintegration time of tablets are complex and diverse, but they have been divided into two:-

a. those variables involved in the disintegration test; and

b. those variables involved in the dosage forms, ie pharmaceutical factors (Wagner, 1971)

a. Variables involved in the disintegration test.

i. The apparatus.

The type of apparatus used determines the intensity of agitation (ie rate of stirring) which is governed by apparatus geometry, presence or absence of turbulence, use of plastic disks, etc. Plastic disks are used to increase solid-to-solid contact (as in the stomach) and to overcome problems of tablets floating in test fluids. Disks may however introduce errors or deviation in the test because many tablets may adhere to the rising and falling disks, or

adhere to the bottom of stainless steel wire cloth. This result in flattening out of tablet core as a result of constant action of falling disk on the same point of the tablet surface.

ii. The composition of the test media determines its pH, ionic strength,, viscosity, surface tension, etc. Each of these properties affect test result in most cases. For example, the addition of gastric mucin to the disintegration medium caused increase in the disintegration time and the increase was proportional to the viscosity of the mucin or methyl cellulose (Munzel and Kuhn, 1962). It has also been shown that acidic solution and simulated gastric juice resulted in faster disintegration rate than water (Hecht and Huyck, 1964).

iii . Effect of temperature.

The normal body temperature is usually at 37°C and since temperature of test medium is usually at constant 37°C ± 1°C, it may not be regarded as variable.

b Pharmaceutical factors

More often than not, the physical properties of the drug, the pharmaceutical additives employed in the tablet formulation and the manufacturing techniques, procedure and equipment used affect the disintegration rate of tablets.

Surfactants by their wetting properties generally enhance water penetration into tablets by reducing contact angles and therefore increase disintegration rate.

Binders may have significant effect on disintegration and this effect would depend on the nature of the basic materials, binder concentration and pressure used in compacting tablets. For example, binders from gum may form gel barrier around

the tablet and this inhibit disintegration and if the binder concentration is sufficiently large, delayed drug release occurs. (Huber *et al*, 1966).

Lubricants, especially the hydrophobic types, increase disintegration time if present in the tablet formulation in high proportion and magnesium stearate has been found to lengthen disintegration time (Alpar *et al*, 1969).

Compressional force is one of the most important determinants of tablet disintegration time and this was first investigated by Higuchi *et al* (1953) . They investigated the influence of compressional force on the apparent density, porosity, hardness, disintegration time and average particle size of compressed tablets. Among other things, they found that there was a logarithmic relationship between disintegration time and compression force. A plot of logarithmic disintegration time versus compressional force was linear with positive slope indicating that disintegration time increased rapidly with little increase in compaction pressure. Similar result was obtained with starches by Manudhane, *et al* (1969).

These forgoing discussion indicates that the disintegration of tablet is a complex phenomenon depending on the interactions between all variables of formulation and processing.

The routine application of disintegration test and proper evaluation of the data present a simple and useful form of production control. When correlated with in vivo test parameters, the disintegration tests can be used to predict physiological availability and in vivo tablet performance.

f Dissolution rate test

Dissolution rate test affords an objective means of determining the dissolution characteristic of a drug present in a solid dosage form.

Since drug absorption and physiological availability are largely dependent upon having the drug in solution state, simple dissolution characteristics are an importance property of a satisfactory drug production. There are adequate evidences to conclude that the rate at which a drug dissolved from its intact or fragmented dosage form in the gastro intestinal tract often partially or completely controls the rate at which the drug appears in the blood, ie, rate of absorption. This is particularly true for drugs which are poorly soluble say less than 1% in aqueous fluids in the physiological pH range (Wagner, 1971).

Mechanism of dissolution

Higuchi (1967) proposed three processes by which, either alone or in combination, dissolution occurs.

1. **Diffusion layer model.**

This proposes that a static film is adjacent to the solid surface area. Reaction at the solid/liquid film interface is rapid, and dissolution is governed by the diffusional transport of the solute molecules through the liquid firm. Once the solute molecules pass the liquid film/bulk film inter-face, rapid mixing occurs and the concentration gradient is destroyed.

2. **Interfacial barrier model**

This assumes that the reaction at the solid surface is not instantaneous due to a high free energy of activation required. This process at the solid/liquid film interface now becomes rate limiting step with respect to the transport process.

3. **Danckwerts' model.**

In this model, one imagines macroscopic packets of solvents reaching the solid liquid interface eddy diffusion in a random fashion. During its residence at the

interface, the packet is able to absorb solute according to the laws of diffusion. These surface elements are continuously replaced by new packets of solvent. Assuming the solid surface reaction to be instantaneous, the rate at which this process occurs is related to the solute transport rate.

The Dissolution Rate Apparatus

The B.P dissolution apparatus is the most commonly used dissolution apparatus. It consist of

- water bath
- cylindrical stainless steel basket in which the tablet is placed.
- a variable speed motor .

The test is carried out by placing one tablet in the basket which is situated 2 cm above the bottom of the vessel containing 900 ml of 0.1M. HCl or other medium specified in the monograph of the drug. The medium is maintained at a constant temperature of 37 °C ± 1.0^{0}C. The basket is then driven by variable speed motor at the rate specified in the monograph. Samples are withdrawn at specified intervals to determine the amount of the drug in solution by using suitable analytical procedure. The results are plotted as concentration versus time. Values for $t_{50\%}$, $t_{90\%}$ and the percentage dissolved in 30 minutes are used as guides.

A $t_{90\%}$of 30 minutes is satisfactory as USP XVIII has set limits of 60% dissolution in either 20 or 30 minutes in six of the seven tablet monographs that require dissolution test.

Factors that affect dissolution rate

1. Intensity of agitation, rate and type of flow of fluids and geometric factors.

Generally the rate of solution of a drug substance maintaining a constant surface

area during dissolution is described by the Noyes - Whitney equation.(Lachman *et al* 1976)

$dc/dt = KS(C_s - C)$..... 1

Where dc/dt is the rate of dissolution

K = a constant

S = surface of area of dissolving solid

C_s = may be approximated by the solubility of the drug in the solvent and

C = the concentration of the drug in the solvent at time t.

The constant K is equal to D/h where D is the diffusion coefficient of the dissolving material and h is the thickness of the diffusion layer.

Therefore equation can be written as

$dc/dt = D/h\ S(C_s - C)$..... 2

The rate of agitation of the solvent about the dissolving solid significantly affects the thickness of the diffusion layer. The greater the agitation the thinner the layer and the more rapid the dissolution.

2. **Temperature**

For a given drug, the diffusion coefficient, D, and usually C_s increases with increasing temperature. Therefore dissolution rate is temperature dependent.

3. **Viscosity**

Diffusion coefficient D is inversely proportional to viscosity, and therefore dissolution rate decreases as the viscosity of the solvent increases.

4. **pH or nature of solvent**

Changes in the pH or nature of the solvent influences the dissolution rate. The use of different salt, other chemicals or physical forms of the drug which have a

different solubility from the parent drug affect dissolution rate.

5. **Particle size**

Equation 2 indicates a relationship between the surface area (S) of drug exposed to the dissolution medium and the dissolution rate. Increasing S as for example by particle size reduction, will increase the dissolution rate.

1.7 Powders

Powders are collections of discrete particles less than 1mm in diameter (Bangudu, 1985). They are non-homogenous structurally, and consist of particles of different shapes and sizes with interparticulate voids and a multitude of interacting surface, exhibiting complex physicochemical and mechanical properties (York, 1983). They are similar to liquids in that they deform and flow when stressed; and to solids because they are able to exhibit elastic recovery and brittle fracture. Unlike solids however, they can be compressed or consolidated by the application of pressure.

Powders are used in many pharmaceutical processes. The increasing production and use of fine powders in the pharmaceutical industries highlighted the need for reliable method for assessing their mechanical properties and general handling characteristics. Two important properties of the powder to the industrial pharmacist are its flow and packaging properties.

Flow properties are important for maintenance of weight and ultimately uniformity of drug content in each batch of tablets produced. Often flow property of the powder can be improved by granulation to facilitate powder transport and powder feeding from hopper to die cavity.

The packaging property of a powder is the manner in which the particles of

the powder pack together to form a bed and its influence on bulk density.

The bulk density of a powder varies greatly with the size distribution and shape of the particles and these affect the closeness of packaging and the fraction of the bed called void. Vibration and tapping cause rearrangements of the particles and a decrease in the void fraction, thereby increasing the bulk density.

Any variation in the bulk density of powder therefore will cause a variation in the weight and dose of the tablet made from the powder. The manner of packaging also influences the behaviour of a bed when it is compressed.

1.7.1 Adhesion and cohesion of powder

The cohesiveness of a powder is the tendency of its individual particles to stick together and this is due to the operation of various forces between them. These forces include ionic, valency, lattice and van der Waal's forces (Bangudu, 1985). Others include frictional or mechanical forces like interlocking and also capillary and pendular forces arising from the presence of adsorbed films of vapours or liquids on the surfaces of the particles (Rumpf, 1958, Krupp 1967). Therefore, it could be said that cohesive powders do not flow properly and damp powders are more cohesive than dry one. Generally, the smaller the particles of a powder, the more cohesive it is as demonstrated by very fine (<5 μm) particles to form into agglomerates or granules when shaken and their tendency to block pipes and orifice when attempts are made to move them through hopper into tableting machines or capsule filing machines

The cohesive bond in powdered bed is normally very much weaker than the mechanical strength of the particles. This may be as a result of the distortion of the crystal lattice or the distortion of surface films . These prevent contact of the

surfaces and usually, but not always, decrease cohesion. Low cohesion is also due to small area of contact between the surfaces because on the molecular level, surfaces are very rough and the real area of contact will be much smaller than the apparent area. Also the structure of the surface of the particles may be different from the interior structure. Nevertheless, cohesion and adhesion which occur with all particles is appreciable . Ganderton (1968) gave factors responsible for increase in the cohesiveness of power particles as:-

i. moisture which confer cohesiveness by the action of surface tension at points of contact; and

ii. the acquisition of an electric charge by frictional movement between particles confer cohesiveness on the particles.

These two effects depend on the chemical and physical form of the powder, and because they oppose the gravitational and momentum forces acting on particle during flow they are more effective as the weight or size of the particles decrease.

A decrease in the size of the particles increase the number of points of contact in a given area of apparent contact. Cohesion effect often predominates at sizes less than 100μm

iii. Cohesion also depends on the time of contact made between the powder particles. This is as a result of the gradual squeezing of air and adsorbed gases from between the approaching surfaces. This is an important factor in the storage and intermittent delivery of powders.

iv. Fluctuating humidity can also destroy flow properties of powder if a water soluble component is present . The alternating process of dissolution and crystallization can produce very strong bonds between particles and cement them together and

therefore make them more cohesive.

1.7.2 Measurement of the cohesion of powder

a. Measurement of angular characteristics:

I. Angle of repose:-

This is to determine the cohesiveness of the particles of powder in the mass. Mildly cohesive powders have angle of repose between 40 and 60^0. Generally, the higher the value of the angle of repose for a powder, the more cohesive it is. The desired value for pharmaceutical powders should be between 30^0 to 40^0 (Staniforth, 1993).

ii. Discharge of material through orifice by using a flow meter:-

The values are usually determined by pouring a known weight of powder through the flow meter and noting the time taken for it to pass through . The faster the rate (i.e less time taken to pass through) of flow, the less cohesive is the powder.

iii. Carr's compressibility index

This is determined by pouring a weighted powder in a cylinder and noting its volume at time zero which is the poured density, fluff density or bulk density, D_b. The fluff bulk density is then noted. The cylinder with the powder in it is tapped until there is no decrease in volume of the powder mass. The tapped densities is then calculated. The percentage difference between the tapped and fluff density divided by the tapped density multiplied by 100 gives the value of the Carr's index. The higher the value, the less the flowability of the material hence the more cohesive it is. The value below 15 indicates excellent flow while the values over 20 to 30 show poor flow (PC,

1994).

iv. Angle on spatula.

This is an estimation of the angle made on spatula by a powder taken on it. The sample is usually small. The greater the angle, the more cohesive the material and the poorer the flow. The measurements of angular characteristics is affected by particle size. Particles in the size range of 50-150μm exhibit mildly cohesive characteristics. Larger fractions are free flowing while smaller size fractions are strongly cohesive. However, particulate substance like carboxymethyl cellulose can continue to exhibit cohesive properties up to a size range of 300 to 400μm owing to their very irregular shape which allows them to interlock mechanically (Ahmed and Pilpel, 1969). In constrast, substances like aerosil (used as glidant in some tablet formulation) can still confer free-flowing properties to particle size of less than 10μm.

b Split plate method.

The split plate method of Tideswell and Todyfield (Daves, 1952), has been succesfully applied to a wide range of mildly and very cohesive pharmaceutical powders. The method measures the tensile strength stress necessary to divide or split a powder bed. The powder is dredged onto a split plate or contained within a split cylinder and carefully consolidated. The stress is found from the force required to break the bed and the area of the divided surface. Stresses of up to 1,000 dynes cm^{-2} are necessary to divided a bed of fine powders (Ganderton, 1968). The value increases as the bulk density increases. Changes in cohesiveness with time (eg during

storage) and the severe changes in the flow properties of some powders which occur when relative humidity exceeds 80% can be assessed with this apparatus.

c. **Shear measurement.**

This is the measurement of strengths of powder when they are being subjected to a shearing force. The shear stress at failure is measured while the bed is constrained under a normal stress or varied stress. The relationship between these stresses is used in the design of bins and hoppers for the storage and delivery of powder. Starting from the assumption that a dry powder can be treated as a modified coulomb solid, it will fail or start to flow when it is subjected to a certain limiting shear stress, expressed by "Yield locus". The bed of powder fails when the stress attains the limiting value.

Effect of particle size on shear index of powder

It has been experimentally determined that a correlation exists between the shear index and the shapes and sizes of the particles in the powder. The shear index is related to particle size and shape by the expression (Bean *et al* 1971)

$n = 1 + BK/d$ --- 3.

Where n is the shear index, B is a constant dependent on particle shape and has value of about 0.7 for a spherical particle and about 0.4 for mainly elongated particle. K is in the region of 0.6 - 0.7 d is the particle diameter. The cohesive properties of powder depend on the specific surface of the particles and the particle diameter d is therefore selected as the mean diameter as measured for example on coulter Counter. The validity of the above equation can be established only with

particles within ±2μm mean sizes.

Effect of moisture on cohesion of powders.

Using angle of repose measurements, Craik and Miller (1958) showed that by the addition of small amounts of light magnesia to starch it was made less cohesive after it has been exposed to RH of between 4 and 81% for 24 hours. They also obtained similar result with fine sucrose of particle sizes 10μm. With coarse sucrose of 100μm size, the addition of magnesia only caused a reduction in cohesiveness when the powder had been exposed to RH >60%. Kamal (1969) and Harwood (1969) also found that the cohesiveness and tensile strengths of relatively loosely packed starch, lactose and griseofulvin rose as their mositure content was increased and that the shear stress at failure at any particular normal consolidation stress attained a maximum value. Shotton and Harb (1966) also made extensive study of moisture effects on a variety of powdered starches and sugars using the split plate method and they further confirmed that the cohesiveness of a powder increases with increasing moisture content to a maximum and then fell. Particles are deformed when subjected to external forces greater than their yield pressure. Adsorption of water not only increases the area of contact between particles but can also produce a softening of the surfaces of many materials like sugars, starches and water soluble drugs. This causes an increase in the adhesive/cohesive strength of materials for particles whose surfaces do not soften. Rumpf (1958, 1962) and Newitt and Conway - Jones (1958) have distinguished between three different cases as: water is first absorbed as a molecular layer, then increasigly fill the void spaces between the particles. The cohesion between particles measured by the force needed to seperate them therefore increases as a result of their adsorbing moisture on their

surfaces. However, Bowden and Tabor (1954, 1964) have shown the importance of optimum moisture content in powdered materials for consolidation. The adsorbed film of liquid acts as lubricant and reduces the conventional coefficiet of friction between surfaces making it easier for the particles to slide past each other.

1.7.3 Forces that operate in a powder.

Several forces operate in a powder which give rise to the tensile strength of the powder. They include:-

1. **Mechanical interlocking.**

The particles of powder are irregularly shaped with rough surfaces. These surfaces have a tendency to intermesh and mechanically interlock especially when they load.

2. **Molecular forces.**

They are also called Van der Waal's foces. Electron clouds in molecules vibrate in relation to the nuclei inducing instant dipole of defined orientation which in turn induce dipoles in neighbouring atoms, causing attraction between the molecules. Van der Waal's forces vary inversely with the distance apart of the particles raised to the sixth power. They become greater when the particles are less than 50μm in diameter and separated by less then 0.01μm. (Turba and Rumpf, 1964).

3. **Plastic deformation.**

When two particles come into contact, only relatively small parts of their total surfaces actually touch (Bowden and Tabor-1957, Tarbor 1961). When subjected to compaction, pressure develops at their points of contact (also called asperities) and these pressures are very high which may cause plastic flow as well as

elastic deformation. A plastic deformation of the asperities will lead to greater true area of contact and hence an enhanced forces of cohesion between the particles.

4. **Solid bridge forces.**

These may be due to mineral bridge, chemical reaction, partial melting and subsequent cooling and resolidification of binders which harden and crytalizes dissolved substances and deposition of suspended colloidal particles (Rumpf 1958).

5. **Liquid bridges.**

Surface tensile forces may arise in particles containing adsorbed moisture. Fisher (1926) proposed that multilayers of adsorbed moisture on surface of particles could condence to form a lens-shaped ring of water or liquid bridges across the points of contact between the two particles. The adsorbed layers of moisture tend to smooth out irregularities on the surfaces of the neighbouring particles, increasing their area of contact and the van der Waals forces between them. The adsorption of moisture causes the surfaces of some pharmaceutical powders to soften and under compression the area of contact between the particles is increased considerably increasing the cohesive strengths of the particles.

6. **Electrostatic forces**

This can arise on the surfaces of particles for two reasons.

a. If the particles had contact with an ionic substance (like being washed in ionic solution). The ions are transferred to the particle.

b. Shotton (1976) proposed that there could be electron transfer between surface of particles by "contact - charging". Electrostatic forces arise from surface charge which are either permanent or acquired from adjacent surfaces unlike van der Waals

forces which arise from random motion of electrons on surfaces of molecules. Electrostatic forces are weaker forces but act over a wide range and are comparable to van der Waal's forces when particles are less than 2μm in diameter (Gold and Palermo, 1965).

1.7.4 Properties of pharmaceutical powders

1.7.4.1 Particle size and size distribution.

For a solid drug, the dissolution rate, absorption rate, content uniformity, taste, texture, colour and stability are dependent to varying degrees on particle size and size distribution. Particle size also greatly affect the proper and efficient mixing of solid substance and the stability of the resulting mixture. Excipients like diluents, disintegrating agents and lubricants intended for use in the formulation of tablets and capusles in most cases may require an optimum particle size and size distribution. This could be due to the fact that the mixing capability of excipients and active ingredients may depend on their degree of surface contact, which can be increased or decreased by particl size adjustment.

For substances whose dissolution is the rate limiting step in its absorption, a reduced particle size will greatly increase its dissolution rate. There is the need, however, to reduce particles size to an optimum range due to some problems associated with, below certain particle size. These problems include.

a. Adsorption of air at drug- particle surface which prevent wetting of drug by surrounding fluids.

b. Surface electrical charge is prevalent with fine powders. This leads to an electrically induced agglomeration of fine drug particles which can decrease exposure of drug surface to the surrounding dissolution medium.

c. Particle size reduction to extremely small size of less than 10μm may be inadvisable for some drug substances that exhibit polymorphic changes or may lead to more rapid degradation of the compounds if it is exposed to heat, humidity and oxygen.

Acceptable content uniformity in solid dosage form is especially critical with drugs of high potency and low dosage. Since no mixture of solid particles can be consideered absolutely homogeneous, it is essential that the low dose drug particles be reduced to such a size as to give as many particles per dosage unit as possible. This minimises the potency variation that can occur between dosage units in a batch. Particle size and size distribution should therefore be determined, optimized, monitored and controlled.

Methods of determining particle size and size distribution.

i. **Sieving Method.**

This is perhaps the oldest and still the most commonly used method. It is used to determine the size distribution of powders in the size range from 44μ (325 mesh) and above. Usually a nest of sieves are arranged from one with the largest size on top to the smallest below. The powder is placed on the top most sieve screen and the nest mounted on a mechanical sieve vibrator. The time of vibration is adjusted according to desire and the machine switched on. The powder are retained on top of each screen when the particles size is greater than the hole size of the screen. The weight of particles retained on each screen is determined and a particle size distribution oversize graph plotted using weight retained on screen versus the opening of screen. A pharmaceutically desirable powder should give a normal distribution sieve. Screen analysis data usually serve as a rough guideline in evaluating raw materials with regard to the need for milling. The basic disadvantages

of the process are the large sample required, the restriction of size range to available sieve size and the blinding of the screens by particles that get lodged in the mesh openings mechanically or by static charge. Due to its simplicity, and relatively low cost of equipment however, sieving method will continue to be popular.

ii. **Microscopy method**

The method is usually used for powders of subsieve sizes (0.2μ to 100μ). The accuracy of the method depends on expertise of the user to adjust the microscope and prepare the slide for counting suspended particles in liquid having different refractive index from the particles. The sample taken on the slide must be a true representative of the powder. For actual counting, random fields are selected on the slide and the particles counted and sized. There should be no less than 100 particles counted per sample. A frequency distribution curve is plotted using the frequency versus particles size range or average particle size.

iii. **Sedimentation rate method.**

This method is based on Stoke's equation which describes the relationship between the rate at which a particle settles in a fluid medium to the size of that particle.

$d = \sqrt{(18\eta h / (\rho - \rho_o) gt)}$

Where

d	=	particle diameter in micrometers
η	=	viscosity in poise
h	=	height of fall in cm
ρ	=	density of solid in gm / cm^3
ρ_o	=	density of fluid settling medium in gm/cm^3

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g = acceleration due to gravity (981 cm /sec^2)

t = time in seconds.

The equation is based on spherically shaped particles and covers a range of about 3-250 μm. The equipment used is the Andreasen pipette apparatus in which exact volumes of samples are withdrawn at specific liquid depth and at a specific time interval. The suspending medium is evaporated and the sample weighed. Substitution of the sample withdrawal time and the other constants in the equation correlated to the sample weights yield a weight - size particle distribution curve. A proper particle dispersion, good temperature, control of settling medium and particle concentration is important for sedimentation methods.

iv. **Stream scanning method.**

A fluid suspension of the particles is made and passed through a sensing zone in which individual particles are electrically sized, counted and tabulated (eg Coulter counter method). The method is easy and large volume of data can be generated within seconds.

1.7.4.2 Porosity

Porosity is the fraction of the total volume of powder which is void. It is often expressed as percentages. Porosity is related to bulk density by the equation

$$E = 1 - \rho_b / \rho \quad \text{---------5}$$

Where:

ρ = true density of powder

ρ_b = Bulk density of powder

E = Porosity

Porosity is a term used to define the degree of consolidation in a powder.

Powders with wide size distribution have lower porosity than if they had smaller size distribution. This is because some packing of fine particles occurs between the coarsest particles, filling the voids between them. This effect is absent in fine powders which due to their more cohesive nature, the porosity increases as the particles become finer and variation in the size distribution has little effect. In any irregular array, porosity increases as particle shape departs from sphericity because open packing and bridging become more common. Roughness of the surface of particles will increase porosity. The porosity of pharmaceutical powders is useful due to packing of the powders. In operations where powders are poured, chance packing occurs and the porosity is subject to the speed of the operation and the degree of agitation. If the powder is poured slowly, each particle can find a stable position in the developing surface. Interstitial volumes will be small, the number of contacts with neighbouring particles will be high and the porosity will be low. If pouring is fast, there is insufficient time for stable packing. Bridges are created as particles fall together and a bed of higher porosity is formed. Vibration opposes open packing and the formation of bridges. It is often deliberately applied when closely packed powder beds are required.

Packing at a boundary differs from packing in the bulk of a powder. The boundary normally creates a region of more open packing several particles layer in extent. This is important when particles are packed in small volumes. If the particles are relatively large, the region of expanded packing and low bulk density will be extensive and for these conditions, the weight of material which fills the volumes will decrease as the particle size increases. With finer powder, the opposite is true and cohesiveness causes the weight of powder which fills a volume

to decrease as the particle size decreases. Most pharmaceutical powders have porosity ranging between 30-50%.

1.7.4.3 Density.

There are three types of density considered for a pharmaceutical powder.

a. **True density, ρ**

This is mass per unit volume exclusive of the voids, intra particulate pores larger than molecular or atomic dimensions in the particle.

b. **Granular density, ρ_g.**

This is mass per unit volume inclusive of all the cracks and spaces having a maximum size of 10μm. Granular density can be determined by using mercury displacement method using a pycnometer.

c. **Bulk density ρ_b.**

This is mass per unit volume inclusive of all the sizes of cracks and pores.

It is determined using 100ml measuring cylinder.

The density of solid particles affect their flow properties. In physical mixtures of powders, made up of components of different densities, the denser materials tend to settle at the bottom of the powder mass as a result of greater gravity, thus leading to powder segregation. A knowledge of the bulk and tapped density of powder gives an indication of its packing profile and an indirect index of powder flowability.

1.7.4.4 Flowability

Powders are either free flowing or cohesive. The flow property of powder is affected by particle size, particle shape, particle texture, particle size distribution and particle density. A good flow of a powder or granulation ensures efficient mixing

and yields tablets of uniform and consistent weight. Poor flowing powders may be pre-compressed or pregranulated to improve flow by adding lubricant to the granules. Powder flow is determined using the flow meter.

1.7.4.5 Hygroscopicity.

This is the ability of substance to absorb moisture from the atmosphere. Many drug substances exhibit hygroscopicity and this may affect the physicochemical stability of tablets produced from them. The hygroscopic nature of such substnace also negatively influence the flow and compression characteristics of the particles and hence the properties of the resulting tablets.

1.7.4.6 Compressibility

The ability of powders to form a compact (tablet) under pressure depends on the compressibility characteristics of the powder especially where it forms the major components of the drug mass. Powders which form hard compacts under applied pressure without exhibiting any tendency to cap or chip may be highly useful in compressed tablets made by direct compression method. The compressibility potential of any material also determines if direct compression excipient should be incorporated for direct compression method or if wet granulation process using binders should be used to produce compressible granules. A good compressible material should be inert and able to be compacted with no difficulty and may do so even when some other excipients or drugs are mixed with it. Compression characteristics of powders are determined using Carr's compressibility index.

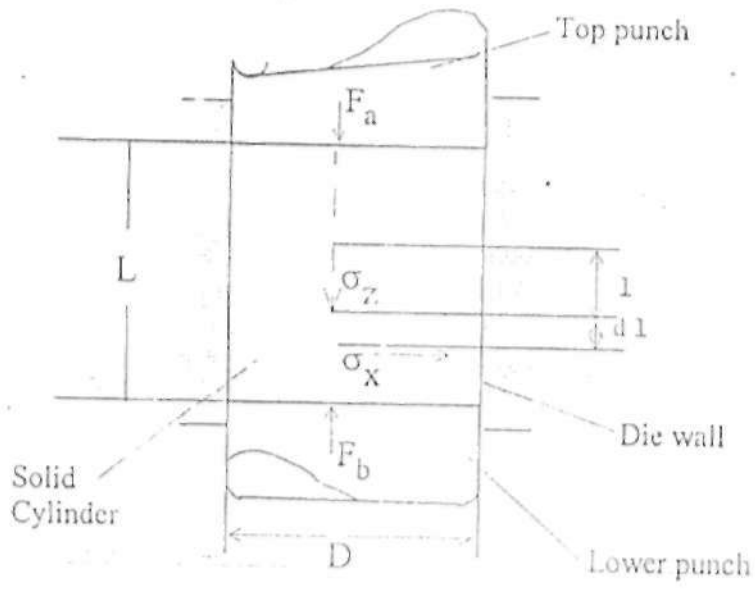
1.8 Theory of Compaction of Tablets

The process by which powdered materials are pressed together to make into a more firm and solid compact is referred to as compression. When pressure is

applied to a particulate or granular system, it results in the formation of a compact which in pharmacy is called a compressed tablet. Tablets contain the active medicinal agents as well as other excipients necessary for the production and bioavailability of the tablet to the patient. It is therefore of utmost importance that each tablet is of the same weight and content of active material within close and acceptable limits. To ensure a constant dosage in tablets, therefore, it is essential to first of all produce a powder with a uniform distribution of the active substances. Several workers have found that compaction of a powder mass into a tablet entails the study of the physics of unit operation of this process in order to form a coherent tablet. There are also other factors that come into play thus affecting the uniformity of density throughout the compacted mass. How economical tablet production is on a large scale has also been studied by instrumentation of the single punch machine. Shotton *et al* (1976) were able to measure tablet punch forces, and this has led to a greater understanding of the physics of tableting process. The application of the instrumentation technique to rotary machines showed that the standardization of tablet production could be controlled and a considerable degree of automation attained. Wray (1967) was able to overcome some of the problems encountered by the rotary machine when he showed that the compression force signal and its relation with tablet weight can activate relays operating both a servo mechanism on the weight adjuster mechanism of the tablet machine and tablet ejection system. Thus a direct automatic control of tablet weight can be maintained throughout the entire batch. In the single punch machine; the force of compression (Fa) is applied through the downward movement of the upper punch. The force exerted through the powder to the lower stationary punch (Fb) is always less than fa,

the applied forces. The difference between Fa and Fb in the rotary machine is less than in the single machine. Within the powder mass, force pattern may be considered as consisting of an axial forces which cause the compression of the powder and a radial force (Fx) exerted upon the die wall. During compression, a fractional force Fd, between the powder and die wall tend to resist consolidation.

Fig.1.1: Theoretical Diagram of Powder Plug Compressed in a Cylinderical die (Shotton *et. al.* 1976).



$F_d = F_a - F_b$

axial stress = σ_z

radail stress = σ_x

$\eta = \frac{\sigma_x}{\sigma_z}$

When μ is the coefficient of friction between the particulate powder and the die wall, then

$Fd = \mu fx$ ..... 6.

But for a pharmaceutical tablet, the mass of granule is constant for a given product, therefore the relationship between Fa and Fb or the corresponding pressure Pa and Pb is practically linear.

Shaxby and Evans (1923) found a logarithmic relation for single punch machines, where the depth of powder is variable as

$Pa = Pb\ e\ x\ p^{4LK/D}$ 7

Where

L = length with the compact

D = compact diameter

K = material constant.

Unkel (1945) verified this equation and has showed that the constant K could be replaced by the product coefficient of friction (μ) and the ratio of the radial to axial stress (η) in the compact.

$Pa = Pb \exp^{4L\mu\eta/D}$ 8

This equation is in practice limited because the knowledge of the stress ratio η is required for its complete elucidation. The equation only shows the importance of a small L:D ratio for the tablet being compacted and the influence of the coefficient of friction μ between the powder and the die wall. The use of powdered materials under high loads create high die wall friction conditions and when L:D ratio is high, there will be a considerable decay of the applied pressure

down the compact length, resulting in a poorly compacted region adjacent to the stationary punch. This is reduced by the use of two punches applying pressure to the compact as in the rotary type tablet machine. The mechanism then produces a more uniformly dense compact with the region of least consolidation at the central plane between the punches and because relatively thin tablets are used in pharmacy, the density differences will not be great. Lubricating the die wall also reduce the friction and therefore obtain a greater uniformity in the compact, thus lubricant is included in the tablet formulation.

Frictional force may be equated to the shear strength of the powder material being because it is considerably less than that of the die wall material and the total area of contact junctions. During compression, the powder mass is forced into intimate contact with the die wall, and eventually a maximum die wall friction equivalent to the production of the shear strength of the compacted mass and the area in contact with the die wall should be obtained. This condition has been demonstrated with magnesium stearate (Shotton *et al* 1976).

A more detailed investigation into distribution of all forces applied during compression showed that they are not uniformly distributed throughout the powder. Train (1956, 1957) measured the pressure distribution in a powder mass while compression was taking place. He discovered that:-

$Vr = L/Lo$ 9

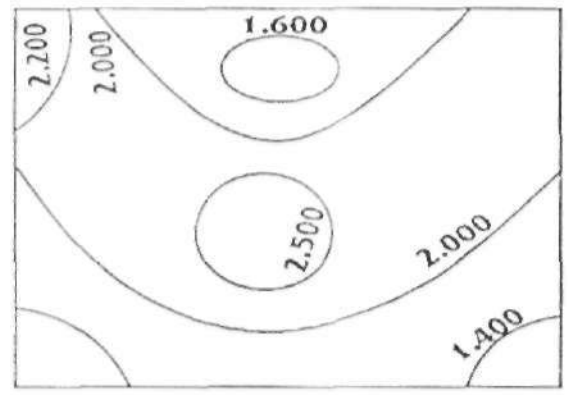
Where: Vr = overall relative volume of compact

L = observed length of compact

Lo = length of compact at zero voidage

Extruded compact was cut through and powder weighed from given volumes of the cut compact to find relative density of distribution.

Fig 1.2 (Distribution of pressure in magnesium carbonate compact compact. Contour level in kg/sq. cm) (Train, 1957)



Zones of high pressure and clarity occurred at the periphery near the moving punch, and another zone of high pressure and density occurred on the axis near the stationary punch which is responsible for lack of complete disintegration of some tablets when immersed in water. The compacts being regular cylinders the region of high density would have been formed by the migration of powder in a radial direction and this Train (1956) was able to prove. He used unlubricated and lubricated die to compresses equal and uniform layers of coloured powders alternating with uncoloured magnesium carbonate. In the unlubricated die, powder at the die wall could not move readily while those at the centre could move until the mass was consolidated resulting in displacement of this bands. In the lubricated die, a more uniform movement occurred and the bands showed less displacement.

The attempt to quantitatively determine the mechanism of powder consolidation during tabletting and the physical mechanical forces effecting the consolidation of powders during compaction has been a recipient of considerable amount of research. This followed immediately after Higuchi et al (1952) published their first series of papers relating to the physics of tablet compression.

The agglomeration of particles during compression is well documented and many hypothesis have been put forward to describe the behaviour of the particles during tabletting. It was proposed by Rumpf (1962) that the mechanism of bonding of powders in the formation of a tablet is related to the interparticulate van der Waal's forces of attraction. The cohesion between solid surfaces depend on forces of atomic attractions which manifest themselves at slighting greater distance than normal inter - atomic spacing (Varsano and Lachman, 1966). Generally the degree of bonding will directly depend on the contact area of the solid surfaces. The greater the effective surface area of contact, the greater is the degree of bonding. Pharmaceutical solids with a tendency for plastic flow will therefore attain a greater contact area under pressure and hence a higher degree of bonding will result. (Jones, 1960). Electrostatic forces may also arise from friction or particle size reduction during the granulation process, the charge developed depend on the materials and the type of motion encountered, whilst with ionic materials there is the added possibility of polarization.

Mechanical interloading, especially when dealing with a fibrous or spongy particles like cellulose, and the formation of solid bridges by friction and junction growth all contribute to the additional strength of the compressed tablet over that of the granules from which it is formed.

On compression of a powder, its density increases, and the degree of consolidation may be monitored by the change produced in its volume. For various materials including sodium chloride, potassium nitrate and ammonium chloride, logarithmic relationship is given:-

$Vr = C - K \log Pa$ ---------- 10 (Walker , 1923)

where Vr = relative volume of tablet

C and K = constants

Pa = applied pressure.

A similar relationship was obtained for sulphathiazole, aspirin and lactose by Higuchi et al (1952, 1954), which applied satisfactorily until the porosity was reduced to about 5%. This type of relationship provide very little basic information on the obviously complex process occurring when a powder mass is subjected to increasing compression pressure and finally form a compact. An improvement was made by Seeling and Wulff (1947) who carried out detailed studies on the effect of pressure on the volume of compressed powder and proposed that consolidation occurs in stages. Initial mechanism involves particle rearrangement and packing down, followed by elastic and plastic deformation and finally cold welding of the compact. Train (1956) postulated that bonding is due to interparticular shearing and shearing along the die wall, and concluded that consolidation proceeded in four stages; viz.

Stage 1 : An application of axial pressure results in interparticulate slipping, re - organisation and rearrangement of the powder particles.

This consequently leads to a decrease in relative volume of the compact i.e. there is a closer packing and increased bulk density.

State 2: Increased resistance to compression pressure is observed and it is probably caused by the formation of temporary struts, column and vaults protecting small voids and generally supporting the imposed load. Formation of struts, column and vaults is due to friction.

Stage 3 : There is failure of friction in stage 2 as they can no longer resist the increasing compressional force. The failure of the structure is as a result of crushing of particles (also called mechanical fragmentation) or plastic flow. Higuchi *et al* (1953) using nitrogen adsorption methods to measure the specific surface area of tablets under varying compressional forces showed that initially there is an increase in surface area with increasing applied pressure up to a maximum value. But further increase in applied pressure caused a significant reduction in surface. This they attributed to fragmentation followed by bonding of the particles. Huffine (1953) on the other hand found that the surface area of sodium chloride crystals continually decreased with increasing applied pressure, owing to the plastic deformation and bonding of the crystals. Armstrong and Griffiths (1970) however showed that if the compression force is raised sufficiently high, a second increase in surface area occurs and on investigation by Armstrong and Haines - Nutt (1972), it was found that increase in surface area was associated with high values for elastic recovery in the compact and not due to comminution of particles within the compact. It is obvious that the deformation characteristics of materials determine the mechanism by which consolidation is achieved during the 3rd stage.

Stage 4 Rebonding is probably taken place at this stage more quickly than fragmentation and the reduction in relative volume (Vr) is due largely to plastic and/ or elastic deformation of the particles. The relief in presure as a result of removal of the punch may lead to elastic recovery of the compact axially. Further elastic recovery is possible radially on ejection from the die wall.

York and Pilpel (1972) relates consolidation of powder during compression to the asperitic melting of the local surfaces of the powder particles. During compression, bigger particles are broken down and the smaller ones are forced to fill voids as they cannot be broken down further. The high degree of shear results in development of frictional heat at the points of contact of the particles. Much higher heat is developed locally at contact points between the asperitis on the particles and higher pressures are also manifested. The combination of high pressures and high temperatures at asperitis lowers the melting points of the materials. The melting causes an increase in the area of contact between particles and hence a pressure reduction acting between them. On release of load, pressure is also reduced leading to some of the melted materials to resolidify and rebonding occurring between the particles.

The importance of consolidation of powder materials to the physical pharmacist lies in the fact that by analysing consolidation data during tabletting, more information might be gained about the process and materials used leading to improvement in techniques and formation. Therefore, the various equations developed to quantify consolidation processes must be able to distinguish between the different mechanisms by which different materials may consolidate.

All the equations developed so far rely on the use of a mean value of the applied pressure. They would therefore be best applied to the compact of minimal thickness compacted on a rotary press as opposed to a single punch press because presure variation down the lenght of the compact is more likely to occur in the single punch press; for example.

$$\frac{Vo - V}{Vo - V\omega} = a_1 e^{-k1/p} + a_2 e^{-k2/p} \text{ --------- } 11$$

Vω is the volume of solids where a_1, a_2 and k_1 and k_2 are constants, Vo is the original volume of powder including the voids and V is the volume at applied pressure, P (Shotton *et al* 1976). This equation satisfies some of the criteria required for greater understanding of the process. The two terms on the right hand of the equation relate to the slippage of the particles early in the compression and to the subsequent plastic deformation respectively.

Another equation relates the relative decrease in volume with applied pressure;

ie $Vo - V/Vo = \frac{a_3 bp}{1 + bp}$ ---------- 12 (Shotton *et al*, 1976)

where a_3 and b are constants.

The difficulty with these equations is the assignment of some physical significance to the constants. It was proposed by Heckel (1961) that the reduction in voidage obeys a first order kinetic relationship with pressure and proposed the equation:

$$\ln (V/V - Vo) = kp + (Vo/Vo - V\omega) \text{ ---------- } 13$$

Where:

V = volume at applied pressure P

Vω = volume of solids

Vo = original volume of the powder including voids

k = a constant.

This equation is linear only at high pressures. The application of this equation to the compaction of pharmaceutical tablets demonstrates its use both for

indicating the mechanism of consolidation and as a measure of the yield pressure of the powder under examination (Hersey and Rees, 1972, and Fell and Newton, 1971).

Another approach to the problem of consolidation involves the use of dimensional analysis. Assuming the significant variables to be the diameter of the compact , D, average particles diameter, d, surface energy of material, Y, and porosity of the compact, E, the dimensional analysis is derived from the relationship between physical quantities which must be dimensionally consistent. By analysing the significant variables involved in the operation dimensionally in terms of length, L, mass, M, and time, T, it is possible to obtain relation between these variables using this approach. For brittle materials that are liable to fracture and rebond during compression, the following equation was derived for such materials:-

$$E.\ E_o^2 = k_1 (Y / Pd)^m \quad \text{----------14}$$

where E_o is the porosity of materials before compaction, m is related to the angle of repose of powder material

Materials which deform plastically under compression do not obey this equation, but rather the data can be correlated by:-

$$E\,(d/D)^n = -\ m' \log\ kp \text{ ---------15}$$

where n and m' are constants.

By the use of equations 14 and 15, it was claimed that materials can be divided into two groups (Shotton *et al*, 1976):

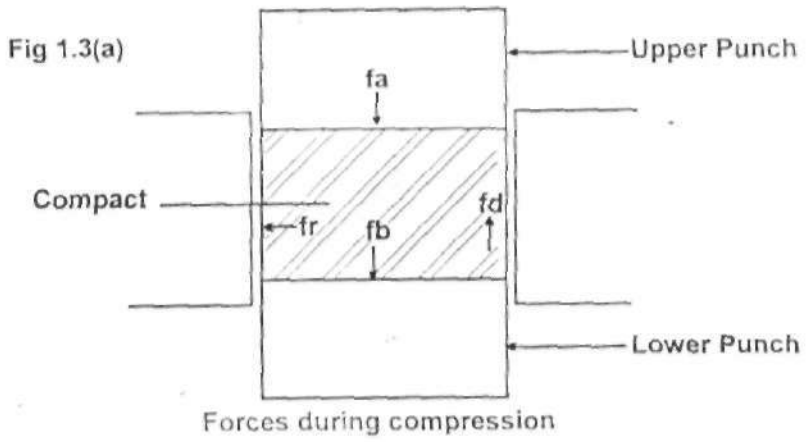
a. those that compact principally by size reduction mechanism; and

b. those that compact principally by plastic deformation.

Generally, the compression behaviour of multiparticulate systems are difficult to characterise due to the several discrete mechanisms operating and overlapping with constant changes as the compression proceeds. Most theories and equations describe only the compression stage of tabletting process whereas a complete tabletting cycle involves the compression stage - where compression force is applied to the material , the relaxation stage (or decompression) where the material is relieved of the compression force, and finally, the ejection stage - when the tablet leaves the die cavity. The decompression stage is as important but not independent of the compression stage in determining whether or not a tablet formation will form a firm and satisfactory tablet.

Fig. 1.3 Physical Conditions during Tabletting (Rawlins, 1977)

Fig 1.3(a)



Forces during compression

Fig 1.4 (b) *Forces at the start of ejections*

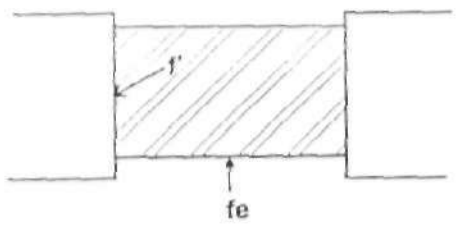
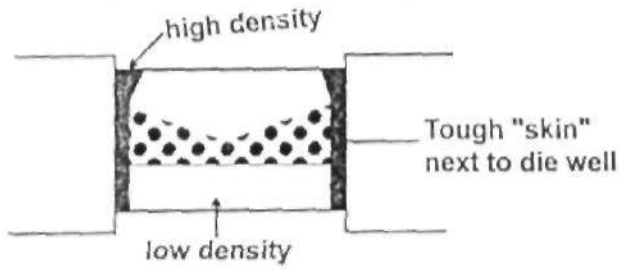


Fig 1.5 (c) *Density Distribution in a Compacts*



f' = force normal to diewall during ejection

fa = *maximum upper punch force* applied to compact

fb = *maximum force transmitted* to lower punch by compact

fd = force lost to die well and fd = fa - fb

fe = maximum force applied to lower punch to initiate ejection

fr = maximum radial force at die well during compaction

1.9 Aims and scope of this present work.

Paracetamol tablet is the most commonly used drug (Ojile 1994, Ojile *et al* 1995, Fletcher *et al* 1998) as an analgesic. The drug is not easily compressed and when the formulation is made the tablet may not disintegrate easily. So in adding the necessary excipients and being an already high dose drug, the tablet could become so bulky as to discourage patient's compliance. All the same, the laborious and costly wet method is the commonest method of its production in Nigeria and perhaps elsewhere.

The cost of excipients like Avicel^{R} (microcrystalline cellulose, MCC) that should have been used for efficient and desired tablet properties is so exorbitant. This excipient could be made easily from agricultural waste such as maize cobs in Nigeria at affordable costs.

Anzah (1997) and Audu - Peter *et al* (1999) have showed that the excipient capacity utilization of MCC or Avicel^{R} for incompressible materials ranges from 25 to 30% in directly compressed tablets. It is therefore envisaged that the production of this most commonly used tablet using exorbitantly imported material that can be produced locally at affordable costs would not only be a contribution to academic knowledge but also a contribution to national economy and to the health care delivery system.

Alpha - cellulose would be extracted from crude maize cobs. Part of it would be partially depolymerised by hot acid treatment to produce cob microcrystalline cellulose (CMCC). Binary produced mixture at different concentrations of CAC and CMCC would be mixed with paracetamol and pelletized into pellets at a high compaction pressure of about 15 metric tonnes. These pellets

would be comminuted through an appropriate sieve mesh to form granules. These granules would be dry mixed with the same intra- pellet concentration of the maize cob derived excipient(s) which are then tableted. The weight of a tablet would contain 500mg dose of the paracetamol. This means that the weight of the tablet would depend on the concentration of the excipient(s).

The properties of the tablets according to the content of the excipient(s) would be evaluated in order to suggest the best formulation bearing in mind that the tablet must not be too bulky as to discourage patients compliance

CHAPTER TWO

2.0 Materials and Methods.

2.1 Materials / Equipment

The following chemicals were used

a. Those manufactured by BDH Chemicals Ltd, Poole, England, ANALAR GRADE:

- Sodium Hydroxide Pellets
- Nitric Acid
- Ammonium Solution
- Benzene

b. Those obtained from other companies:

- Hydrogen Peroxide B.P 20% vol (Novapharm, Division of Brain Munro Ltd, Nigeria).
- Sodium Hypochlorite 3.5% v/v (Nigeria German Chemicals Plc, Lagos Nigeria)
- Sodium Sulphite (Merck, Germany)
- Paracetamol Powders (M & B, Rhone Poulenc Rorer Plc Ikeja, Nigeria)
- Avicel$^{(R)}$ PH101 (Honey Well and Stein Ltd, U.K)
- Distilled water
- Filter papers,

The following equipment/instruments were used :-

a. The apparatus used which were made by Erweka Apparatebau, G. M. B. H, Germany :-

- Powder flow meter apparatus type GDT
- Tablet friability tester type TA 3R

- Tablet disintegration apparatus Type ZT3
- Single station tabletting machine model AR 400, EKO

b. Other equipment made by companies other than Erweka were as follows :-

- Hot air oven (Gallenkamp, B.S size three, England)
- Endecott test shaker (Endecott Ltd, London, England)
- Nest of sieves (75μm, 125μm, 150μm, 500μm) and 1.00mm sieve. (Endecotts sieves, London, U.K)
- Locally fabricated grain milling machine.
- Analytical Balance Type H 35 AR (Mettler, Switzeland).
- Blender (Moulinex, France.)
- Pycnometer bottle
- Funnels, measuring cylinders of various volumes, beakers, conical flasks, thermometer, petridishes, evaporating dishes
- Hot plate (6B - 8547E, Gallen-kamp Ltd, England.)
- Hardness tester (Monsanto, England)
- Stop clock
- Porcelain mortar, pestle and stainless steel spatula
- Hydraulic pelletising press (Model P/N 25. 011, Specac Ltd, London,U.K.)
- Dessicator
- Humidifier.
- Micrometer screw gauge (Moors and Wright, England)
- brush.
- Wooden mortar and pestle
- 5L Stainless Steel vessel.

2.2 Methods.

2.2.1 Extraction of Cob alpha-cellulose (CAC).

Dry maize cobs were selected from a local maize seed harvesting and shearing mill in Samaru Village, Zaria Nigeria. Debris, Leaves and other dirts were removed with a brush. These cobs were crushed into smaller pieces using a locally made wooden mortar and pestle and spread on stainless steel tray to be sun dried for 48 hours. These were then dried in the hot air oven for 4 hours at 60°C. The coarse powder was then milled into finer powdered mass at a local grain milling machine whose milling chamber was thoroughly washed and dried before use. The powder was sieved with a nest of Endecott sieve set on Endecott sieve shaker set to vibrate for 15 minutes. Fractions that sieved through the sieve mesh of 500µm but retained on 250µm sieve mesh and below were collected. The method used by Okhamafe and co-workers (1991) was adopted with a little modification.500g of the powdered material was placed in a 10 L stainless steel vessel 5 L of 3.5% v/v nitric acid containing 50 mg sodium nitrite were added and stirred to thoroughly disperse. The vessel was placed in a water bath set at 90°C and left for 2 hours. This treatment dissolved lignins which was then washed off thoroughly with distilled water and filtered off, leaving the residue. 5 L solution containing 2% w/v sodium hydroxide and 2% sodium sulphite was prepared in the 10 L stainless steel vessel. The vessel was placed in a water bath set at 50°C. The residue of material was dispersed in the solution and left for one hour. The residue that was undissolved was thoroughly washed with distilled water and filtered. The residue was then bleached in 0.625 L of 50% v/v sodium hypochlorite solution (pH 5-8) with the vessel placed in water bath set at 40°C for one and half hours. The residue so produced was thoroughly

washed with distilled water and filtered. This was the holo-cellulose containing alpha-, some beta- and some gamma- cellulose. To obtain only alpha -cellulose, the holo-cellulose residue was dispersed in

0. 625 L of 17.5% w/v sodium hydroxide contained in a stainless steel vessel immersed in water bath set at 80°C. The treatment was allowed to stay for half an hour and this was meant to dissolve beta- and gamma-cellulose leaving only the alpha-cellulose as the residue. The residue was then washed with distilled water and bleached using 0.625 L of 20% volume hydrogen peroxide placed in the water bath set at 40°C for one and half hours. The residue was then washed with distilled water, filtered, pressed to remove excess water and dried at room temperature for 24 hours and then at 60°C for 1 hour. This was the cob alpha-cellulose (CAC). It was milled, sieved and the powder retained on 150 µm sieve mesh or those that passed through, were collected and stored in a dessicator. The yield of CAC was 21% ie 105.0 g was obtained. The procedure was repeated four times to obtain sufficient CAC.

2.2.2 Production of Cob-microcrystalline-cellulose (CMCC) from CAC.

100 g of cob alpha-cellulose produced was subjected to the hydrolytic action of 2.5 N hydrochloric acid at the boiling point temperature of about 105°C for 15 minutes. Amorphous cellulose materials and crystalline cellulose were formed. The amorphous cellulose materials which were floating on top of the solution were skimmed off. Then the crystals at the bottom of the conical flask were filtered, thoroughly washed with distilled water and aqueous ammonia until the solution became mental. The residue was wet milled using the Moulinex wet will blender.

Water was pressed out of the residue with the aid of filter paper and denied at room temperature for 24 hours and then at 60^0C in a hot air oven for one hour. The dry powder was then re-milled in Moulinex mill in the dry state.

The powder was sieved in the next of sieves and fractions retained on 150 mm and those passing through were collected and stored in a dessicator.

The yield from CAC was about 90% i.e. about 90.00 g was obtained.

2.2.3 Characterisation of CAC, CMCC and Avicel$^{(r)}$ Powders.

2.2.3.1 Preliminary Investigations.

a. The identification tests of CAC, CMCC and Avicel^R were carried out as follows.

Test for alpha-cellulose

To about 1.0mg of sample, three drops of chlor-zinc-iodine solution was added, and observed for blue colouration.

Test for microcrystalline cellulose (performed on CMCC and Avicel^R

The method used by Brain and Turner (1975) was used. 1 ml of phosphoric acid was added to 1 mg of sample and heated on the water-bath for 30 minutes. 4 ml of 0.2% solution of catechol in phosphoric acid was then added, and further heated for another 30 minutes. It was then observed for red colouration.

b. **Other Tests were carried out on the powder.**

Test for Lignin

To the powdered samples on the tile were added conc. HCl, warmed and drops of phlorglucinol added. Samples were taken and observed under the light microscope for red colouration to indicate presence of lignin.

Test for free reducing sugars.

To about 0.1g of sample on a tile Rutherium red was added and observed for any red colouration to indicate presence of glucose, pentose and uronic acids.

To about 0.1 g of sample in a test tube, Barfoed's solution was added and heated for 2 minutes and observed for colour change to indicate the presence of monosaccharide sugars

c. **Particle size distribution Analysis using light microscope.**

The eye piece graticle was calibrated with reference to a stage micrometer. This was done by placing the stage micrometer on the stage and the eye piece was focused onto its scale using the low-power objective. The eye piece scale was super-imposed on the stage scale as the eye piece was rotated until the axes of both scales were parallel and then the stage micrometer was moved from side to side until some of the lines on each scale were precisely matched. The number of the eye piece divisions which exactly super-imposed on as many divisions of the stage micrometer as possible were noted. The stage micrometer has a known scale, each divisions being equivalent to 100µm. Thus from the number of stage micrometer division which matched those of the eye piece division, the eye piece division could be calibrated.

The samples were each prepared by placing a small sample on a slide and mounted in dilute glycerol to adequately disperse particles and prevent agglomeration. The sample was then viewed using the X40 objective lens and X10 eye lens. The diameter of about 100 particles per sample of each powder sample were randomly selected and measured.

The mean particle size, the standard deviation and the size distribution were determined for each of the powder sample. Plots of the frequency Vs particle size range and of the cummulative percent frequency Vs particle size range were plotted.

d. Determination of Moisture Content.

The B.P (1980) method was used to determine the moisture content in the three samples of powders, CAC, CMCC and Avicel^{R}. This was carried out thus:- The hot air oven was heated to a temperature of 120°C. 1.0 g of each powder sample was put on an evaporating dish whose weight has been predetermined. The three evaporating dishes each containing a sample of a powder were then placed in the hot air oven and left there for four hours. The evaporating dishes were then taken out of the oven and allowed to cool in a dessicator and then re-weighed with its content. The ratio of the weight lost with the final weight expressed in percentage was the moisture content.

e. Determination of the moisture sorption capacity of the powder samples.

1.0 g of each powder sample was taken and evenly spread on a petri-dish as thinly as possible. This was so as to obtain maximal moisture sorption by the samples. A humidifier was allowed to equilibrate to 100% relative humidity (RH) by pouring some distilled water in it. This was sealed and then left for three days. The powder samples evenly spread on predetermined weighed petri dish were then placed in the humidifier equilibrated to 100% RH; and sealed for seven days. The samples were then re-weighed and the weight gained expressed as percentage was the sorption capacity for each sample.

2.2.3.2Determination of the particulate and consolidation characteristics of CAC, CMCC and Avicel®

a. Angle of repose measurement.

20.0 g of each powder sample of CAC, CMCC and Avicel® was taken and the angle of repose determined by passing through a funnel whose tip was 10.0 cm from the plane on which the powder were made to fall to make a heap. The height and diameter made by the powder was measured and the angle of repose was calculated using the formular;

$\tan \theta$ = height/radius.....16

b. **Flow Rate**.

The Erweka flow rate funnel was filled to level with powder sample and the time taken for the whole sample to pass through the orifice noted. This was determined for each sample and the weight of the powder passing through certain time taken. The flow rate was given by the amount of powder that passes through in a given time, i.e. it is the ratio of the mass of powder per unit time.

c. **Carr's index determination.**

To calculate these indices, the bulk and tapped densities of each powder sample were first determined.

The bulk density was determined by pouring enough quantity of powder upto the 100ml mark of a measuring cylinder. The measuring cylinder was then tapped in a cummulative way. The volume decrease was noted at 0 tap, 3 taps, 25 taps and 50 taps.The weight of the powder was then taken. The process was repeated three times for each powder sample and the bulk and tapped volumes taken. From these the bulk and tapped densities were determined based on the equation :-

Density (g/ml) = mass(g)/volume (ml) 17

The average of the three values per each sample was used as the bulk and tapped densities for each powder sample.

The values obtained from the above equation were subsequently used in calculating the Carr's index for each powder sample of CAC, CMCC and Avicel^R using the equation

CI = 100(TD - BD)/TD,.....18

Where CI = Carr's index

TD = Tapped density

BD = Bulk density.

d. Determination of True densities.

The pycnometer bottle method was used with Benzene as the solvent.

The weight of the pycnometer bottle was taken with its stopper in place. Benzene was then poured into the bottle and the stopper placed and then weighed. Benzene was then drained out of the bottle.

3.0 g of each powder sample was weighed in the pycnometer bottle.

The sample was poured into the pycnometer bottle and benzene added to it while it was gradually stirred to suspend the powder particles and dislodge air particles. More benzene was added to make up the pycnometer bottle volume. The stopper was placed and reweighed. The true density of each sample of powder was calculated by using the equation

$D_t = WS /((a+W) - b)$..... 19

D_t

Where D_t = true density,

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W = weight of powder sample taken

S = specifi gravity of the solvent, benzene

a = weight of bottle and solvent

b = weight of bottle, solvent and powder sample.

2.2.4 Tablet Production.

A non-self compressible high dose drug, paracetamol (500mg/tablet) was employed in the tablet formulation with CAC, CMCC and Avicel^{R} used as sole excipient in 10%, 15% 20%, 25% and 30% contents.

The working formulae in Table 2.1 was used and the powder samples binders were used intragranularly and extragranularly or as binary mixture in equal proportions.

TABLE 2.1

PARACETAMOL TABLETS FORMULATION USING DIRECT COMPRESSION METHOD.

Batch	Concentration of Paracetamol Powder (%)	Powder Sample Concentration (%)		Tablet Weight in mg
		Intrgranular	Extragranular	
1 i	0	100	0	500
1 ii	0	100	0	500
1 iii	0	100	0	500
1 iv	100	0	0	500
2 i	90	5 CAC	5 CMCC	556
2 ii	85	7.5 CAC	7.5 CMCC	588
2 iii	80	10 CAC	10 CMCC	625
2 iv	75	12.5 CAC	12.5 CMCC	667
2 v	70	15 CAC	15 CMCC	714
3 I	90	5 CMCC	5 CAC	556
3 II	85	7.5 CMCC	7.5 CAC	588
3 III	80	10 CMCC	10 CAC	625
3 IV	75	12.5 CMCC	12. CAC	667
3 V	70	15 CMCC	15 CAC	714
4 i	90	5 CAC	5 CAC	556
4 ii	85	7.5 CAC	7.5CAC	588
4 iii	80	10 CAC	10 CAC	625
4 iv	75	12.5 CAC	12.5 CAC	667
4 v	70	15CAC	15 CAC	714
5 I	90	5 CMCC	5 CMCC	556
5 II	85	7.5 CMCC	7.5 CMCC	588
5 III	80	10 CMCC	10 CMCC	625
5 IV	75	12.5 CMCC	12.5 CMCC	667
5 V	70	15 CMCC	15 CMCC	714

TABLE 2.1 CONT'D.

Batch no	Concentration of Paracetamol Powder (%)	Powder Sample Concentration (%)		Tablet Weight in mg
		Intragranula	Extragranular	
6 i	90	2.5 CMCC + 2.5 CAC	2.5 CMCC + 2.5 CAC	556
6 ii	85	3.75 CMCC + 3.75 CAC	3.75 CMCC + 3.75 CAC	588
6 iii	80	5 CMCC +5 CAC	5 CMCC +5 CAC	625
6 iv	75	6.25 CMCC + 6.25 CAC	6.25 CMCC + 6.25 CAC	667
6 v	70	7.5 CMCC + 7.5 CAC	7.5 CMCC + 7.5 CAC	714
7 i	90	5 Avicel^{R}	5 Avicel^{R}	556
7 ii	85	7.5 Avicel^{R}	7.5 Avicel^{R}	588
7 iii	80	10 Avicel^{R}	10 Avicel^{R}	625
7 iv	75	12.5Avicel^{R}	12.5Avicel^{R}	667
7 v	70	15 Avicel^{R}	15 Avicel^{R}	714

The method used for producing the tablets was by direct compression method via pelletization.

Table 2.1 shows the formulation of paracetamol with its percentage dry mix concentrations in the tablets from batches 2i to 7v. Batches 1i, 1ii, 1iii, and 1iv were the batches for pure compacts of the dry powders of CAC, CMCC, Avicel^{R} and paracetamol respectively.

For each batch, the batch size was for 60 tablets. 30.0g of the paracetamol powder and depending on the batch and the ratio of dry binder, intragranular binder were weighed on the Mettler balance according to its concentration. The two powders were then mixed by the doubling up techniques for one minute on each addition in a 25 ml porcelain mortar using a stainless steel spatula with a wooden handle. Further mixing of all the paracetamol and dry

powder proceeded in one direction at constant rotatory rate for 5 minutes, at the end of which the batch is ready for pelletization. Similarly, all the other batches were prepared in the same way except for the powders of the pure samples which were only passed through a 1.0mm mesh sieve to remove lumps and the required amount weighed out for pelletization.

Pelletization and Tabletting.

The hydraulic pelletizing press fitted with a 22 mm punch and die set was used to pelletize 2.0 g portions of the dry mix at 15 metric tonne force. The pellets were then comminuted manually through a 1.0 mm sieve mesh kept taut on a 10.0 cm radius of a 20 cm tall stainless steel cylindrical hollow container and hitting the pellets with a porcelain pestle over the sieve to comminute through the sieves. The comminuted granules were then weighed and then mixed by the doubling up techniques with the required amount of dry extragranular excipient for 5 minutes. The powder mix was then tableted using a 12.5 mm punch and die tooling of the Erweka single station tabletting press, and compacted at the maximal compaction force beyond which the compaction fly wheel could not be rotated to compact the granules and this would depend on the batch. The compaction forces ranged from 5.5 – 11.5 metric tonnes.

The pure sample of paracetamol was able to be pelletized at 15 metric tonne force, but the granules so obtained were not able to be tabletted using the single station tabletting press at any of its compaction force, hence it was discarded.

2.2.5 Evaluation of the Properties of the Tablets.

2.2.5.1 Weight Variation Test

The U.S.P XX method was used. Twenty tablets were individually weighed and then all the twenty were weighed together on the mettler analytical balance. It is expected that not more than two of the tablets differ from the average weight by more than double the 5%. The mean and percentage mean deviation were calculated.

2.2.5.2 Hardness Test

This is an unofficial test. The hardness values of the tablets were determined using the Monsanto hardness tester. Five tablets from each batch were tested. The hardness of the tablets were determined by applying increasing pressure to the spring by screwing on the knob until the tablet cracked or shattered. The point at which the tablet broke was taken as the hardness of the tablet. The mean and the mean deviation were calculated.

2.2.5.3 Tablet Friability

This is an unofficial test used to measure how fragile the tablets can become when subjected to the scoopings and bangings of the friabilating machine. This measure provides how resistant the tablets are when handled during packaging and dispensing. Five tablets were randomly selected and weighed together. They were then placed in the Erweka tablet friabilator which had been set to rotate for four minutes at 25 rounds per minute. The tablets were thereafter dusted free of fines and re-weighed. The loss in weight expressed as percentage was the friability, F, which is expressed as

where W_1 was the initial weight of the 5 tablets and W_2 was the weight of the 5 tablets after the friabilation test.

Two determination were made for each batch and the average was taken.

2.2.5.4 Tablet Thickness.

The thickness of a tablet could be a function of the volumetric fill of the die and the pressure applied during compaction. The thickness was measured by placing each of five tablets between the jaws of the micrometer screw gauge, screwing it on until it just held the tablet firmly. At this point, the value was read off as the thickness of the tablet. Since each tablet must contain 500mg of the drug and different concentrations of the excipients were employed, there were different weights of the tablet, depending on the batch. Specific tablet thickness, which was the mean thickness of the tablet per milligram weight of the tablet was adapted to be a more comparative measure.

2.2.5.5 Disintegration Time Test.

It is expected that an oral tablet, (except chewable, enteric coated, or sustained release tablets,) should disintegrate within fifteen minutes unless other wise indicated in the monograph (B. P., 1980). The Erweka tablet disintegrating machine was used. Distilled water at 37 $\pm$ 1°C was used as the disintegration medium for all the batches. One tablet was placed in each of the 6 transparent disintegrating tubes of the tablet disintegration test machine. The time taken for each of the 6 tablets to disintegrate and pass through the 10 - screen mesh was noted and the mean and deviation from the mean calculated. However, it should

be noted that the official time was the time taken for the last tablet to disintegrate.

CHAPTER THREE

3.0 RESULTS

3.1 Characterisation of cob alpha cellulose (CAC), cob microcrystalline cellulose (CMCC), and Avicel^{R}.

3.1.1 Identification tests:

The results of tests performed on CAC which were to identify the presence of cellulose, the absence of monosaccharides, lignin, pentose and uronic acid are presented in Table 3.1

Table 3.1 **Identification tests on the CAC.**

	Test	Observation	Inferences
1.	To about 0.1g of the powdered sample, 3 drops of chlor - zinc- iodine solution was added.	Blue colouration was observed.	Presence of cellulose in sample.
2.	Some powered sample were suspended in Barfoed's solution, then heated for 2 minutes.	There was no colour change.	Monosaccharide Sugars were absent.
3.	To the powdered sample were added conc HCl, warmed and drops of phlorglucinol added. Sample was observed under light microscope	No red colouration Observed.	Absence of lignin
4.	To the sample was added Rutherium red	No red stain was seen.	Absence of glucose, pentose and uronic acids.

Table 3.2 below shows the results of the specific tests for microcrystalline cellulose in the cob microcrystalline cellulose (CMCC) and

Avicel^{R} (Brain and Turner 1975, Musa 1996). Avicel^{R} is a commercially available form of microcrystalline cellulose and tests to show whether the CMCC and Avicel^{R} contain lignin, monosaccharides, pentose and uronic acids were also presented in the table.

Table 3.2. **Identification tests performed on the samples of CMCC, and Avicel^{R}**

	Tests	**Observation**	**Inference.**
1.	*Sample + Iml phosphoric acid,* heated for 30 mins on water bath, + 4 ml of 0.2% solution of catechol in phosphoric acid. Again it was heated for 30 minutes	*Both samples of CMCC* and Avicel^{R} produced red colouration	*Presence of* microcrystalline cellulose.
2.	Sample + conc. HCl, warmed to dryness, + drops of phlorglucinol. Sample was observed under microscope	No red colouration in both samples of CMCC and Avicel^{R}	Absence of Lignin.
3.	Sample + Barfoed's solution, heated for 2 minutes	No colour change in both CMCC and Avicel^{R}	Absence of monosaccharides sugars
4.	Sample + Rutherium red.	No red stain in either CMCC or Avicel^{R}	Absence of glucose, pentose and uronic acids.

3.1.2 Tables 3.3 (i) to 3.3 (iii) show the particle sizes and size distribution of the 3 products, Avicel^{R}, CMCC and CAC.

Table 3.3 (i) **Analysis of particle size and size distribution of Avicel**[R]

Class interval	Frequency	Class Mark, X	X^2	FX	FX^2	Cum. Freq.	% Cum. freq
1 - 30	56	15.5	240.25	868	13454	56	56
31 - 60	28	45.5	2070.25	1274	57967	84	84
61 - 90	6	75.5	5700.25	453	34201.5	90	90
91 - 120	5	105.5	11130.25	527.5	55651.25	95	95
211 -150	2	135.5	18360.25	271	36720.5	97	97
151 - 180	2	165.5	27390.25	331	54780.5	99	99
181 - 210	1	195.5	38220.25	195.5	38220.25	100	100
Total			**1083111.75**	**39200**	**290995**		

Table 3. 3. (ii) **Analysis of particle size and particle**

Size distribution of CMCC.

Class interval	Frequency	Class Mark X	FX	X^2	FX^2	Cum freq.	% cum freq.
1 - 20	14	10.5	147	110.25	1547	14	14
21 -40	46	30.5	1403	930.25	42791.5	60	60
41 - 60	30	50.5	1515	2550.25	76507.5	90	90
61 - 80	6	70.5	423	4970.25	29821.5	96	96
81 – 100	2	90.5	181	8190.25	16380.5	98	98
101 - 120	2	110.5	221	12210.25	24420.5	100	100
Total			**3890**	**28961.5**	**191468.5**		

Table 3.3 (iii)

3.1.2 Analysis of particle size and particle distribution of CAC

Class interval	Freq.	Class mark X	X^2	FX^2	FX	Cum Freq	% Cum freq
1- 30	21	15.5	240.25	5045.25	325.5	21	21
31 -60	39	45.5	2070.25	80739.75	1774.5	60	60
61 -90	23	75.5	5700.25	131105.75	1736.5	83	83
91 -120	11	105.5	11130.25	122432.75	1160.5	94	94
121 -150	5	135.5	18360.25	91801.25	677.5	99	99
151 -180	1	165.5	27390.25	27390.25	165.5	100	100
Total			**64891.50**	**458515**	**5840**		

Table 3.3 (iv) The mean size, standard deviation (SD) and standard error of the mean (SEM) values of CAC, CMCC and Avicel^R.

	CAC	CMCC	Avicel^R
Mean particle size (μm)= $(\sum FX/\sum F)$	58.40	38.90	39.20
Standard deviation SD $=\sqrt{(\sum FX^2 - \sum FX^2/n/n-1)}$	34.40	20.10	37.20
Standard error of the mean SEM $= (SD/\sqrt{n})$	3.95	2.01	3.70

Figures 3. 1.(i) and 3. 1 (ii) show the percentage frequency and cumulative frequency of the sizes of the 3 products, CAC, CMCC and Avicel^R.

Fig. 3.1(i): Frequency Vs Particle Size Analysis for Avicel, CMCC, CAC

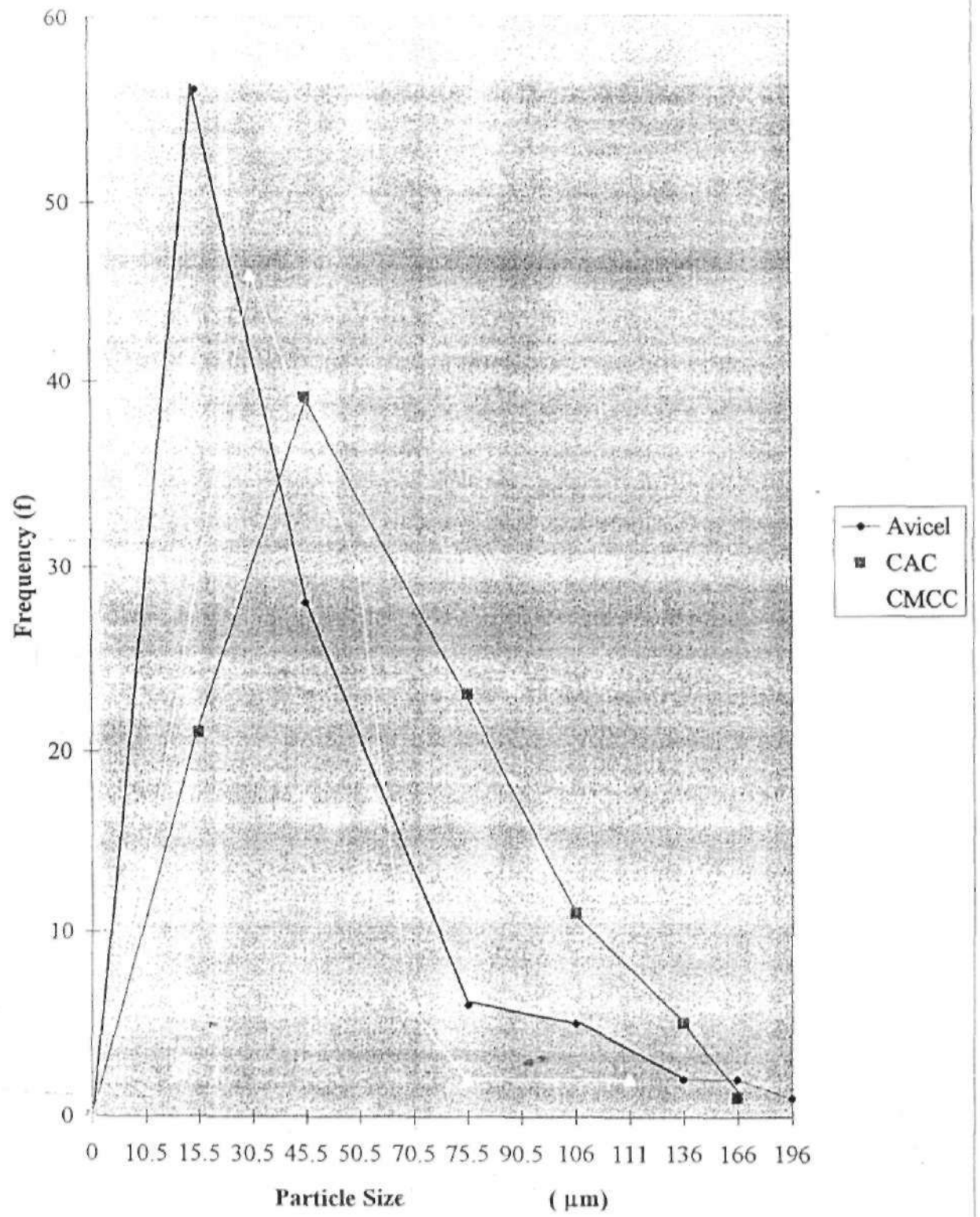
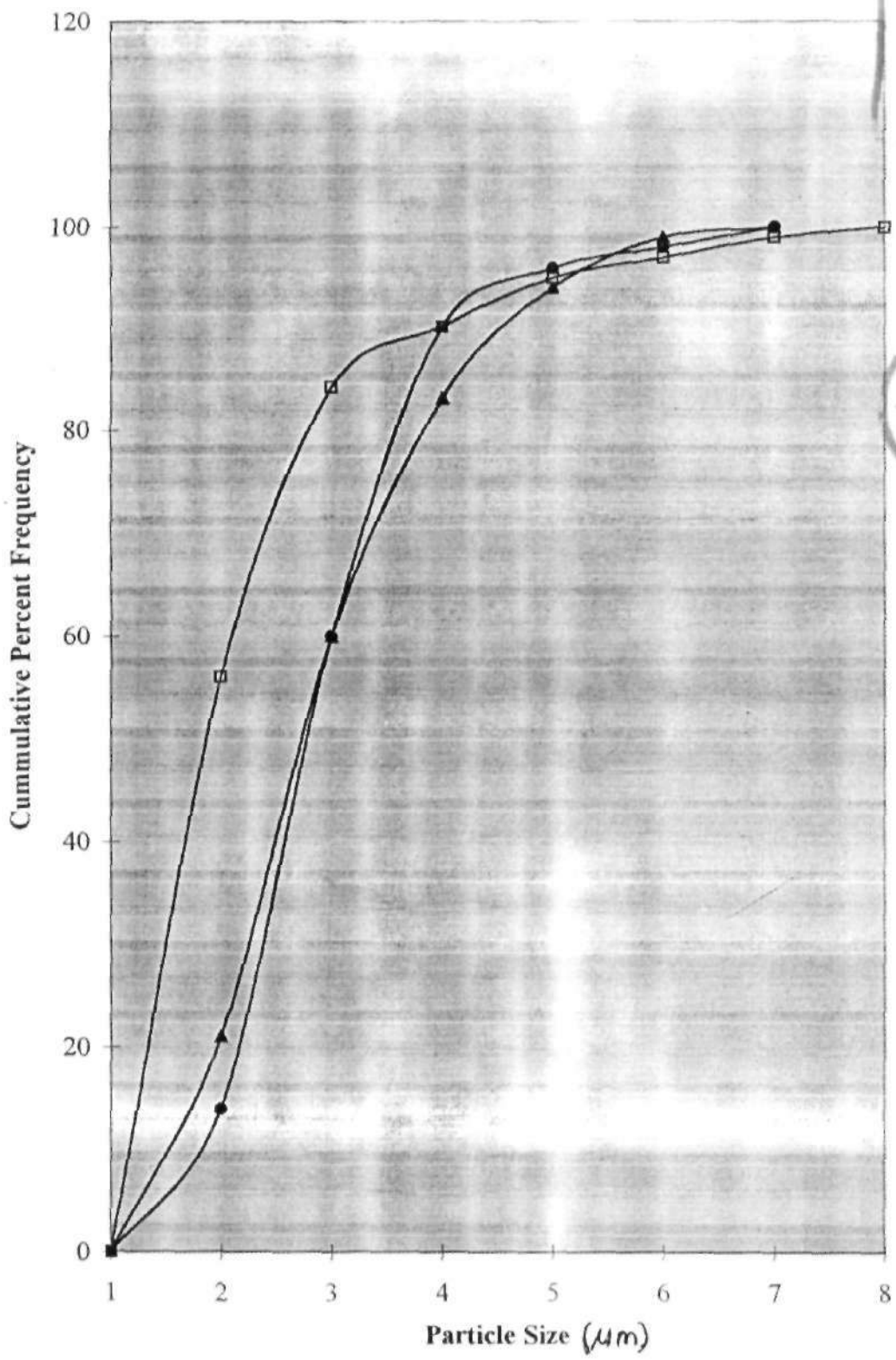


Fig. 3.1(ii) Cummulative Percent Frequency Vs Particle Size for Avicel, CMCC, CAC.



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3.1 .3 Moisture content and moisture sorption capacity. **Table 3.4 shows the moisture content and the moisture sorption capacity of the 3 products, CAC, CMCC and Avicel^{R}.**

Table 3.4 Values of moisture content and moisture sorption capacity.

Powder Sample	Moisture content (%)	Moisture Sorption capacity (%)
CAC	3.1	23.4
CMCC	2.9	22.1
Avicel^{R}	2.9	11.4

3.1.4. Particulate and packing characteristics of CAC, CMCC and Avicel^{R}.

The particulate and packing properties of the 3 materials are as shown on Table 3.5

Table 3.5 Particulate and packing properties of CAC, CMCC and Avicel^{R}.

Properties	CAC	CMCC	Avicel^{R}
Fluff bulk density (gcm $^{-3}$)	0.244	0.219	0.266
Tapped bulk density (gcm $^{-3}$)	0.356	0.348	0.374
Carrs' index (%)	37.10	37.06	28.88
Flow rate (g s $^{-1}$)	0.908	0.807	0.987
Angle of repose (degree)	47.54	41.54	45.93
True density (gcm $^{-3}$)	1.503	1.473	1.408
Hausner's index	1.46	1.59	1.41
Packing fraction	0.15	0.15	0.19
Bed porosity (%)	85	85	81

3.2 *Evaluation of the 3 excipients (CAC, CMCC and Avicel^{R}) on properties of paracetamol tablets*.

3.2.1 Tablet weight and weight deviation.

The mean tablet weight and the mean tablets weight deviation are shown in Fig. 3.2. (i) 3.2 (ii) respectively.

Fig. 3.2(i): Mean Tablet Weight (mg) Vs. Content of Excipients (%w/w).

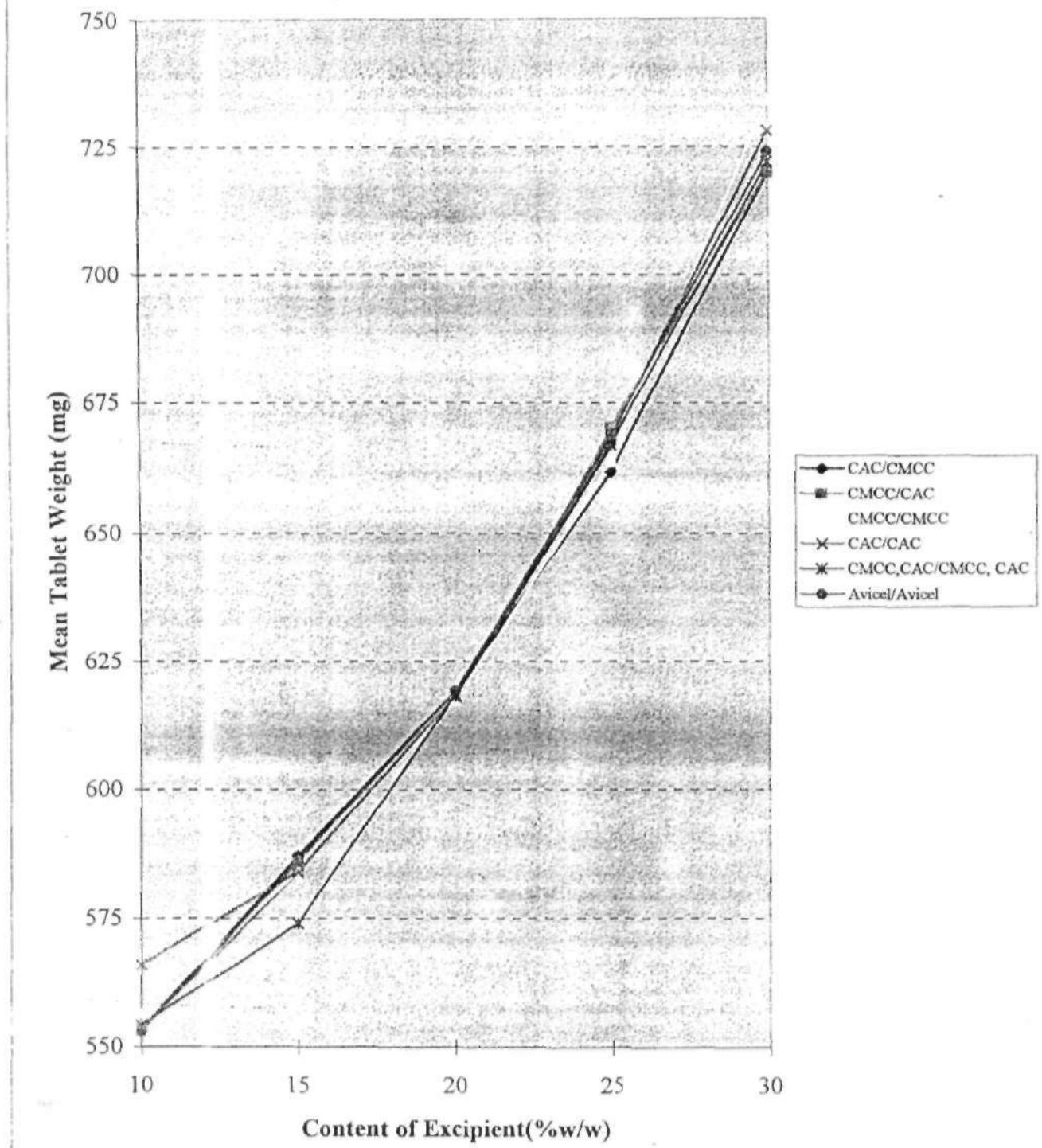
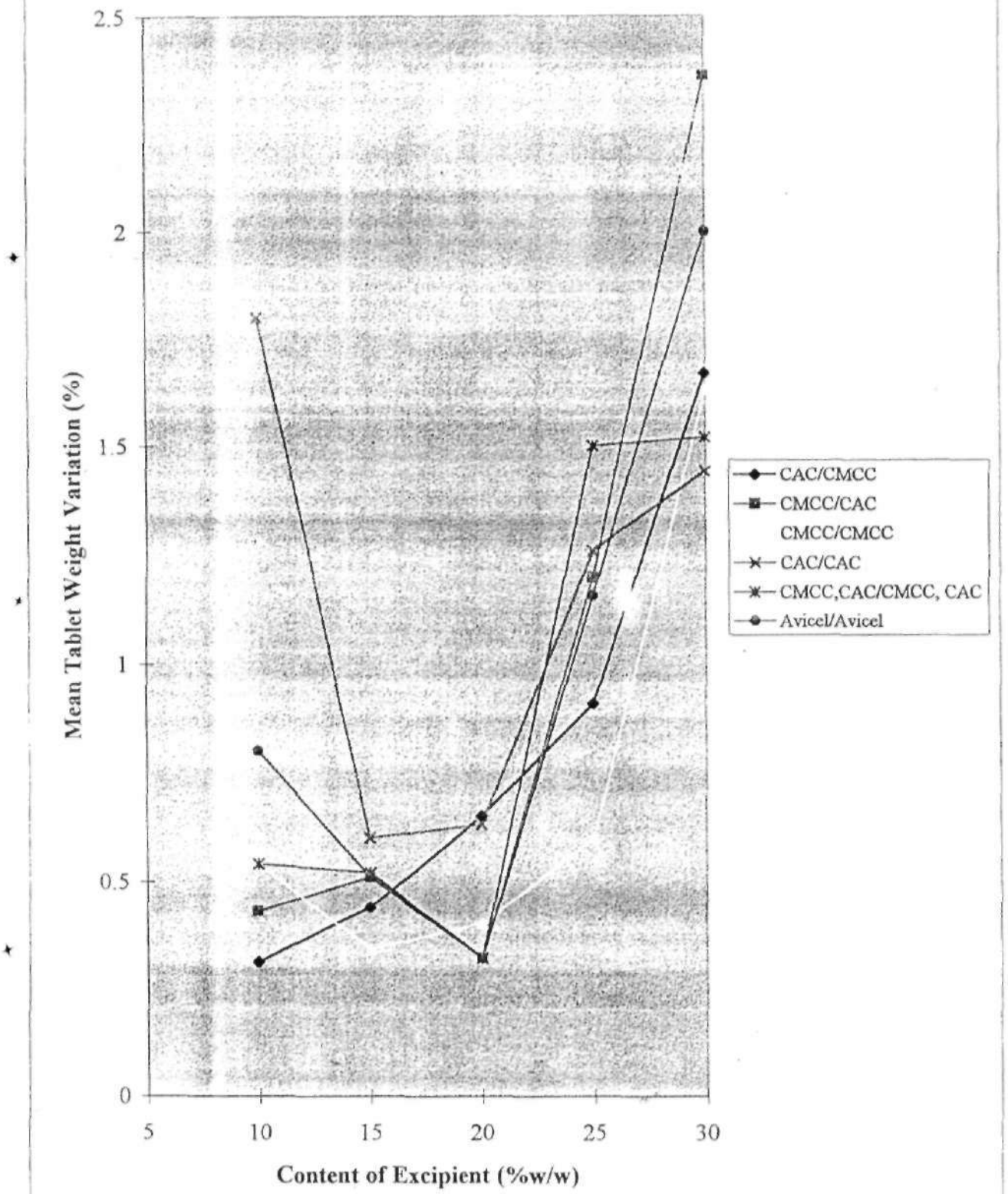


Fig. 3.2(ii): Effect of Content of Excipient on Mean Tablet Weight Variation



3.2.2. Tablet thickness and tablet specific thickness.

The thickness of the tablets is shown in Figure 3.3 (i) and the specific tablet thickness which is the mean thickness per unit milligram weight of the tablet is shown in Figure 3.3 (ii)

3.2.3 Tablet hardness

The effects of the contents of excipient on the hardness of paracetamol tablets is shown in Fig 3.4

3.2.4. Tablet friability.

Fig 3.5. shows the effect of excipient content as dry binder on the friability of tablets. The friability decreases with increase in dry binder concentration until 25% excipient content was reached. Beyond that to 30% content, the friability value increased slightly but this value was lower than that of the values for 20% dry binder (excipient) content.

3.2.5. Tablet disintegration time.

Fig 3. 6. gives the effect of the dry excipient/ binder content on the tablet disintegration time. In all cases, the least disintegration time was achieved with 20% w/w excipient content.

Fig.3.3(i): The Effect of The Excipient Content on The Tablet Thickness.

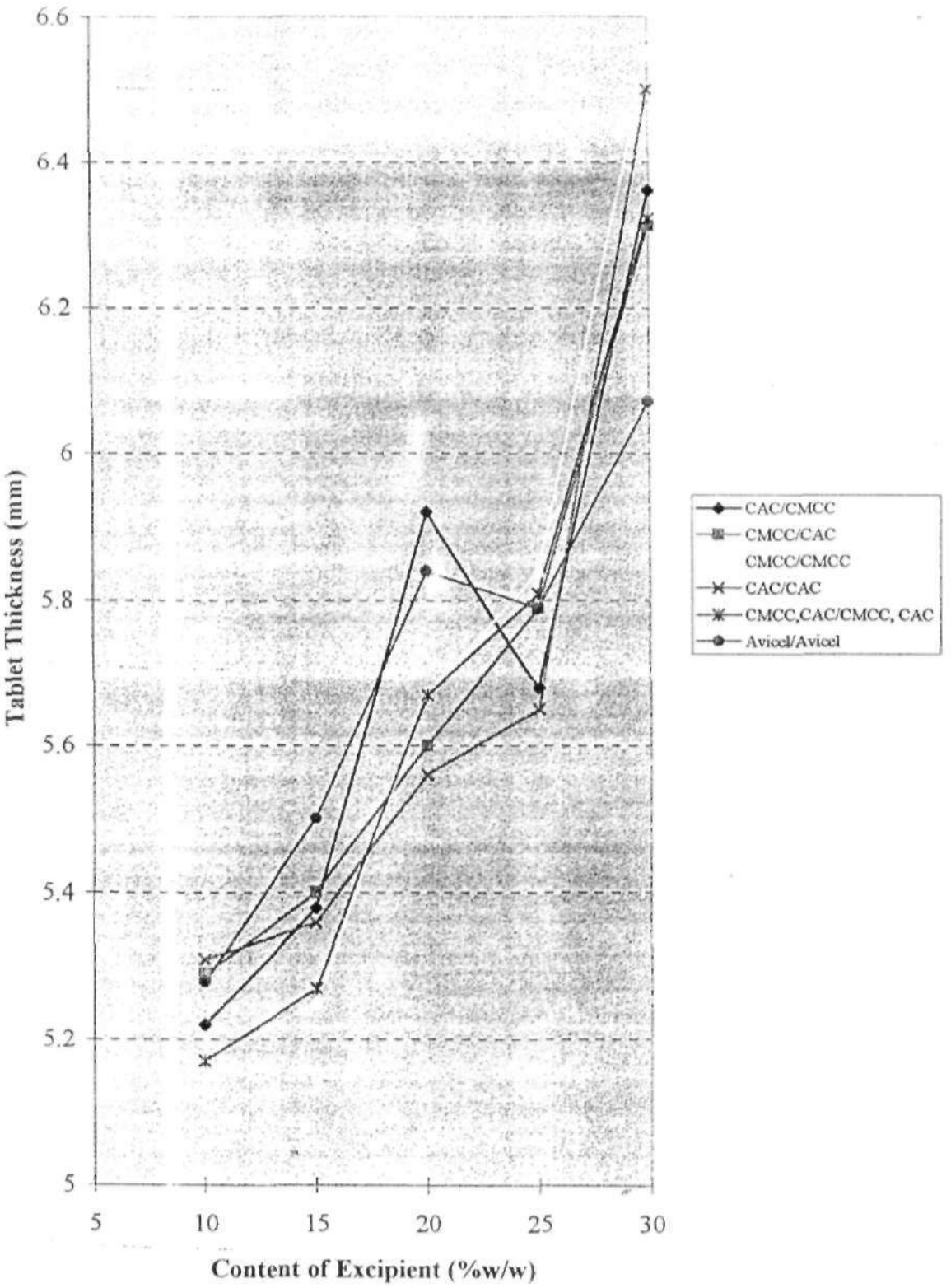


Fig. 3.3(ii): Effect of Content of Excipient on Specific Thickness of The Tablet.

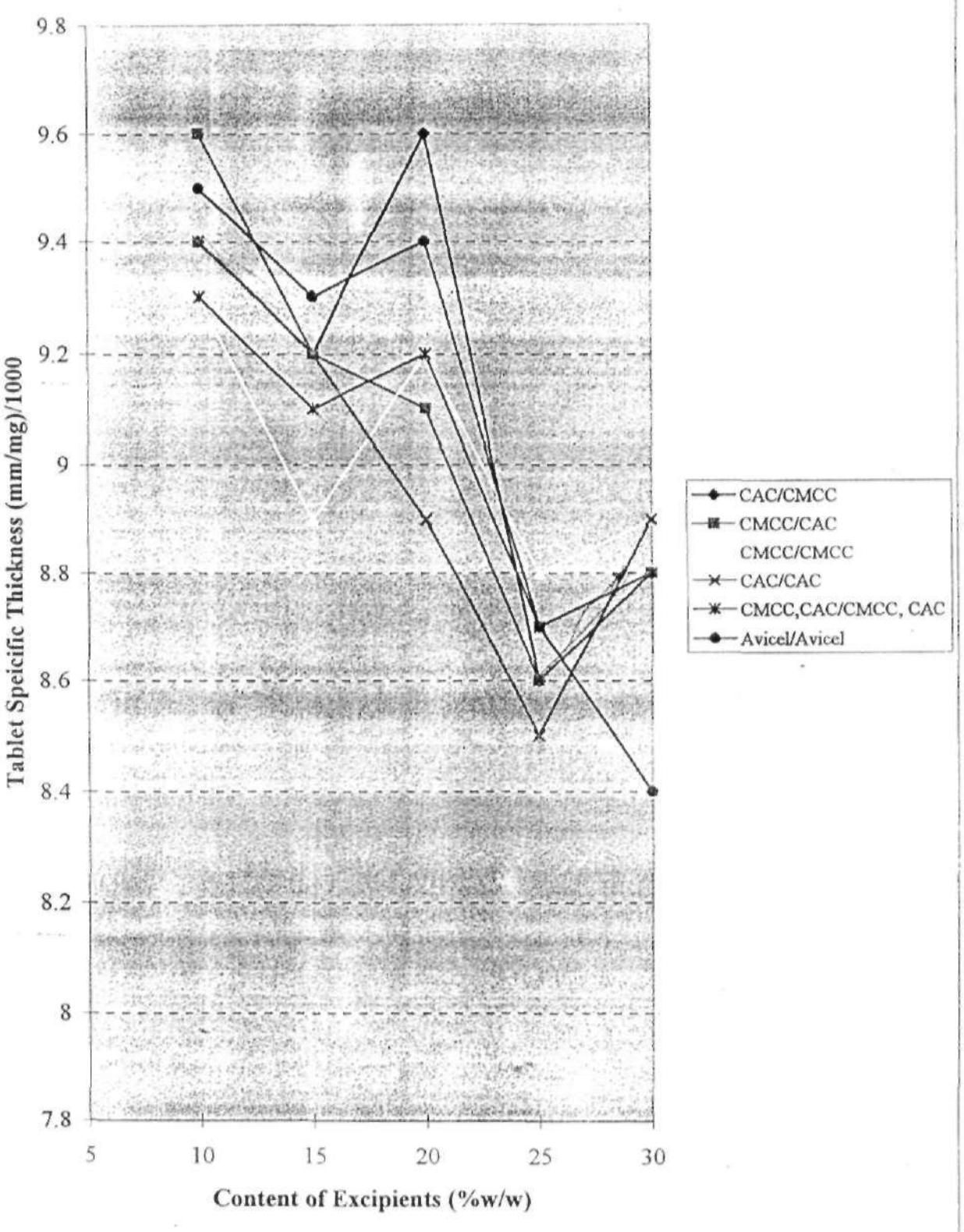


Fig. 3.4: The Effect of the Content of Excipient on the Hardness of Paracetamol Tablets

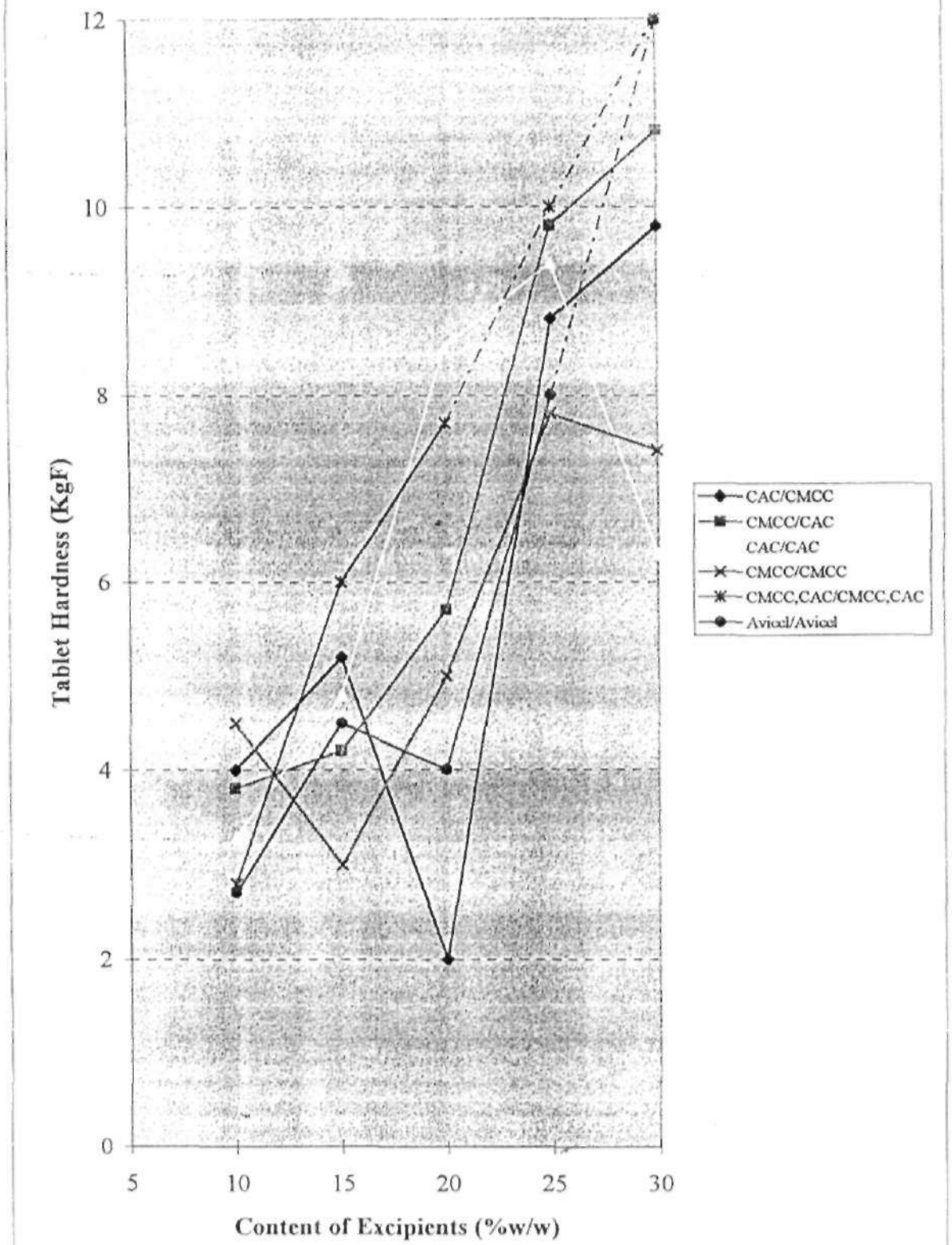


Fig. 3.5: Effect of Excipient Content as dry binder on Tablet friability.

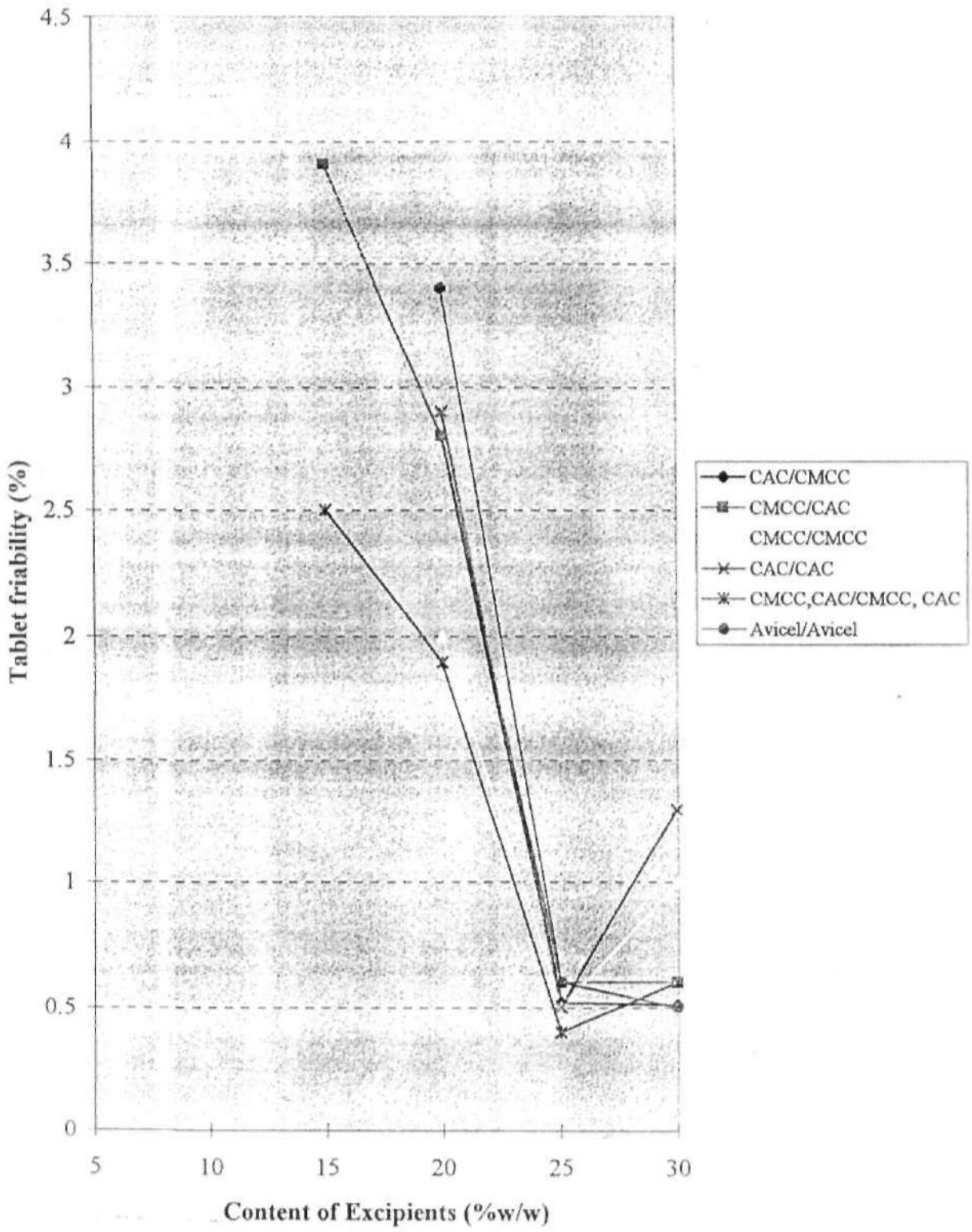
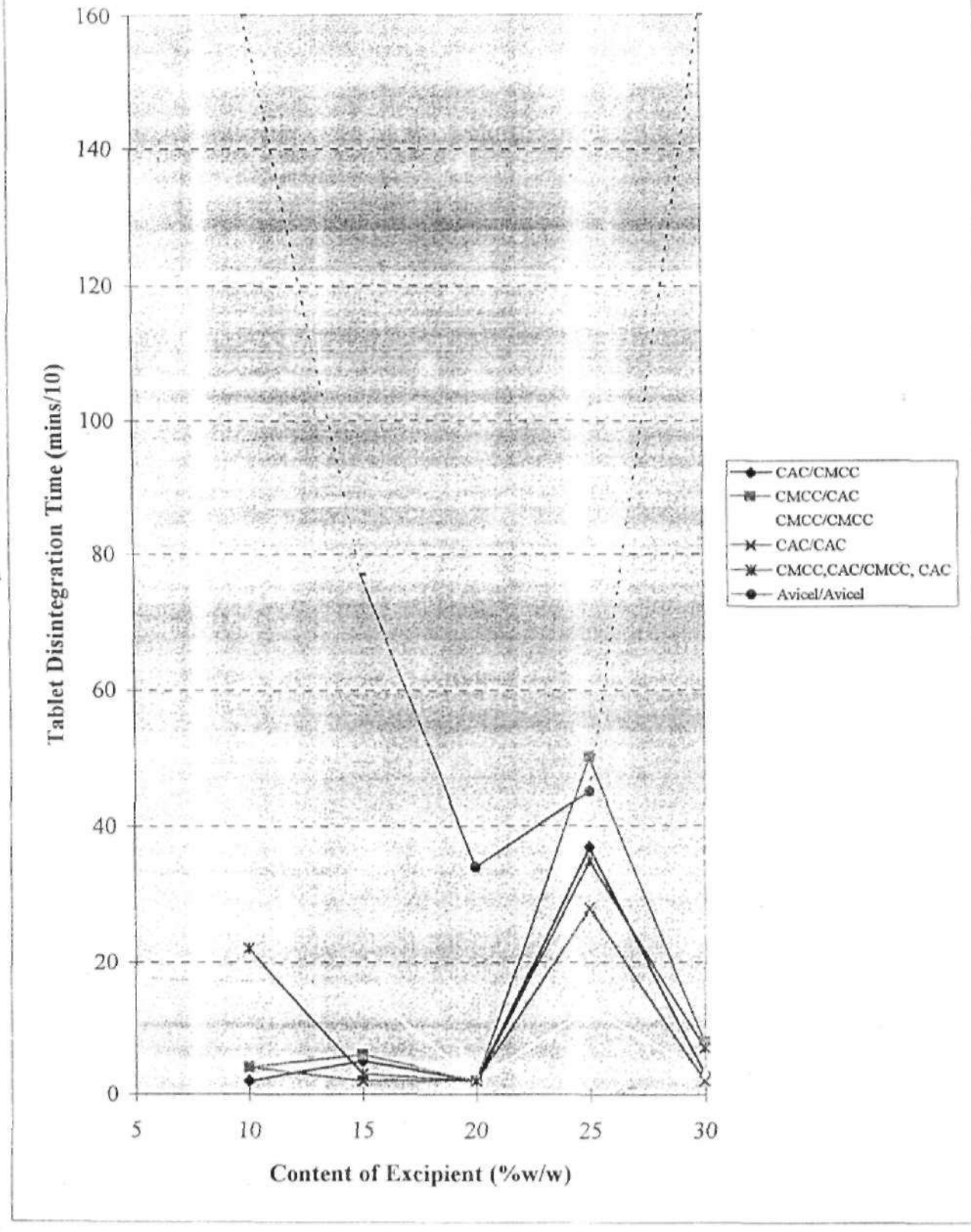


Fig. 3.6: Effect of Content of Excipient on Tablet Disintegration Time.



CHAPTER FOUR

4.0 DISCUSSIONS

4.1. Characteristics of the Three Excipient Materials (CAC, CMCC and Avicel[R]).

The 3 excipient materials - cob alpha - celullose (CAC), cob microcrystalline cellulose, (CMCC) and Avicel[R] PH 101 are hereby discussed under four subtitles viz :-

: Chemical identification characteristics,

: Particle size and size distribution;

: Moisture contents and moisture sorption capacities

: Particulate and packing or consolidation characteristics

4.1.1 Chemical identification characteristics.

Tables 3.1 and 3.2 show the results of the chemical identification characteristics and others for presence or absence of possible contaminants carried out on the three powdered samples. The tests showed that cob alpha cellulose (CAC), cob microcrystalline cellulose (CMCC) and Avicel[R] were identified as alpha- cellulose, microcrystalline cellulose and microcrystalline cellulose respectively. The chemical tests also showed that CAC, and CMCC were totally free from presence of lignin as a result of lignin solubilizing treatment with 3. 5.% v/v nitric acid. They were also free of tannins and other pigments as a result of the extractive treatments with alkali, acid, washings and bleachings. The treatment with 2% NaOH and 2% sodium sulphite also were intended to digest the cob fibres (Okhamafe *et al*, 1991), loosening them for

further action by subsequent chemical reactions. Further treatment with 17.5% NaOH was successful for dissolving β and γ - cellulose, being soluble in the solvent while α- cellulose was left intact as it is not soluble in the 17.5% NaOH solution (Okhamafe *et al*, 1991). The final residue obtained was therefore cob alpha cellulose (CAC) as identified by the chemical tests as shown on Table 3.1.

Tests for monosaccharide sugars, pectin, lignin and uromic acids gave negative results meaning that the process used in extracting the CAC was adequate (Musa-1996, Brain and Turner, 1975).

The yield for CAC was 21% while CMCC yield from CAC was 90%. The low yield observed with CAC could be improved upon with more efficient milling machines. Additionally more efficient suction pump would be needed during the washing processes. In this way, there would be less losses incurred during washings. It is envisaged that since NaOH solution could also dissolve lignin and alkaline hydrolysis of plant polymers is a very slow process (Balami *et al*, 1988), a higher CAC yield would ensue had HNO_3, which was documented to accelerate the hydrolysis action of partial depolymerisation, been substituted with NaOH.

4.1.2 Particle sizes and size distribution of CAC, CMCC and Avicel^R.

Tables 3.3 (i) 3.3 (ii) 3.3 (iii) show the result of the particle size distribution analysis for , Avicel^R. CMCC and CAC respectively; while Fig. 3.1. (i) and 3.1 (ii) show the frequency Vs particle size distribution and cumulative percent frequency Vs particle size distribution respectively for the three powders.

Table 3.3 (iv) shows the comparative analyses for mean particle size, standard deviation (SD) and standards error of the mean, SE of the three samples. CAC has mean particle size of 58.4μm, which was larger that that of CMCC (38.9μm) and Avicel^{R} (39.2μm). The larger particle size of CAC could be attributed to unhydrolysed bonds in the cellulose structure, giving larger particles which were subsequently partially hydrolysed and broken down or partially depolymerised with hot HCl treatment to give microcrystalline cellulose. Thus from Fig. 3.1(i) , the frequency Vs particle size distribution shows CAC to have wider distribution of large size particles compared with CMCC and Avicel^{R}, whose particles are narrower in size range with their mode being at 25.0 μm for Avicel^{R}, and 35.0 μm for CMCC. The mode for CAC was 45.0 μm. Thus CAC particles were more amorphous and longer when observed under the microscope than CMCC particles (Musa, 1996) and being more fibrous than CMCC (Okhamafe *et al* 1991, Staniforth, 1993). The way the particles orientate themselves on the micrometer stage of the microscope led to larger average particle sizes than the more uniform particles of CMCC and Avicel^{R}. The particles sizes of Avicel^{R} and CMCC are closer in range than with CAC. This could be attributed to the spheronization and crystallization processes they were subjected to in their production; reducing amorphous and fibrous nature of the particles to a more spherical than amorphous nature. However CMCC from Fig 3.(i) has narrower size range with some particles on both sides of the normal curve with the mode in the centre. Powders with such particle size distribution are desirable in tabletting technology (Staniforth, 1993). Avicel^{R}, on the other hand, has no tail towards the left, only to the right. Size distribution of

powders for tabletting is of great importance in tabletting technology as it influences the subsequent physical performance of the drug product and thereafter the pharmacological performance of the drug. Particle sizes of powders or granules for tabletting or encapsulation influence the uniformity of tablet weight as what determines weight is the volumetric fill of the die with the powdered or granular particles. Therefore any alteration may interfere with the dose of drug incorporated into the tablet or capsule, thus reducing content uniformity of the medicine. Powders with different particle sizes have different flow and packing properties which alter the volumes of powder filling the dies for tabletting. To avoid such problems, particle sizes of the powders and other drug excipients are controlled.

Solubility (dissolution) of the drug depends on several factors, one of which is the particle size of the drug. Particle sizes also greatly affect the proper and efficient mixing of solid substances and the stability of the resulting mixture. Excipients for tabletting in most cases require an optimum size and size distribution. This could be due to the fact that mixing capability of powders depend on their degree of surface contact, which can be increased or decreased by particle size adjustments.

A pharmaceutically desirable powder should give a normal distribution curve, which is symmetrical about a vertical axis (the mode). It means that most of the particles lie in the centre while both ends of the curve show smaller numbers of large and smaller sizes of the particles. CAC and CMCC gave this pattern but not Avicel^{R} as observed on Fig 3. 1 (i). However, it was found that the size - frequency distribution of milled materials is usually skewed with the

number of particles increasing with decreasing sizes (Staniforth, 1993) and this can be observed from Fig 3.1. (i).

Particle size and particle size distribution are important parameters because they largely determine the magnitude of forces (gravitational and inertia) which can cause inter particulate friction when interparticulate forces are higher than gravitational forces. Only few powders of less than 100□m mean particle sizes are free flowing.

From the values of mean particle sizes for the three powdered samples in Table 3.3 (iv) and Tables 3.3 (i), 3.3 (ii) and 3.3 (iii) and their modes (Fig 3.1 (i)) most of the particles are below 100□m in size. Therefore it was not surprising that Table 3.5 showed poor flow for the powders. Avicel^{R} had been known to have poor flow.

4.1.3 Moisture Contents and Sorption Capacity Evaluation.

Table 3. 4. shows the result of moisture contents and sorption capacities of the three samples of powders. CAC had the highest values of moisture contents at 3.1% while CMCC and Avicel^{R} were found to have the same moisture content values of 2.9%. The presence of higher moisture in CAC would be attributed to its larger sized particles and hence presence of moisture in the bond structure than in CMCC and Avicel^{R} whose hydrolysable bonds have been destroyed giving smaller particles sizes.

The determination of moisture content for a pharmaceutical powder for tableting is important. Workers like Rees and Shotton, 1971 reported that moisture (from water, light liquid petroleum or decahydronaphthalene) produced several interrelated effects during the compaction of sodium chloride, which

included die wall lubrication, interparticulate lubrication, hydrodynamic resistance to consolidation and expression of interstitial liquid to the die wall. On further study of compacts containing the above three liquids, Rees and Hersey (1972) reported that moisture decreases the compact strength by reducing the strength of the interparticulate bonds. Except at low compression force, this effect cancelled out increase in strength due to other mechanisms. Determination of moisture content is also important as it is critical for proper and free flow of powder. Excessive moisture in tablet excipient may lead to sticking and erratic flow of powder and also, mottling of coloured tablets may occur when prepared with such excipients.

Excessive moisture contents encourage microbial and fungal growth on tablet surfaces. Below its critical level of moisture content however, the powders may become brittle and static electric charges develop between particles and die wall. Adhession to hopper may also occur leading to particle seggregation and erratic flow. A critical level of moisture content is therefore desirable for formation of some bonds or bridges between the excipient, which is necessary in tabletting. Formulation scientists generally consider 3% moisture content as the maximum, especially if the chemical stability of a hydrolysable drug contained in the solid dosage form from is to be assured (Okhamafe *et al* 1991). This is consistent with 2.9 and 3.1% obtained for the 3 excipient in these investigations.

The moisture sorption capacities of the three samples show that CAC has the highest capacity at 23.4%, followed by CMCC and Avicel^{R} at 22.15% and

11.4% respectively. The amorphous and fibrous texture of CAC (Musa 1996) could be responsible for its higher sorption capacity, and the spheronization methods of preparing Avicel^{R}, eliminating rough edges on particles, may be responsible for its low moisture sorption capacity compared with CMCC.

The sorption capacity gives an indication of the excipients affinity for water, subsequently swelling leading to distortion of bonds formed with other ingredients of the tablet. The powder sample that showed the greatest tendency towards absorbing moisture can be considered to posses a better disintegration property therefore. Thus CAC will be expected to perform better as a disintegrant, followed by CMCC and lastly, Avicel^{R} as shown in Fig. 3.6.

4.1.4 Particulate and packing or consolidation characteristics of the three materials:-

Table 3.5 shows the flow and packing characteristics for CAC, CMCC and Avicel^{R} powders. Avicel^{R} was observed to have a higher bulk density followed by CAC and then CMCC. The bulk density of a powder is an indication of its packing geometry. However, a powder may have a certain bulk density by virtue of its occupying a certain volume. Any slight vibration of the bed will mobilize the particles so that on stopping the vibration, the bed comes into static equilibrium but occupies a different spatial volume from the initial one. A change in bulk volume therefore occurs as a result of rearrangement of the packing geometry of the particles. Such geometric rearrangement results in a transition from loosely packed particles (fluff bulk density) to more compactly packed particles (tapped bulk density). Thus a more compactly packed powder

requires a higher driving force to produce powder flow than a more loosely packed one. Bulk density is a characteristic of a powder rather than individual particles and it is always less than the true density of its component particles (Table 3.5) because the powder contain interparticulate pore and voids.

A powder can only possess a single true density using a particular method but have different bulk densities, depending on the way it was packed and the bed porosity. A high bulk density in a powder for direct compression tabletting is desirable. Elucidation of the values of the bulk densities of the three powders showed that the values are comparable and since Avicel^{R} is regarded as a good direct compression excipient and since the materials are chemically closely related, CAC and CMCC can be adduced to be good compression excipients too.

Avicel^{R} was observed to have lower bed porosity value than CAC and CMCC and could therefore be said to be more densely packed and this was supported by its high bulk density value.

The Hausner□s indices show that while CAC and CMCC were less free flowing (1.46 and 1.59 respectively), Avicel^{R} with 1. 41 would be expected to flow better. The higher indices for CAC and CMCC would be associated with the shapes of the particles of the powders which were irregular and not as spherical as that of Avicel^{R}. Therefore higher interparticulate friction may be observed with CAC and CMCC than with Avicel^{R} powder. This can be corroborated from the result of the flow rate which showed that Avicel^{R} flows better with a faster flow rate followed by CAC and CMCC. CMCC was

expected to flow better than CAC since its particles were more spherical and hence less interparticulate friction expected in the powder. However, presence of higher moisture contents in CAC may be responsible as it has been shown that moisture reduces interparticulate friction (Rees and Shotton, 1971).

Carr's index values are the percentage compressibility of the powder and believed to be a direct measure of the potential powder arch or bridge strength and stability necessary for good compression (Staniforth 1993). All three powders have high Carr's index (CI) values indicating poor flow, hence they are cohesive powders.

In view of the poor flow properties of the three powders, and as observed by other workers (Tsai *et al* 1998), the use of larger particles size of microcrystalline cellulose (MCC) is advised for better flow or granulation is often recommended when microcrystalline cellulose is used in direct compression of tablets. Akande *et al* (1997) also showed that a combination of high precompression and smaller main compression pressures are more advantages in direct compression tableting of a 1:1 acetaminophen: MCC than a high single compression pressure.

The powder mixtures with paracetamol were therefore precompressed at 15 metric tonnes and then the main compression carried out at compression pressures of between 5 . 5. to 11. 5 metric tonnes.

4.2 Evaluation of Tablet Properties.

4.2.1 Physical observation of tablets.

The compacts made from pure samples of CAC, CMCC and Avicel^{R} ie batches 1(i) 1 (ii) and 1 (iii) respectively were free from physical defects. In batches 2 (i), 3 (i), 4 (i), 5 (i), 6 (i) and 7 (i), some tablets exhibited tablet defects like lamination and capping. These could be attributed to inadequate dry binder concentration since only 10% were used as intra- and extra - granular dry binder. Thus these batches were observed to have produced greater fines when pellets where being micronized to granules. Since the fines were mostly of the paracetamol powder, they could not contribute to bond formation and so more defects were observed in the batches. In batches 2 (ii),3 (ii), 4 (ii), 5 (ii), 6 (ii) and 7 (ii), containing 15 % w/w of dry binder / excipient which was a higher content, less surface defects were observed within the batches than the previous batches mentioned above. The rest of the batches from 3 (iii) to 7 (v), ie with dry binder excipient content from 20% w/w to 30%, showed no physical defects. Thus dry binder concentration of 20%w/w to 30%w/w of equal proportion of intra - and extra- granular binder addition to the formulation was found to be adequate for production of a physically satisfactory tablet using direct compression.

An attempt to tablet paracetamol granules was unsuccessful despite the fact that it was able to be pelletized at 15 metric tonnes.

4.2.2 Tablet weight uniformity.

As the paracetamol formed a greater part of the tablet mass, the dosage is linked to tablet weight (Armstrong, 1993). All batches passed the B.P and USP weight variation tolerance for uncoated tablets. Fig. 3.2 (i) shows the relationship between tablet mean weight and excipient content. The increase in the concentration of excipients from 10% to 30% w/w also caused a progressive increase in tablet weight as each tablet must contain 500mg of paracetamol plus the given concentration of the excipient per tablet. The graph also showed that as concentration of the excipient decreased or increased, mean tablet weight between the three powder samples becomes distinct, but at the centre i.e at 20% w/w excipient concentration, they have almost the same value of mean weight of between 615 to 620mg.

Since the graph of each sample are close together, their weight were therefore maintained at expected weight during production.

Fig 3. 2. (ii) shows the effect of content of excipient on mean, tablet weight variation for each concentration. Greater variations were observed at extreme values of concentration 10%w/w and 30% w/w. The greater variations at 10%w/w could be due to segregation of particles as a result of wide size ranges when the dry binder concentration could not produce enough binding action at that concentration. The greater variation at 30% w/w could also be as a result of lack of fines to fill in voids when the granules fill the die. Therefore, because of greater binding action, granules made were more or less of same size

and depending on the orientation of each granules in the die, which would not be the same as the next die fill, variation becomes more prominent.

The middle concentrations of 15%w/w and 20%w/w had fewer variations and this could be due to adequate production of fines (not too much and not too low as with 10%w/w and 30%w/w respectively) with subsequence almost equal amount and size of granules filling the die each time. Overall, however, CMCC/CMCC combination (batch 5) showed fewer variations. This can be attributed to the particles size range of the CMCC powder which showed a normal distribution curve (Fig 3.1 (i)) and thus said to be the best for tableting (Staniforth 1993).

4.2.3 Tablet thickness and specific tablet thickness.

Figs 3.3 (i) and 3.3(ii) graphically showed the effect of excipient content on tablet thickness and tablet specific thickness respectively. The thickness of tablet is directly related to the level of compressibility to a certain extent. More compressible materials are bound to deform plastically, making thinner tablets. Thickness of tablet is therefore a function of compression force, compressibility of materials and formation of bonds within the tablet. A desirable tableting vehicle should have high bulk density to fill large volumes, but when compressed it should produce a small compact in terms of volumes. Fig 3.3 (i) shows that at concentration of 25%w/w for all powdered samples, the thickness of the tablets are comparable, with the smallest thickness being exhibited by the CAC/ CMCC combination. This was followed by CAC/ CMCC, Avicel^{R} / Avicel^{R},CMCC:CAC/CMCC:CAC and lastly CMCC/CMCC binary mixture.

The result can be explained by the higher moisture content of CAC, followed by CMCC and Avicel^{R} (Table 3.4).Presence of moisture enhances bonds formation and especially for direct compression excipient, it provides optimal compression properties (Ahlneck and Zografi, 1990). As the weight of the excipient varied according to the admixed component, a better comparative measure adopted was the tablet specific thickness, which was the thickness of each milligram weight in the tablet. Specific thickness indicates compressibility of the vehicle, and the smaller the value, the better the compressibility of the vehicle. Fig 3.3 (ii) showed that as the concentration of the binary mixtures of the samples increase, specific thickness decreased, and this was expected as it means that the increase in concentration of CAC, CMCC and Avicel^{R} in the tablet led to increased compressibility. Avicel ^{R} was observed to show decreasing specific thickness as its concentration increased in the tablet, while the other binary mixture of CAC and CMCC showed decrease with increased concentration, and then after 25%w/w there was an increase in specific thickness. This implies that after 25%w/w concentration, there was no added advantage of increasing the concentration of the vehicle for better compressibility property.

4.2.4 Tablet hardness.

Fig 3.4 shows the influence of effect of the content of excipient on tablet hardness. The hardness of directly compressed tablet is of utmost importance. Hardness of about 6kgf and above are considered acceptable as hardness is a function of tablet thickness, diameter and the compactional force to a certain degree. The graph showed that hardness increased with increase in concentration

of excipient except for CAC/CAC binary mixture. CMCC: CAC/CMCC:CAC and Avicel^{R}/ Avicel^{R} binary mixtures produced extremely hard tablets that were greater than 10kgf from 20%w/w and 25%w/w excipient concentrations respectively. The hard tablet produced by Avicel^{R}/Avicel^{R} binary mixture could be explained by the fact that as its concentration increased compressibility increased as observed from specific tablet thickness Fig 3.3. (ii). Whereas the hardness produced by CMCC: CAC/CMCC: CAC binary mixture could be attributed to greater bond formation as a result of higher moisture in CAC with a compressible material of CMCC.

The hardness of CAC/CAC binary mixture decreased after 25%w/w concentration, and this can be seen from Fig 3.3 (ii) also which showed that after 25%w/w further increase in concentration led to decreased compressibility. This could be due to the fibrous texture of CAC particles and hence limited packing that could be achieved which therefore led to decreased compressibility.

4.2.5 Tablet friability.

Fig 3. 5 shows the effect of excipient content as dry binder on tablet friability. Lower concentrations of dry binder (the samples) produced highly friable tablets as this concentration was not adequate for efficient binding action. It was also paradoxically observed that after 25%w/w concentration, more friable tablets especially with CAC/CAC were produced. This also support the conclusion drawn from its decreased compressibility at 30%w/w concentration. Friability is a measure of surface hardness of tablet when subjected to abrasive action, and it is a particularly useful index to show how successful a directly

compressed tablet was formulated. In most industries, the friability of uncoated compressed tablets should not exceed 1% weight loss. Therefore, only at concentrations of 25% of binary mixtures for the three powdered samples was this achieved. This can then be said to be the optimal concentration for direct compression of paracetamol tablet using these three powder samples.

4.2.6 Tablet disintegration time.

The disintegration of a directly compressed tablet determines its bioavailability. The tablet should disintegrate rapidly in an aqueous medium to release its active medicament. From Fig 3.6 it was observed that with increase in disintegrant concentration (ie the samples), there was a decrease in disintegration time upto 20%w/w concentration, and then an increase in the disintegration time at 25%w/w concentration before decrease in time at 30% w/w. The result may be explained by the fact that from 10%w/w to 15% w/w, the decrease may be associated with more rapid disintegration property of the binary mixtures with tablet hardness playing smaller role. Then at 20%w/w, disintegration property predominates giving a virtual instant disintegration characteristics except with Avicel^{R} Avicel^{R} binary mixture. At 25%w/w concentration of the binary mixtures of the powders, binder property predominates, and it was at maximum, hence disintegration time was longer than at 20%w/w. Avicel^{R}/Avicel^{R} binary mixture exhibited this more obviously as after 25%w/w, the tablets disintegration time exceeded 15 minutes.

From the result therefore, it can be correlated with other results in Figs 3.3(i) 3.3(i), 3. 4 and 3.5 that at 25%w/w concentration of binary mixture all the powder samples produced the best batches of tablets, viz:

It was the concentration that produced the least friability, produced the hardest tablets, produced the thinnest tablets and produced tablets with reasonable disintegration time.

A too rapid disintegration as observed with 20%w/w was not desirable as tablet could crumble easily in the mouth when it comes into contact with the saliva. The disintegration time result also shows generally that the derived materials disintegrated more rapidly than Avicel^{R} binary mixtures. This can be explained by the amorphous structures of CAC and CMCC particles compared to Avicel^{R} and it was discovered that amorphous states enhance among other things permeability of water (Ahlneck and Zografi, 1990). Therefore, amorphous materials preferentially absorbs water as shown from the smallest disintegration time observed with CAC and CMCC binary mixtures compared to Avicel^{R} binary mixture.

4.3 Conclusion

In conclusion, it has been observed that compression of paracetamol tablets was possible by direct compression using CAC and CMCC derived from maize cobs.

The powder characteristics of Avicel^{R} compared favourably with CAC and CMCC. It was also observed that tablet properties were comparable between the three powder samples when used as the only tabletting excipient.

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Therefore, CAC, and CMCC could be used as vehicle, disintegrant, and binder in direct compression method of tabletting to impart compressibility, disintegrant and cohesion characteristics to such tablets.

It was also observed that at lower concentration of 10 - 15%w/w disintegrant properties of CAC and CMCC predominate more than the binder and compression characteristics. At higher concentrations of 25%w/w however, the binder and compression characteristics predominate, producing harder, less friable and highly compressible paracetamol tablets. It was also observed that higher concentrations of 30% w/w did not produce better tablets than 25% w/w concentration. In fact, softer, more friable, and more bulky tablets were produced which was attributed to the amorphous state of CAC and CMCC structures leading to disintegrant property predominating. With Avicel^{R} however, this was not observed.

Therefore, the aim of producing a pharmaceutical grade of microcrystalline cellulose and alpha - cellulose for use in direct compression of macrodose drug like paracetamol was achieved.

Further work that need to be done includes the production of various particle sizes of the CAC and CMCC to improve their flow properties, or perhaps their production could be done using method of spheronisation like Avicel^{R} so that a grade with better flow properties could be obtained.

Other works that could be done include the measurement of forces in tablets made from CAC and CMCC and assessment of their compressibility profile using the aforementioned Heckel relationship, for example.

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Appendix 1

Calculations of the result for mean particle size standard deviation SD and standard error of the mean SEM.

1.1 Avicel^{R}.

Mean particle size = $\sum F X / \sum F$ ----------(1)

= 3920/100

= 39.20μm

SD = $\sqrt{(\sum FX^2 - (\sum FX)^2/n/ n-1)}$ .....(2)

= $\sqrt{(290995 - (39020)2/100/99)}$

= 37.24

SEM = $SD/\sqrt{n}$ .....(3)

= $37.24 /\sqrt{100}$

= 3.74

Using the same equation as nos 1,2, and 3, the mean particle size, standard deviation, (SD), and standard error of the mean (SEM) for CAC and CMCC were similarly calculated.

1.2 CAC.

Mean particle size = $\sum FX/\sum F$

= 5840/100

= 58.40μm.

SD = $\sqrt{(\sum FX2 - (\sum FX)^2/n/n - 1)}$

= $\sqrt{(458815 - (5840)^2/100/99/}$

= 34.49

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SEM = SD/√n

= 39.49/√100

SEM = 3.949

1.3 CMCC

Mean particle size = $\sum FX/\sum F$

= 3890/100

= 38.90μm

SD = $\sqrt{(\sum FX^2 - (\sum FX)^2/n/n - 1)}$

= $\sqrt{(191468.5 - (3890)^2/100/99)}$

= 20.14

SEM = SD/√n

= 20.14/√100

= 2.014.

Appendix 2

Batch No 2	Excipient content	Compcation presure (metnc tonnes)	Mean weight (mg)	Mean thickness(mm)	Specific thickness(mm/mg) x10⁻³	Friaibility (%)	Hardness (kgf)	Disintegration Time (Mins)
1 (i)	CAC	9.0	503 ± 1.1%	4.56	9.0	0.7 ± 0.001	6.7 ± 1.4	2.8 ± 0.59
1 (ii)	CMCC	7.0	503 ± 0.6%	4.69	9.3	0.3 ± 0.001	▯10.0	3.6 ± 1.6
1 (iii)	AVICEL®	5.5	497 ± 0.4%	4.97	9.6	0.2 ± 0.001	▯10.0	2.1 ± 1.22
2 (i)	CAC/CMCC (10%)	6.0	553 ± 0.3%	5.22	9.4	Capped	4.0 ± 1.6	0.2 ± 0.11
2 (ii)	CAC/CMCC (15%)	7.0	587 ± 0.4%	5.38	9.2	Capped	5.2 ± 0.9	0.2 ± 0.18
2 (iii)	CAC/CMCC (20%)	7.0	619 ± 0.7%	5.92	9.6	2.8 ± 0.007	2.0 ± 0.9	0.5 ± 0.03
2 (iv)	CAC/CMCC (25%)	10.5	662 ± 0.9%	5.68	8.6	0.5 ± 0.001	8.8 ± 1.3	3.7 ± 1.90
2 (v)	CAC/CMCC (30%)	10.5	720 ± 1.7%	6.36	8.8	0.5 ± 0.001	9.9 ± 1.1	0.3 ± 0.10
3 (i)	CMCC/ ACC 10%	6.0	584 ± 0.5%	5.40	9.6	Capped	3.8 ± 1.3±	0.4 ± 0.23
3 (ii)	CMCC/ CAC 15%	7.0	584 ± 0.5%	5.40	9.2	3.9 ± 0.001	4.2 ± 0.80	0.6 ± 0.19
3 (iii)	CCMCC/ CAC 20%	7.0	617 ± 0.3%	5.60	9.1	2.8 ± 0.001	5.7 ± 2.2	0.2 ± 0.05
3 (iv)	CMCC/ CAC 25%	10.0	670 ± 1.2%	5.79	8.6	0.6 ± 0.001	9.8 ± 1.1	5.0 ± 1.37
3 (v)	CMCC/CAC 30%	11.0	720 ± 2.4%	6.31	8.8	0.6 ± 0.001	10.8 ± 1.1	0.8 ± 0.22
4 (i)	CAC/CAC 10%	6.0	566 ± 1.8%	5.31	9.4	Capped	3.3 ± 1.2	0.4 ± 0.25
4 (ii)	CAC/CAC 15%	6.5	584 ± 0.6%	5.36	9.2	Capped	4.8 ± 1.2	0.2 ± 0.06
4 (iii)	CAC/CAC 20%	7.5	618 ± 0.6%	5.56	8.9	2.9 ± 001	8.5 ± 0.9	0.2 ± 0.04
4 (iv)	CAC/CAC 25%	10.0	668 ± 1.3%	5.56	8.5	0.5 ± 0.001	9.4 ± 1.0	2.8 ±2.36
4 (v)	CAC/CAC 30%	11.5	728 ± 1.4%	6.50	8.9	1.3 ± 0.001	6.3 ± 0.5	0.2 ± 0.05
5 (i	CMCC/CMCC1 0%	5.5	566 ± 0.5%	5.17	9.3	Capped	4.5 ± 1.0	1.5 ± 0.52
5 (ii)	CMCC/CMCC 15%	6.5	584 ± 0.3%	5.25	8.9	Capped	3.0 ± 0.5	1.6 ± 0.60