

**FORMULATION STUDIES OF ACACIA *SIEBERIANA* GUM IN CHOROQUINE AND
METRONIDAZOLE MATRIX TABLETS**

BY

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**FORMULATION STUDIES OF ACACIA *SIEBERIANA* GUM IN
CHLOROQUINE AND METRONIDAZOLE MATRIX TABLETS**

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SHITTU ABIODUN OYETUNJI

**A THESIS SUBMITTED TO POST GRADUATE SCHOOL AHMADU BELLO
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AWARD OF THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICS**

**DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY,
FACULTY OF PHARMACEUTICAL SCIENCES,
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NOVEMBER 2006

DECLARATION

I hereby declare that this thesis was written by me as a record of my research work, carried out under the supervision of Dr. (Mrs) A. R. Oyi and Prof. J. A. Onaolapo. There is no portion of this thesis that has been presented in any previous work for award of a degree. The works of other investigators were acknowledged and references were made accordingly.

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CERTIFICATION

This thesis entitled “Formulation studies of *Acacia sieberiana* gum in chloroquine and metronidazole matrix tablets” submitted by SHITTU ABIODUN OYETUNJI meets the regulations governing the award of the degree of MASTER OF SCIENCE (PHARMACEUTICS) of the AHMADU BELLO UNIVERSITY, ZARIA and is approved for its contribution to science and literary presentation.

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DEDICATION

This work is dedicated to the league of Pharmaceutical scientists and solid dosage (matrix) formulation experts.

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I give all glory to Almighty God for making it possible to see the beginning and end of this research work.

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ABSTRACT

The crude plant gum from African *Acacia sieberiana* was purified and investigated for use as a matrix excipient for chloroquine phosphate and metronidazole tablet formulations. The chromatographic analysis of the acid hydrolysed gum revealed the presence of rhamnose, galactose, ribose, xylose and fructose. The viscosity was found to increase with increase in concentration of the gum. Ten percent mucilage had pH of 5 and pH change has no effect on the viscosity of the mucilage. Both the swelling and hydration capacity showed that water penetration and retention of the gum were very high, as such it could not maintain slow release for a long period. The various particle size fractions of the gum had good flow rate with angle of repose less than 30°. The compressibility (densification) of the different particle sizes was investigated and found to be highly compressible at low compression pressure (1.8 to 3.1×10^5 N/m²). The compactibility studies revealed that radial tensile strength of the gum increases with increase in compression pressure. The compactness was found to increase with decrease in particle size, while the dissolution rate decreased with decrease in particle size of the gum. The $t_{90\%}$ for the matrices made of >125-150 μm and >150-250 μm particle sizes were 2h 12 min and 38 min respectively. The effects of concentration of the gum on compactness and dissolution rate of compacts directly compressed revealed decrease in compactness with decrease in concentration of gum. Increase in concentration of gum was found to have profound effects on drug release rate from tablets formulated by direct compression method. The chloroquine phosphate matrices

containing 60 %,50 %, and 40 %, corresponding to batches 1, 2 and 3 respectively, were subjected to dissolution test. The $t_{90\%}$ s for the three batches were 3 h 30 min, 1 h 45 min and 1 h 40 min respectively. The dissolution efficiencies (DE) at 1 h for the three batches were found to be 37 %, 71 % and 75 % respectively. The release rate of chloroquine and metronidazole (wet granulation method) was evaluated based on $t_{90\%}$ and dissolution efficiency (DE) at 1 h. The DE (1 h) for the batches 1 of test gum chloroquine matrix, test gum metronidazole matrix and standard [*Acacia Senegal*] gum chloroquine matrix were: 98 %, 34 %, and 92 % respectively. The USA,FDA similarity factor “ f_2 “value for the dissolution data between test and standard gum was found to be >50 , this signifies that, there is no significant difference in dissolution. While the f_2 value for the test gum matrices of chloroquine and metronidazole dissolution data was <50 , this indicate a significant difference in dissolution between the two formulations. In conclusion, *Acacia sieberiana* gum has been found to be directly compressible, a good material for wet granulation, and a potential gum matrix excipient for delaying the release of drug, particularly poorly soluble drugs.

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ABBREVIATIONS

F.D.A (U.S.A)	Food and Drug Administration ,United State of America.
M C C	Microcrystalline cellulose.
P. S	Particle size.
CQ	Chloroquine phosphate.
MN	Metronidazole
f_2	Similarity factor
B.P	British Pharmacopoeia
B.P.C	British Pharmaceutical Codex
U.S.P	United State Pharmacopoeia
D.E	Dissolution Efficiency

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INTRODUCTION AND LITERATURE REVIEW

CHAPTER ONE

1.1 GUMS

1.1.1 Definition, Sources and Uses of Gums

i) Definition

Plant gums are polysaccharides and are also known as biopolymers. They are produced by various plants as exudates (gum acacia), seed gums (guar gum,), seaweed extract (carrageenan) and plant extract (pectins).

The gums obtained from acacia are pathological exudates secreted by the plant under certain unfavourable conditions of growth or following an injury to serve as a protective agent. They are generally insoluble in alcohol and organic solvents, but dissolve or swell in water to form a viscid mucilaginous mixture called hydrocolloid (Ghani, 1988).

ii) Source of Gum Acacia

Whenever the cell wall tissues of acacia plant undergo degenerative changes due to enzymatic action it produces a gum. The exuded gum harden on exposure to air forming amorphous, translucent solids through a process called gummosis (Denston, 1951; Ghani, 1988). There is no adequate information about gummosis, the little information available, is that it is probably caused by bacterial activity (Denston, 1951). Two kinds of bacteria were isolated from gum exuded from *Acacia penninervis*, the most important one is called *Bacterium acacia*, when grown on artificial media, liberate a slime

which contained gum of the arabin –galactin (Williams and Phillips.,2000). A similar bacterium was also isolated from *Acacia senegal*.

Scorching of the gum producing trees would not induce exudation, due to destruction of the bacteria and enzyme. From the information above, bacteria are now assumed to play a vital role in gum formation.

Gums are found in plant organs such as the epidermis of linseed, Psyllium and Ispagbula, and gummosis is known to occur in the trunk of such trees (Denston, 1951).

iii) Uses of Gum in Pharmaceutical and Health Care Products

In pharmacy, gums are used as binders and drug release retardant in oral solid dosage form such as tablets. They are used as emulsifying agent in lotions and protective creams in cosmetics. They are also used in colloidal suspension of salts of heavy metals such as calamine and magnesia suspensions. They are used as demulcent agent in diabetic and non-sugar flavoured syrups.

Gums are used as foam stabilizer in liquid soap (Williams and Phillips, 2000).

Gums from acacia have been widely used in confectionary and cosmetics. It is used as dispersing agent for insecticides. The gum is used to adjust viscosity of milk to prevent separation of the components (Dalziel, 1971).It is also employed in processed foods such as jam, soft drinks, cake mixes, sauces, salad dressing, ice creams, yoghurts and processed meals.

The Bark of acacia catechu is used in the treatment of cancerous tooth, toothache, rhinitis and diarrhoea. *Acacia polyacantha* is used in the treatment

of gonorrhoea. *Acacia sieberiana* bark is used for eliminating tapeworms (Dalziel, 1971). Different parts of the plant may be employed for different purposes. *Acacia tarnesiana* flowers are used as antispasmodic and aphrodisiacs. The fruits are recommended for gynaecological disorders. The decoction of both the root and bark of *Acacia sieberiana* is used in French Guinea as a taenifuge and in urethritis. In Tanzania, decoction of the bark is used in the treatment of gonorrhoea. In Congo, the exudates, bark and leaves are used together as an emollient and astringent for diarrhoea, haemorrhage, cold and ophthalmia (Dalziel, 1971).

1.1.2 Acacia

Synonyms: Acacia gum, gum Arabic, *Acacia gummi*.

These refer to the dried gummy exudates from the stem and branches of various species of Acacia tree, family Leguminosae.

1.1.3 Acacia Plant

The plants are thorny with average height of 6 meters. In the past, the chief native countries were Sudan and Senegal, but today some species such as *Acacia sieberiana*, *Acacia nilotica*, *Acacia senegal*, *Acacia seyal* are found in Nigeria, mostly around Sokoto, Jigawa, Bornu and Yobe States (Ghani.,1988).

The tree has a grayish-white bark and a bushy growth bearing grayish-white long thorns. The trees are grown from seeds and the highest yield of biopolymer is obtained from trees growing in strictly poor dry soil with traces of soluble salts (Denston, 1951).

The difference in length, colour and number of thorns found at the base of the leaf stalk formed the basis for identification of the various species of the Acacia trees (Denston, 1951).

1.1.4 History

Acacia was derived from the Greek Word “Akakia” referring to the pointed and thorny nature of the plant. In the past, the Gum from Kordofan (Sudan) was recorded as the best but recently, some species from Senegal and Nigeria are found to produce gums of good quality (Trease and Evan 1983). Acacia gum was obtained from Egypt and Turkey during the middle ages. The Portugese imported the West African gum during the 5th Century (Trease and Evans, 1983).

1.1.5 Collection and Preparation of Acacia Gum

The method of collection of gum from the plant is called tapping and is best done after rainy season. A transverse incision is made with a small axe in the bark of the tree; caution must be observed not to damage the cambium and xylem. This process involves the removal of a strip of 5 cm wide and 60 cm long. The exudation of gum is almost immediately after incision in hot and dried weather, while in cold weather exudation is slow. The activity of microorganisms was believed to reduce at lower temperature (Denston, 1951). The exuded gum solidified on coming in contact with the atmospheric air due

to the presence of an oxidizing enzyme believed to be as a result of minor proteins present in the gum (Williams and Phillips, 2000).

The gum, which has been transformed to a solid mass are then collected in 3 to 4 weeks or 7 to 8 weeks in cold weather after incision (Denston, 1951). It takes the Acacia trees 6 to 7 years to mature for tapping. The gum collected is translucent, friable and cracky.

1.1.6 Description of Acacia Gum

The acacia gum from Kardofan (Sudan) has been established as the best variety for decades (Denston, 1951). It appears in ovoid or rounded tears with a yellowish opaque tinge. The gum is brittle in nature and easy to break into smaller pieces, which are transparent angular fragments with glittering surface. The gum has bland mucilaginous taste and odourless. The white species or those with a yellowish tinge constitute the best quality while those that are yellowish, reddish or reddish-brown contain tannins and are of lower quality.

1.1.7 Constituents of Acacia Gum

The acacia gum, also known as hydrocolloid, usually comprises mixtures of long chains of sugar molecules, together with minor amount of protein (arabinogalaetan protein). The complex mixture contains calcium, magnesium and potassium salts of di-arabinan-tetragalactan arabic acid known as arabin (Williams and Phillips, 2000). The arabic acid is a branch polysaccharide, which yields *L*-arabinoside, *D*-galactose, *D*-glucuronic acid and *L*-rhamnose on hydrolysis. The main chain of the molecule contains 1, 3-linked *D*-

galactopyranose units as its backbone, while the terminal residues of the 1, 6-linked side chains are primarily uronic acids.

The composition of acacia gum includes: protein 2-3 %, ash 3-8 % (consisting of calcium, potassium and magnesium carbonates), soluble dietary fiber 85 %, others 9.3 % (Williams and Phillips, 2000).

The plant gum contains several enzymes (oxidases, peroxidases and pectinases) that could make formulations unstable. These enzymes are denatured at high temperature of up to 100° C. The gums from Acacia have a very broad molecular weight, confirmed by three molecular weight fractions obtained from the whole gum by sodium sulphate precipitation. The mean molecular weight was found to be “580,000 “(Anderson and Dea., 1967).

Gums from some species of acacia are not completely soluble in water e.g *Acacia depariobotium* (Anderson and Dea., 1967).

1.2 MECHANISM OF DRUG RELEASE FROM POLYMER DEVICES

The concept of controlled drug release involves the release of an active agent from a material in a precise and engineered manner. Essentially, the main goal of drug delivery is to achieve effective therapies while eliminating the potential for both over and under dosing. Other advantages with controlled drug delivery are: maintenance of drug levels within a desired range, fewer administrations, and optimal use of the drug itself (Lee., 1980).

Polymers are suited as materials of construction for drug delivery systems because their permeability can be modified and controlled. Active ingredients and property modifiers can be incorporated easily, and most plant polymers are non toxic. The biodegradable polymers act as matrix in which the active ingredient is dispersed or dissolved (Lee, 1980).

For a biodegradable polymer, diffusion plays an important role in the discharging of drugs. Diffusion occurs through bulk erosion of the material or through surface erosion of the polymer (Lee., 1980). In bulk erosion, the rate of water penetration into the solid device exceeds the rate at which the polymer transforms into water-soluble materials. As the water enters the polymer, erosion transpires throughout the whole volume. Cracks and crevices form in the polymer, and it rapidly disintegrates. Meanwhile, the drug diffuses out of the polymer as more and more cracks are formed in the material.

On the other hand, surface erosion presents a different outlook. The rate at which water enters the polymer device is less than the rate of polymer transformation to water-soluble materials. The surface area of the polymer matrix limits the process. In time, the device becomes thinner while maintaining its structural integrity. To achieve this condition, the polymer needs to have a certain degree of hydrophobicity (Lee., 1980)

The release mechanism is directly related to the nature and level of the polymer. Polymers which are hydrophilic essentially erode by bulk erosion.

Polyanhydrides and polyorthoesters are hydrophobic and degrade by surface erosion.

For bulk erosion, there are two stages in the release mechanism. The first stage is dictated by the hydration of the device or how much water diffuses into the polymeric device. The second stage involves the diffusion of the drug through the polymeric matrix. For surface erosion, the device erodes like a bar of soap. The release rate is influenced by the degradation of the polymeric material and is therefore proportional to the surface area of the system.

The diffusion profile of polymeric matrix is better determined by Fick's law and the Higuchi model. Fick's law describes the diffusion behaviour of particles. The Higuchi model is used to describe a process involving both diffusion and drug dissolution. For the bulk erosion, diffusion is dependent on the concentration of the drug and the molecular weight of the drug itself. For the surface erosion, the diffusion depends upon the surface area of the device.

1.3 PHARMACEUTICAL TABLETS

The tablet is today the dominating pharmaceutical dosage form, available in various forms and mostly administered orally. The advantages of this dosage form are manifold: tablets are cost effective to manufacture, convenient to dispense and store, and easy for the patient to administer, and they provide a versatile means of delivering the drug. Altering the design and content of the formulation to meet biopharmaceutical and pharmacological requirements can

control release of drug from the tablet. Since this is a dry dosage form, tablets provide a supportive environment for drug stability and generally have a relatively long shelf life when compared to other dosage forms.

The production of tablets involves different processing steps including operations where particles are engineered with the intention of optimizing functional properties such as technical performance during tableting and drug release properties. The manufacture of tablets requires certain qualities of the powder, such as, low segregation tendency, good flowability and compatibility being examples. It is also important that the materials constituting a tablet, that is, drug and excipients are chemically and physically stable during processing and storage.

The concept of engineering materials to improve their functionality is applied within many disciplines and knowledge of relationships between structure and functional properties clearly leads to a more rational approach to material science. The term structure, used here, covers a wide range of features from those on a macroscale, visible to the eye, down to those on a nanoscale, corresponding to interatomic distance.

Tablets are manufactured by applying pressure to a powder bed, which compresses the powder into a coherent compact. The powder may consist of either primary particle (as in direct compression) or aggregated primary

particles (as in granules). When these are compressed, bonds are established between the particles or granules, thus conferring a certain mechanical strength to the compact.

The properties of the tablet (for example, mechanical strength, disintegration time and drug release characteristics) are affected by both the properties of the constituent materials and the manufacturing process. Excipients such as diluents, binders and lubricants are generally needed in a formulation in order to facilitate the manufacturing process, and also to ensure that the resulting tablets have the desired properties. For instance, tablets should be sufficiently strong to withstand handling during manufacturing, transportation and usage, but should also disintegrate and release the drug in a predictable and reproducible manner. It is thus important to choose the appropriate excipient and manufacturing process when developing a new tablet formulation.

In the production of pharmaceutical tablets, it is common to prepare particles with the aid of a liquid that is subsequently removed by drying. In this context, the most common particle preparation method is wet granulation, in which fine particles (often drug and excipient) are aggregated under convective mixing and by addition of an agglomeration liquid. Liquid bridges are created to hold the fine particles together and when the liquid is removed by drying, cohered aggregated particles remain (Fuhrer, 1977; Sebhatu et al, 1997).

Another frequently used particle preparation technique is preparation from a liquid ; for example, crystallization and spray drying, where the material is dissolved or suspended in a liquid, which then is removed by drying (Sebhatu et al, 1997).

Preparation of pharmaceutical particles, using procedures of the kind described above subjects the materials to different processing stresses such as exposure to liquids, mechanical stress and heat. These stresses may significantly affect and change particle structural properties (physical and solid-state properties), with consequences on properties like tableting behaviour, drug release and stability. Stresses occurring during the removal of a liquid by drying may, for instance, produce amorphous materials and influence on the porosity of granules, with subsequent effects on the dosage form. Thus, obtaining mechanistic knowledge regarding relationships between processing stresses, structural and functional properties of particles is of obvious interest in order to be able to predict and optimize functionality of solid dosage forms. In this context, there is a need for increased understanding of relationships between stresses during the removal of a liquid by drying and structural properties of particles critical for functional behaviour, and an awareness of how these stresses can be used to engineer particles with desired pharmaceutical properties (Fuhrer, 1977; Sebhatu et al, 1997).

Tablets are usually prepared by uniaxial compression using eccentric presses or rotary tableting machine. The compaction of a pharmaceutical powder results in an anisotropic and heterogeneous tablet with variations in such properties as density, porosity and mechanical strength throughout the tablet (Train, 1956; Kandeil *et al.*, 1977; Nystrom *et al.*, 1993). When a particle bed in a die is subjected to an external load, its volume is reduced and the interparticulate porosity is decreased. The tablet porosity of most materials is about 5 to 30 %. This means that even at relatively high compaction pressures, tablets will rarely be non-porous.

1.3.1 Compressibility of Pharmaceutical Powders

The term compressibility is often used to describe the volume reduction ability of a material, whilst the compactibility is the ability of a material to form a tablet of a specified mechanical strength (Leuenberger, 1982).

1.3.2 Compaction of Pharmaceutical Powders

When pressure is applied to a powder bed, the bulk volume of the powder is reduced and the amount of air is decreased. During this process, energy is consumed. As the particles are moved into closer proximity to each other during the volume reduction process, bonds may be established between the particles. The formation of bonds is associated with a reduction in the energy of the system as energy is released (Coffin-Beach and Hollenbeck, 1983; Rowlings *et al.*, 1995). In the literature, the term compression is often used to

describe the process of volume reduction and the term compaction is used to describe the whole process, including the subsequent establishment of bonds. The strength of a tablet composed of a certain material can be used as a measure of the compactibility of that material. Volume reduction takes place by various mechanisms and different types of bonds may be established between the particles depending on the pressure applied and the properties of the powder.

1.3.3 Volume Reduction Mechanisms

The first thing that happens when a powder is compressed is that the particles are rearranged under low compaction pressures to form a closer packing structure. Particles with a regular shape appear to undergo rearrangement more easily than those of irregular shape (York, 1978). As the pressure increases, further rearrangement is prevented and subsequent volume reduction is accomplished by plastic and elastic deformation and /or fragmentation of the tablet particles (Train, 1956; Duberg and Nystrom, 1986). Brittle particles are likely to undergo fragmentation, that is,. breakage of the original particles into smaller units. Plastic deformation is an irreversible process resulting in a permanent change of the particulate shape, whereas after elastic deformation the particles resume their original shape. This is a reversible process. The degree of volume reduction that a pharmaceutical powder bed undergoes depends on the mechanical properties of the powder and the type of volume reduction mechanism involved. Particle size and speed of compression in turn

influences the mechanical properties of the material (Roberts and Rowe, 1987a). For example, reduction in particle size has been related to a decreased tendency to fragment (Alderborn and Nystron, 1985). Some materials appear to have a critical particle size at which a transition from brittle to ductile behaviour occurs as the particles become smaller (Robert and Rowe, 1987b, Roberts *et al.*, 1989).

Brittle materials which undergo extensive fragmentation generally result in tablets of relatively high porosity because of the large number of bonding points that are created which prevent further volume reduction. A ductile material, on the other hand, will often result in tablets of low porosity because the high degree of plastic deformation enables the particles to move very close to each other. The deformation of surface asperities will play a special role in this context.

1.3.4 Methods for Characterization of Volume Reduction Mechanisms

Both deformation and fragmentation can occur in different stages of the volume reduction process (Duberg and Nystrom, 1986). One mechanism often predominates however, and various techniques are available for characterization of the dominating volume reduction mechanism. As mentioned above, the mechanical properties of a material have some influence on its volume reduction behaviour. These properties can be obtained by measuring the hardness and Young's modulus of a material in order to assess

its plasticity and elasticity (Roberts and Rowe, 1987a). Attempts have also been made to obtain mechanical properties by extrapolating tablet measurements of elasticity and brittleness to corresponding values for a tablet of zero porosity (Mashadi and Newton, 1987). Furthermore, a brittle fracture index has been proposed as a method of assessing the brittleness of a material (Hiestand and Smith, 1984).

Several mathematical equations, based on the measurements of porosity changes as a function of applied pressure (for example, the Heckel, Kawakita and Cooper-Eaton equations) have been developed in an effort to quantitatively describe the volume reduction behaviour of a powder (Heckel, 1961a, b; Paronen and Illka, 1996). The applicability of these equations depends on the pressure or porosity range studied. When measuring the change in porosity during compression and decompression may be obtained by using the reciprocal of the slope of the linear part of the Heckel plot (Heckel, 1961a, b). This value is defined as the yield pressure of the material (Hersey and Rees, 1971). When the measurements are made in-die, that is, during one compression cycle, this yield pressure value is considered to reflect both plastic and elastic deformation (Duberg and Nystrom, 1986; Paronen, 1986). Out-of-die measurements are based on the porosity of the tablet after ejection, thus allowing for elastic expansion to take place. The yield pressure obtained is therefore regarded as a reflection of the extent of plastic deformation (Paronen, 1986). Yield pressure values obtained in-die is generally lower because of the

influence of the elastic component (Fell and Newton, 1971; Paronen and Juslin, 1983). Consequently, a small difference between these yield pressure values indicates a low degree of elastic deformation (Fell and Newton, 1971; Paronen, 1986) The extent of elastic deformation of the powder bed during compression can also be assessed by measuring the relative difference in porosity (Duberg and Nystrom, 1986) or tablet weight (Armstrong and Haines-Nutt, 1972) during and after compression.

It appears that some experimental variables can affect the outcome of Heckel plots, and limitations to their use for prediction of compaction behaviour have been proposed (Rue and Rees, 1978; York, 1979; Sonnergaard, 1999). For example, compression speed and particle size can affect volume reduction behaviour (Rue and Rees, 1978). There also appear to be limitations to the Heckel function at high compaction pressures or low tablet porosity (Paronen and Illka, 1996). Determination of the volume reduction behaviour of a material is generally performed in bulk and does not take changes in surface properties (for example, deformation of asperities) into account. The deformation of asperities can affect the performance of the powder when compressed and the possibility of forming interparticulate bonds (Bowdeen and Tabor, 1950; Train, 1956). Nonetheless, Heckel plots have been found valuable as a means of comparing materials with differing volume reduction behaviours, as long as the experimental conditions are kept constant (York, 1979; Duberg and Nystrom, 1986).

Other methods for characterizing the volume reduction behaviour of a material have been presented in the literature. These include scanning electron microscopy (Hardman and Lilley, 1970; de Boer *et al*, 1978; Krycer *et al.*, 1982), the use of ratios from axial and radial tensile strength measurements (Duberg and Nystrom, 1982), and measurement of surface area changes during compaction using permeametry (Alderborn *et al.*, 1985 a, b), gas adsorption (Hardman and Lilley, 1973; Alderborn *et al.*, 1985a) and mercury porosimetry techniques (Vromans *et al.*, 1985; Vromans *et al.*, 1986).

1.3.5. Bonding Mechanisms

The dominating bonding types adhering particles together in a tablet made of dry powders by direct compression are considered to be distance attraction forces, solid bridges and mechanical interlocking (Fuhrer, 1977).

The term distance attraction forces include Van der Waals forces, hydrogen bonds and electrostatic forces. The common feature is that these bonds act between surfaces that are separated by some distance. Van der Waals forces can occur over distances up to 100 to 1000 Å and the strength of the Van der Waals forces is dependent on the distance between the attracting molecules, ions or particles and the medium surrounding them (Israelachvili, 1992). Hydrogen bonds occur primarily through electrostatic interaction and may occur both intra-molecularly and intermolecularly (Israelachvili, 1992). Microcrystalline cellulose is an example of a material where hydrogen bonds

are considered important for the tablet strength (Reier and Shangraw, 1966) Electrostatic forces may arise from triboelectric charging during mixing and compaction. However, electrostatic forces are neutralized relatively quickly over time and are not considered to be of significance in tablets of pharmaceutical materials (Nystrom *et al.*, 1993).

Solid bridges can be formed where there is particle-particle contact at an atomic level. These bridges can be considered as a continuous phase of powder material between particles. The molecules or ions in the solid bridges are assumed to be arranged and bonded in the same manner as those inside each particle. Certain prerequisites are considered to facilitate the development of solid bridges, for example, a simple chemical structure, a certain degree of plastic deformation and the concentration of high stress levels at interparticulate contact points (Fuhrer, 1977; Addofsson *et al.*, 1997). Solid bridges are regarded as relatively strong bonds because of their structures and materials bonding with such bonds, such as sodium chloride, form relatively strong tablets on compaction. Tablets containing these strong bonds are also associated with an extended disintegration time (Fuhrer, 1977). The ability to bond with solid bridges has been shown to increase with an increase in particle size and compaction pressure (Adolfsson *et al.*, 1997). It has also been proposed that amorphous materials are more likely to bond with solid bridges (Fuhrer, 1977; Sebhatu *et al.*, 1997) and that the presence of moisture in a

tablet increases the likelihood of solid bridges developing (Sebhatu *et al.*, 1997).

Mechanical interlocking describes the hooking and twisting together of particles in a tablet. This is possible because of particle irregularities and roughness on the surface of the particles (Fuhrer, 1977).

1.3.6 Methods for Characterization of Bonding Mechanisms

Several methods for determining the dominating bonding mechanisms in tablets have been proposed. The results generally conclude that the dominating bond type in pharmaceutical tablets is distance attraction forces, and especially Van der Waals forces (Luangtana-Anan and Fell, 1990; Karehill and Nystrom, 1990)

When distance attraction forces in tablets were filtered out using magnesium stearate (Nystrom *et al.*, 1993) or liquid with different dielectric constants (Karehill and Nystrom, 1990; Olsson *et al.*, 1996; Adolfsson *et al.*, 1997), the tablet strength of various compounds decreased. This reduction in tablet strength was comparatively less for tablets made from some materials, such as sodium chloride. The remaining (unfiltered) tablet strength of sodium chloride is attributed to solid bridges, since these are able to develop even though magnesium stearate or liquid surrounded the sodium chloride particles. The proportion of solid bridges in a tablet can thus be calculated.

Another approach to estimating the dominating bonding mechanisms has been to calculate the surface specific tablet strength (Nystrom *et al.*, 1993; Adolfsson *et al.*, 1999). The rationale behind such an approach is the assumed proportionality between tablet surface area and the surface area participating in bonding. The surface specific tablet strength would then give a high value for materials predominantly bonding with distance attraction forces. The results are in agreement with other methods for estimating bond types (Karehill and Nystrom, 1990; Olsson *et al.*, 1996; Adolfsson *et al.*, 1997).

1.3.7. Mechanical Strength of Tablets.

The mechanical strength of pharmaceutical tablets is frequently assessed as an in-process control during manufacturing and as a means to understand the compaction behaviour of a material (Davies and Newton, 1996). The force necessary to break the tablet can characterize the mechanical strength of a tablet. When a tablet is subjected to such a force, the response can be interpreted on the basis of the bond summation or fracture mechanics concept, focus is on the propagation of cracks in the tablet during strength testing. The aim of both concepts is to describe the mechanical strength of a tablet, the discrepancy between the theoretical and the measured mechanical strength may although vary between them. The two concepts are discussed under theoretical models of mechanical strength.

1.3.8 Measurements of Mechanical Strength

There are several methods for measuring the mechanical strength of tablets such as the breaking strength, diametral compression, axial tensile strength and bending tests. However, the results vary according to the method applied. The variations may be attributed to the stress conditions induced by the test and also to the heterogeneity and anisotropic nature of tablets, with variations in, for example, the interparticulate bond and pore distribution (Newton *et al.*, 1992). Furthermore, the mode of failure and the dimensions of the tablet have to be taken into consideration. Consequently, the strength values obtained may be considered to represent specimen properties rather than material properties (Newton *et al.*, 1992; 1993).

The most common strength test in pharmaceutical applications is the diametral compression test, which is used to calculate the radial tensile strength of a tablet (Fell and Newton, 1970a). In order to calculate the radial tensile strength, the force applied should be just enough to cause break in tension (Newton *et al.*, 1992). During radial tensile strength measurements, the fracture occurs through a predetermined diametral cross section of the tablet. The radial tensile strength is likely to reflect the average strength of tablet rather than the strength of the weakest plane in the tablet.

Another method for determining mechanical strength is to measure the axial tensile strength. The force necessary to break the tablet is obtained by pulling the tablet parallel to the applied force during the compaction of the tablet and

this force is then used to calculate the axial tensile strength (Nystrom *et al.*, 1978). During axial tensile strength measurements, the fracture occurs through the weakest plane in the tablet. Consequently, this method allows detection of capping tendencies in a tablet.

1.3.9 Theoretical Models of Mechanical Strength

Different theoretical models for describing the mechanical strength of tablets have been proposed in the pharmaceutical literature, some of which are reviewed below.

1.3.9.1 Bond Summation Concepts

The mechanical strength of a tablet has traditionally in the pharmaceutical literature been regarded to depend on the dominating bonding mechanism between the particles and the surface area over which these bonds act (Nystrom *et al.*, 1993). This so-called bond summation concept is based on the theories proposed by Rumpf (1962), where the agglomerate strength is considered to depend on the interparticulate bond structure. The strength of a given plane within a tablet is described by the sum of all attraction forces between the particles in that plane. It is assumed that all interparticulate bonds in the failure (weakest) plane break more or less simultaneously. Proponents of the fracture mechanics concept, have criticized such a simplification. Several expressions originating from Rumpf (1962) have been proposed in order to describe the mechanical strength of both single component and mixtures in a more

quantitative manner (Leuenberger, 1982; Jetzer, 1986; Eriksson and Alderborn, 1995).

Considering the importance of the bonding surface area for the mechanical strength, it would be desirable to measure the actual surface area participating in bonding. Direct measurements of the bonding surface area are however difficult. Instead more indirect methods have been applied, for example, to measure the surface area of the powder and compare it with the surface area of the tablet (Hardman and Lilley, 1973; Stanley-Wood and Johansson, 1978; Nystrom and Karehill, 1986). The results of studies using these methods suggest that the surface area participating in bonding is very small compared with the total surface area (Nystrom and Karehill, 1986). It has been proposed that the external tablet surface area obtained by permeametry holds the best proportionality to the bonding surface area (Alderborn *et al.*, 1985a). Other techniques, such as gas adsorption (Westermarck *et al.*, 1998) and mercury porosimetry (Westermarck *et al.*, 1998), also take into account the contribution of an eventual intraparticulate surface area, which does not participate in interparticulate bonding.

1.3.9.2 Fracture Mechanics Concepts

The application of fracture mechanics has also been studied in relation to the mechanical strength of pharmaceutical tablets (Mashadi and Newton, 1987; York *et al.*, 1990; Rowe and Roberts, 1994; Al-Nasassrah *et al.*, 1998). The fracture mechanics concept stresses the importance of defects and flaws in the tablets, which can be considered as starting points for the fracture. The propagation of fracture is considered a kinematic process (Muller *et al.*, 1987; Kendall, 1988). A fracture may be regarded as either brittle or ductile. A brittle fracture generally propagates rapidly, whereas a ductile fracture is characterized as being preceded by plastic deformation (Amidon, 1995). The crack in the tablet grows and the fracture develops when the stress in the tablet has been raised to a critical value, referred to as the critical stress intensity factor, which describes the resistance of a material to fracture. The size and shape of the pores in a tablet can be assumed to be of importance for the propagation of the fracture. It may however be difficult to accurately estimate the size of the flaw where fracture is initiated.

1.3.9.3 Percolation Theory

In the percolation theory, the tablet is seen as consisting of clusters of particles which form a network. This theory has been used to describe the formation of the tablet and the distribution of pores and particles within it (Leuenberger and Leu, 1992; Picker, 1999). A number of tablet properties are directly or

indirectly related to the relative density of a tablet and the percolation theory relates changes in tablet properties such as mechanical strength, to the appearance of percolation thresholds. The percolation theory has been applied to describe the compaction of both single components and binary mixtures (Blattner *et al.*, 1990; Leuenberger and Leu, 1992; Picker, 1999). For example, property changes associated with a change in the composition of a binary mixture were interpreted using this theory (Blattner *et al.*, 1990).

1.3.10 Effect of Particle and Powder Properties on Mechanical Strength

Extensive fragmentation during compaction of a brittle material may result in a large number of interparticulate contact points, which in turn provide a large number of possible bonding zones. Consequently, tablets made of these materials can have a high mechanical strength. Extensive elastic deformation, on the other hand, may cause a pronounced decrease in the mechanical strength of the tablet, due to breakage of interparticulate bonds when the compaction pressure is released. Plastic deformation is considered beneficial to the mechanical strength since it enables the particles to move very close to each other, thereby creating a large surface area over which bonds may be established. As the distance between the particles is decreased during compaction of plastic materials, particle interactions are also favoured. Several studies have investigated the effect of the size of the particles of powdered material on the mechanical strength of the tablet; a reduction in particle size is

generally associated with an increase in mechanical strength (Shotton and Ganderton, 1961; Alderborn and Nystrom, 1982a; McKenna, and McCafferty, 1982; Alderborn *et al.*, 1988) The increase in mechanical strength is attributed to an increase in the surface area available for interparticulate attractions, as the particles become smaller. It has been pointed out that the relationship between surface area and mechanical strength may be affected by particle size (Eriksson and Alderborn, 1995).

Particle shape and surface roughness affect the mechanical strength of a tablet. Milling the powder prior to compaction can induce changes in the shape and roughness. More irregular particles generally contribute to higher mechanical strength of the tablet (Shotton and Obiorah, 1973, Alderborn and Nystrom, 1982b; Alderborn *et al.*, 1988; Wong and Pilpel, 1990). It has been suggested that an increased proportion of irregularly shaped particles increases the number of possible bonding points. (Alderborn *et al.*, 1988). Furthermore, an irregular shape and high surface roughness of the particles would favour plastic deformation, because of a higher degree of surface asperities and crystal defects in such particles (Wong and Pilpel, 1990). The mechanical strength of tablets of materials with a high fragmentation tendency has been shown to be less affected by particle shape and surface texture (Alderborn and Nystrom, 1982b; Wong and Pilpel, 1990).

Milling of the particles prior to compaction may further change the surface characteristics, by rendering the surfaces more disordered or amorphous.

Such changes in the solid state structure may increase the deformability and thus improve the ability of forming interparticulate bonds (Huttenrauch, 1977). Because of the effect of the above mentioned particle and powder properties on mechanical strength it is obvious that a thorough characterization of these properties is essential in studies of the compaction behaviour of a material.

1.3.11 Pore Structure of Tablets

The pore structure of a tablet can be expressed in terms of porosity and pore size distribution and is influenced by the mode of volume reduction during compaction and the compacting pressure applied (de Boer *et al.*, 1986).. Increasing the compaction pressure brings the particles closer to each other resulting in a reduction in tablet porosity. Tablet properties such as mechanical strength and disintegration are in turn affected by the pore structure.

The porosity of tablets made of plastically deforming materials has been shown to increase with increased compression speed (Armstrong and Palfrey, 1989). This is consistent with a decrease in the available room for plastic deformation as the compression speed increases. Also, a decrease in particle size of the powdered material has been shown to increase tablet porosity (Mckenna and McCafferty, 1982; de Boer *et al.*, 1986).

The pore size distribution of a tablet may be assessed by methods such as gas adsorption (Stanley-Wood and Johansson, 1980; Westermarck *et al.*, 1998) or mercury porosimetry (Stanley-Wood and Johansson, 1980; Juppo, 1996;

Westermarck *et al.*, 1998). These techniques are complimentary in that mercury porosimetry can be used to measure large pores while gas adsorption allows measurement of smaller pores.

1.3.12 Disintegration of Tablets

The disintegration time of a tablet can be affected by the pore structure and bonding structure within the tablet. A high porosity and the presence of large pores facilitate rapid water penetration into the tablet with a subsequent rupture of bonds, followed by disintegration of the tablet (Shangraw *et al.*, 1980). The Washburn equation and numerous subsequent expressions have been used to quantify factors, such as viscosity of the penetrating liquid and average pore size, which influence the penetration of water into tablets (Washburn, 1921; Groves and Alkan, 1979). It has also been proposed that the disintegration medium may weaken the intermolecular bonds thus facilitating the disintegration of tablets (Ferrari *et al.*, 1996).

The inherent problem with many conventional tablet formulations is inadequate disintegration properties. Disintegrants, which swell extensively in contact with water, are often added to such tablet formulation in order to facilitate the rupture of bonds during disintegration (Shangraw *et al.*, 1980). The efficacy of disintegrants is said to depend on tablet porosity. A tablet with low porosity was shown to be most effective for the action of a disintegrant since the swelling of the disintegrant particles would then exert more impact on the

surrounding (Khan and Rhodes, 1975; Shangraw *et al.*, 1980; Ferrari *et al.*, 1995). A tablet produced from non-porous granules will exhibit longer or no disintegration and hence delay the release of drug.

1.4 Binders (and Filler-Binders) as Strength-Enhancing Materials in Pharmaceutical Tablets

A binding agent is a material that is included in a formulation to improve the mechanical strength of a tablet. In direct compression, a binder should have a high compactibility to ensure the mechanical strength of the tablet. The binders that are amorphous in nature which undergo pronounced plastic deformation have been suggested to provide an effective means of creating a large surface area available for bonding (Nystrom *et al.*, 1993). The actual mechanisms behind the strength enhancing effect of a binder are yet to be uncovered, but with extensive knowledge of the binder properties it is possible to predict the function of a binder in a formulation. Increasing knowledge of the functionality of binders enables more rational approach to tablet formulation. The use of powder mixtures in tablet formulation give knowledge of how different materials interact with each other.

The introduction of direct compression as an alternative method to wet granulation has stimulated efforts to improve and modify the various binders used in direct compression (they are commonly referred to as filler-binders) (Bolhuis and Chowhan, 1996; Armstrong, 1997). In the past, attempts have

been made to combine two materials in order to obtain a mixture with improved compaction behaviour and functionality as binders (Wells and Langridge, 1981; Larhrib and Wells, 1997).

1.4.1 Effect of Binders on Mechanical Strength of Directly Compressed Tablets

The presence of binders has been found to change the surface properties of coarse compound particles as they are covered by the binder particles. This surface coverage increased the surface area available for interparticulate bonding, thus increasing the number of bonds, hence creating stronger bonds, with the resultant increased mechanical strength (Nystrom *et al.*, 1982; Duberg and Nystrom, 1985; Nystrom and Glazer, 1985). A binder that increases elasticity can decrease the tablet strength due to breakage of bonds as the compaction pressure is released (Nysrom *et al.*, 1982). The presence of a binder in a compound has been discovered to affect and modify the volume reduction behaviour of the compound (Wells and Langridge, 1981; Yu *et al.*, 1989). In another development the volume reduction of the materials constituting a binary mixture occurred independently of each other (Humbert Droz *et al.*, 1983).

If we are working with a binary mixture consisting of components A and B, three types of bonds may occur after compaction. A-A, A-B and B-B (Leuenberger, 1982). A quantitative expression based on compressibility and

compactibility parameters of pure materials has been used to estimate and predict the behaviour of mixtures (Leuenberger, 1982; Jetzer, 1986). The compaction characteristics of mixtures were principally governed by the behaviour of individual's materials and the interactions were most likely to occur with mixtures of components with dissimilar compaction mechanisms (Jetzer, 1986).

The results of some studies have shown that the strength of a tablet formulated from two components can be linearly related to the composition of the materials constituting the mixture (Fell and Newton, 1970b; Sheikh – Salem et al., 1988; Riepma *et al.*, 1990). The strength of tablets made from the mixture can then be predicted from the strengths of tablets of the individual materials. In another development, non-linear relationships observed (Newton *et al.*, 1977; Wells and Langridge, 1981). Hence it is difficult to obtain a general relationship between tablet strength and composition. The type of relationship obtained depends on the materials constituting the mixture.

In many cases, combination of two materials yielded a tablet strength that is higher than the tablet strength of the individual materials (Newton *et al.*, 1977; Cook and Summers, 1985; Vromans and Lerk, 1988;). The explanation was that this high mechanical strength occurred because the bonds between different particles were stronger than those between the same types of particles (Newton *et al.*, 1977). The unexpectedly high tablet strength was caused by increased

densification of the mixture compared with the pure materials (Vromans and Lerk, 1988).

The studies discussed above do not consider binders specifically but rather any possible mixture of excipient that may involve materials with binding properties as a directly compressible excipient. The results imply that if the correct combination of materials is chosen a tablet of a desired mechanical strength can be designed.

1.5 Basic Physico-mechanical Properties and Binding Functionality of Direct Compression Binders / Fillers

A good direct compression binder must have adequate flowability, excellent compressibility and extremely good compact hardness. A good direct compression excipient, will perform as binder because of its plastic deformation under pressure, for example, microcrystalline cellulose. Fragmentation is predominant in the case of excipient such as; lactose.

When formulating direct compression tablets, the choice of direct compression excipient / binder is extremely critical. It must fulfill certain requirements: good binding functionality and powder flowability are essential. A well designed particle size distribution provides favourable mixing conditions. Compatibility with other excipients or drugs is also essential, as is the ability to carry high amounts of active ingredient (Bolhuis *et al*, 1996). Understanding of

the physico-mechemical properties of these direct compression binders are critical for their proper use.

The process of direct compression is a process of applying pressure (via an upper and a lower punch) to materials held in a die cavity. The events that occur in the process of compression are:

1. Transitional repacking
2. Deformation at point of contact
3. Fragmentation and/or deformation
4. Bonding
5. Deformation of the solid body
6. Decomposition and
7. Ejection (Parrott, 1990).

The compressibility under pressure, which is predominantly determined by material properties such as surface energy and deformation, is also very important for direct compression binders. The compressibility of a powder bed could be obtained from the relationship between porosity and applied pressure (Paronen and Illka., 1996).

1.6 Model Drugs

a) Chloroquine Phosphate

It is a 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline diphosphate (B. P. C, 1979).

It is an odourless white powder with a bitter taste. It discolours on exposure to light.

It is soluble at 20 °C in 4 parts of water; very slightly soluble in alcohol, in ether and in chloroform (B. P. C, 1979).

A ten percent weight in volume solution of chloroquine in water has a pH of 3.5 to 4.5.

The moisture content is about 1.5 % when determined by drying at 105 °C.

It absorbs in – significant amounts of moisture at temperature up to 37°C at relative humidities up to about 80 %.

Chloroquine phosphate occurs in two polymorphic forms, one of which melts at about 194 °C and the other at 216 °C (B. P. C, 1979).

In 0.1 N hydrochloric acid, chloroquine phosphate has ultraviolet absorption maxima at 257 nm (E 1 %, 1 cm is equal to 340), 331 nm (E 1 %, 1 cm is equal to 330), and 340 nm (E 1 %, 1 cm, is equal to 360).

Chloroquine is used in the treatment of malaria. It kills malaria schizonts at all stages of development (B. P. C, 1979).

Chloroquine was chosen to represent the highly water soluble drugs due to its high water solubility.

a) Metronidazole

It is a 2 – (2 – methyl - 5 – nitroimidazol - 1 – yl) ethanol(B. P. C, 1979).

It is a white or creamy – white crystalline powder with a slight odour and a bitter and saline taste. It is soluble at 20 °C, in 100 parts of water, in 200 parts of alcohol, and in 250 parts of chloroform; very slightly soluble in ether (B. P. C, 1979).

It melt at temperature of about 160 °C,

In 0.1 N hydrochloric acid, metronidazole has ultraviolet absorption maximum at 277 nm (E 1 %, 1 cm is equal to 380).

It is used in the treatment of trichomoniasis and amoebiasis and in the prophylaxis ad treatment of anaerobic infections (B. P. C, 1979).

Metronidazole was chosen to represent sparingly or poorly water soluble drugs due to its poor water solubility.

1.7 AIM AND OBJECTIVES OF RESEARCH

1.7.1 Aim

The aim of this research is to investigate the tableting properties of local *Acacia sieberiana* gum as a matrix device.

1.7.2 The objectives of this investigation are:

1. To purify the crude gum obtained from *Acacia sieberiana*, using 95 % ethanol
2. To determine the formulation properties

- a) To investigate the compaction properties of *Acacia sieberiana* gum using direct compression method at different compression pressures
 - b) To investigate the effect of particle size of the gum on compactness of the tablets, using direct compression method
 - c) To evaluate the gum for sustained release, using both direct compression and wet granulation methods
- 3 a) To Characterise the physico-chemical properties of the gum such as swelling capacity, effects of pH on viscosity and hydration capacity
- b) To evaluate the effect of the physico-chemical properties of the drug (e.g. solubility) on compactibility and release rate/ availability from the hydrophilic matrix.

1.8 JUSTIFICATION

- 1) Polymers have a place in controlled release solid dosage form technology. If the gum is developed, it will serve as excipient for both local pharmaceutical industries and as an export commodity.
- 2). It will serve as source of foreign exchange for the nation.
- 3) Since direct compression and sustained release dosage forms make easy the formulation and presentation of tablets, the cost and time utilized on conventional drugs with repetitive dosing (or short half-lives) will be reduced.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 *Acacia sieberiana* gum

Acacia sieberiana gum was obtained from Jigawa State Ministry of Agriculture, Dutse. Samples of the leaves, stems and thorns were taken to the Herbarium, Department of Biological Sciences, Ahmadu Bello University, Zaria, Nigeria where the plants was authenticated.

2.1.2 Excipients

Microcrystalline cellulose (Avicel PH 101) and Crystalline α lactose monohydrate.B.P.(Veghel, Netherlands),Corn starch (BDH, England).

2.1.3 Reference materials

Rhamnose, galactose. arabinose, xylose, fructose, glucose and standard acacia (all from Sigma – Germany).

2.1.4 Solvents

Ethanol (95%) (Sigma – Aldrich), Aniline phthalate solution, n- butanol, acetic acid (BDH, England)

2.1.5 Model Drugs

The main drugs used throughout this research were chloroquine phosphate and metronidazole (Liaoyuam Pharm. Chaina). Thus, chloroquine phosphate and metronidazole were both assumed to be suitable models for the study of release rate and compaction of the gum.

2.2 METHODS

2.2.1 Collection of the Plant Gum

The crude gum was collected from Jigawa State Ministry of Agriculture (Forestry Division), Dutse.

2.2.2 Purification of the Crude Gum

The method of purification of gums and mucilage by Karawya *et al.* (1971) was adopted. The dried gums were size reduced using porcelain pestle and mortar. One kilogram of the gum was dispersed in 2 litres of hot distilled water to hasten dissolution. The hydrocolloid was then filtered through 75 μm size linen. The gum was precipitated from the aqueous medium by adding slowly, while stirring, one litre of 95 % ethanol. The precipitate obtained was washed several times with more ethanol (95 %) until the gums crumbled in the ethanol signifying complete precipitation and total separation from water. For the 1 kg

crude gum, 6 litres of 95 % ethanol was expended and the gum was recovered from the medium with the aid of 75 μm size linen.

The gum was dried in a hot air oven (Gallenkamp, England) at 60 $^{\circ}\text{C}$ until a constant weight was obtained. The drying lasted for 48 hours. These procedures were repeated for a 5 kg batch of gum.

2.2.3 Percentage Yield

The gum recovered after drying was weighed. The percentage recovery was calculated from the initial and the final weights recovered.

2.2.4 Evaluation of Gum Powder

2.2.4.1 Particle Size Analysis (Sieve Analysis).

The simple method of particle size reduction was adopted according to U. S. P (2003). The dried gums were grounded in a standard porcelain mortar with a pestle continuously for an average time of 30 min when the entire powder appeared physically uniform.

The U.S.P (2003) standard method of sieve analysis was used. The set of sieves used were: 500 μm , 250 μm , 150 μm , 125 μm , and 90 μm arranged in that order.

The sieves were arranged on an electric shaker, and 100 gm of the powder was placed on the 500 μm sieve size. The sieves were shaken for 15 min, after which the sieves were dismantled, the weight of powder retained by individual

sieve was determined and the percentage calculated. The particle size distribution of the *Acacia sieberiana* gum was then established (Fig 1).

2.2.4.2 Microscopic Analysis of the Purified Gum

Each particle size of the gum was examined under an electric microscope (magnified, X100) by placing a specimen on a slide and covered with film of glycerin and the slide cover (magnified, X100).

2.2.4.3 Determination of Flow Rate and Angle of Repose

A clean glass funnel was placed in a ring on a retort stand, so that the tip of the funnel was exactly 10 cm from a piece of paper (20 cm x 25 cm) placed below the funnel assembly.

A neatly cut cardboard was carefully placed on the lower ring (orifice) of the funnel so that it fits tightly but loosely enough to be removed. Fifty grams (50 g) of the whole powder was transferred into the funnel. The cardboard was removed and the stop clock was started simultaneously. The stop clock was stopped immediately all the powder passed through the funnel. The height of the powder heap was measured with a ruler in millimeter (mm). A circle was drawn round the powder heap (that is, the circular base). The radius of the circle was then recorded.

The angle of repose θ was then determined as the tangent of the height of the cone, 'h' divided by the radius r. This is the modification of the method of Jones and Pilpel (1966).

$$\tan \theta = (h/r). \quad (1)$$

The procedure was repeated and the mean value of angle of repose was determined.

The same procedure was repeated for each particle size of the gum and to determine the angle of repose for the powder mixture containing the gum and the model drug for direct compression. The flow rates were determined with the aid of flowability tester (GDT,Erweka, Germany)

2.2.4.4 Bulk Density and Tapped Density

Bulk and tapped densities were determined by the modification of Kumer and Kothan (1999) method.

Sixty gram (60 g) of the acacia gum powder was weighed and transferred into a 100 ml- measuring cylinder. The volume (V) was recorded as the bulk volume. The total weight of the powder and cylinder was noted. The bottom of the cylinder was raised 10 cm above the slab and made to fall on the platform continuously for 100 taps. The volume (V_t) of the powder was recorded, and this represents the volume of the gum minus the voids and is called the tapped volume.

$$\text{Bulk volume} = V$$

$$\text{Bulk density} = \text{Mass}/V \quad (2)$$

Tapped volume = V_t

$$\text{Tapped density} = \text{Mass}/V_t. \quad (3)$$

2.2.4.5 Swelling Properties

The method of Bowen and Vadino (1984) was adopted. Five gram (5 g) of the gum powder was placed in a 120 ml-measuring cylinder and was tapped 200 times. The volume (V_t) was recorded; this was followed by addition of 85ml of the distilled water. The volume was made up to 100ml, and left to stand for 24 hours, after which the volume (V_v) was recorded.

The swelling capacity Φ is the ratio of the final volume (V_v) to the initial tapped volume (V_t).

$$\Phi = V_v / V_t \quad (4)$$

2.2.4.6 Hydration Capacity

This is also known as water retention capacity. The method of Ring (1985) was employed. One gram (1 g) of *Acacia sieberiana* gum powder was placed in a centrifuge tube and covered with 10 ml of purified water. The tube was shaken manually and intermittently over 2 h period and left to stand for 30 min. This was then centrifuged for 10 min. at 3000 rpm. The supernatant was decanted and the weight of the gum powder after water uptake and centrifugation, was determined as **X**.

$$\text{Hydration capacity} = X/Y$$

(5)

Where X is weight of moist powder after centrifugation and Y is the initial dried powder (1 g). The value of hydration capacity was the mean of two determinations.

2.2.4.7 Determination of the Apparent Viscosity

One hundred millilitre mucilage volume of the gum samples were prepared at different concentrations (10 %, 20 % and 30 %). The apparent viscosity of each concentration was determined using a Brookfield synchro-lectric viscometer (model RUT). The instrument was operated by immersing the spindle in the mucilage. The strain was detected by the string and registered as a deflection on the assignment dial.

2.2.4.8 Effect of Increase in Mucilage Concentration on Viscosity

Acacia sieberiana gum solution of 10 %, 20 %, and 30 % concentrations were prepared and their viscosities determined at shear rates of 10, 20, 50 and 100 rpm.

2.2.4.9 Effect of pH on Viscosity

Using an Ostwald viscometer, the effect of pH on the viscosity of 10 % w/v of the *Acacia sieberiana* gum was determined. The mucilage of the following pH value were prepared; 1, 3, 5, 7, 9, 11 and 13., using 0.1N HCl and 0.1N NaOH. The pH value were determined using a pH meter .

2.2.4.10 Chromatographic Analysis

To one gram (1 gm) of *Acacia sieberiana* gum was added 10 ml of purified water and 10 ml of 7 % sulphuric acid (H_2SO_4) and the mixture was refluxed for 3 h on a water bath. Five millilitres (5 ml) of purified water was added, followed by extraction with ethyl acetate. Barium carbonate powder was then added to the supernatant solution (upper aqueous layer) containing the sulphate ions and then filtered. The filtrate was concentrated on a water bath and the residue collected. The residue was then dried over activated silica gel placed in a desiccator. This was weighed and used for the chromatographic analysis.

2.2.4.11 Descending Paper Chromatographic Method for Sugar Analysis.

Seven percent weight per volume of the hydrolysed samples and the reference samples (7 % w/v rhamnose, xylose, galactose, arabinose, mannose, glucose, ribose and fructose sugars) were applied using a capillary tube on Whatman No. 1 chromatographic paper. The system (chromatogram) was then developed in a chromatographic tank, by the ascending technique. The development of the chromatogram lasted for 30 h. The solvent system used was n-butanol: acetic acid: water in the ratio 4:1:5. After the expiration of the exposure time, the chromatogram was air dried, activated in an oven at a temperature of 40 °C and then sprayed with aniline phthalate solution. The level of separation of each sugar in respect to the references were marked and recorded .

2.2.4.12 Moisture Content

The moisture content (MC) of the purified gum was determined by weighing 100 gm of the powder after which it was heated in an oven at a temperature of 105 °C until a

constant weight was obtained. The moisture content was then calculated with the

$$MC = (1 - \frac{W_t}{W_o}) \times 100 \quad (6)$$

following formula:

$$W_o$$

Where W_t and W_o represent weight of acacia gum after time 't' and the initial weight before heating respectively.

2.2.5 Preparation and Evaluation of Direct Compression Powder Mixture.

The methods of Bamba et al (1979) were employed. The procedures involved preparation of seven batches with each batch consisting of the mixture of the model drug, gum and anhydrous lactose. The percentage of model drug was fixed at 40 % w/w throughout the batches, while that of gum was altered in a decreasing order of 60, 50, 40, 30, 20 and 10 % w/w. For every 10 % w/w deduction in gum content, an equivalent weight (10 % w/w) of anhydrous lactose was added to fill the vacuum (see Table 1)

A batch of 100 tabs was fixed for the batches 1 to 7. Each batch had a total weight of 50 g. For the first batch, 20 g (40 % w/w) of the model drug (chloroquine phosphate or metronidazole) were weighed and 30 g (60 % w/w) of gum, both were mixed in a twin Z-blade mixer (UG. Erweka, Germany) for 5 min. These procedures were repeated for each of the batches.

Table 2.1: Composition of the various batches of the tablets.

	BATCH 1	BATCH 2	BATCH 3	BATCH 4	BATCH 5	BATCH 6	BATCH 7
MODEL DRUG (%)W/W	40	40	40	40	40	40	40
GUM (%)W/W	60	50	40	30	20	10	0
LACTOSE (%)W/W	0	10	20	30	40	50	60

The figures represent the percentage composition of each component in weight by weight. The tablet weight is 500 mg and the model drug content is 200 mg per tablet.

2.2.5.1 Determination of Bulk Density and Tapped Density for Direct Compression Powder Mixtures

The method described earlier for the determination of bulk and tapped density for pure gum was employed for each batch under investigation.

2.2.5.2 Determination of Flow Rate and Angle of Repose

The same procedures used for the evaluation of the flow rate and angle of repose for the pure gum was employed. (See section 2.2.4.3.1)

2.2.6 Wet Granulation by Massing and Sieving Method and Evaluation of Granules

(a) Preparation of Starch Paste (Mucilage)

Five gram (5 g) of maize starch was weighed and 25 ml of distilled water was added in a 250 ml beaker. The mixture was stirred until a uniform suspension was formed. Seventy millilitres (70 ml) water was placed in a separate 250 ml beaker and was heated on a hot plate until it boiled. The starch suspension was then added to the hot water and stirred vigorously with a glass rod until a translucent gel was formed and the weight made up to 100 gm with hot distilled water.

(b) Preparation of the Granules

Table 2.2 illustrates the formula and the percentage composition of the granules. The wet granulation process was carried out for the batches 1 to 7 comprising 60, 50, 40, 30, 20, and 10 % gum respectively.

The model drugs for the two granulations were chloroquine phosphate and metronidazole. For batch 1, 20 g of the chloroquine were weighed and 30 g of fine powder of gum (<90 µm particle size), both were mixed in an Erweke twin Z-blade mixer for 5 min.

The mixture was transferred into a mortar and the starch paste added little at a time while mixing with a pestle until a uniform semi-solid moist mass (matrix) was obtained which easily balled in mind. The total mixing time was 3 min. The above procedure was repeated for batches 2 to 7. The entire procedures were repeated for metronidazole. For each batch of granulation, five millilitre (5 ml) of the starch paste was expended. The amount of maize starch used was calculated (see Table 2.2).

(c) Drying of the granules

The wet semi-solid was spread on sheet of brown cardboard paper in a hot air oven (B.S. Gallenkamp, England). The drying was carried out at 40 °C until a constant weight of dried flake-like solid was obtained. The resultant flake-like solid was forced through a 1.5 mm mesh.

Table 2.2: Formular for 100 Tabs of Gum Matrix Tablets of Chloroquine Phosphate and Metronibazole Compacts

Batch	1	2	3	4	5	6	7
	(gm)						
Drug	20	20	20	20	20	20	20
Gum	30	25	20	15	10	5	-
LACTOSE	-	5	10	15	20	25	30
Starch 5% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	50.5	50.5	50.5	50.5	50.5	50.5	50.5

This formular was employed for the production of granules by wet granulation method. Each tablet weighed 505 mg.

2.2.6.1 Evaluation of Granules of Chloroquine Gum Matrix and Metronidazole Gum Matrix

(a) Size distribution

The following sets of sieves were set vertically in the order of: 500 μm , 250 μm , 150 μm , 125 μm , and 90 μm . The granules were subjected to size analysis as described earlier (section 2.2.4.1). The weight retained was determined and the percentage retained calculated. The size distribution of the gum matrix granules was then established.

(b) Determination of Flow Rate and Angle of Repose

The flow rate and the angle of repose were determined by the methods as described under section 2.2.4.3.

2.2.7 Compaction of Tablets

2.2.7.1 Compaction of Purified Gum Tablets Using Direct Compression Method

Tablets of purified gum were compacted in single punch machine (AR 400.Erweka, Germany) at 500 mg using 12 mm diameter flat faced punch. The tablets were compacted at different compression forces ranging from 20 to 120 N. The compaction procedures were conducted for gums of particle size: 90, 125, 150, 250, and 500 and $>90 - 250\mu\text{m}$. The effect of varying compression pressure on compaction of tablets was studied. The effect of particle size on compactness of tablet was also evaluated. Microcrystalline

cellulose (Avicel PH101) was employed as reference material varying the compression pressure as for the purified gum.

2.2.7.2 Compaction of Mixture of Model Drug and Gum Using Direct Compression Method

The method of Bamba (1979) was employed. The powder mixes prepared under section 2.2.5 were used, using the formula in Table 2.1.

The chloroquine phosphate- gum matrix and metronidazole – gum matrix were compacted in a single punch machine (AR 400 Erweka, Germany) using 12 mm diameter flat faced punch.

The tablets were produced at compression force of 40 N for chloroquine phosphate -gum matrix tablet, and 50 N for metronidazole gum matrix tablet each weighed 500 mg. The effect of particle size and concentration of the gum on compactness of the tablet were the parameters of study.

2.2.7.3. Compaction of Chloroquine Phosphate-Gum Matrix and Metronidazole Gum Matrix Granules

The granules produced were used to formulate chloroquine phosphate and metronidazole gum matrix tablets. The tablets were compacted as described earlier using various concentrations as shown in Table 2. The tablets weighing 505mg were compressed at 40 N compression forces for both drugs.

2.2.8 Evaluation of Tablets

The tablets were evaluated to make sure they met the official quality. The tablets were subjected to the following tests.

2.2.8.1 Weight Variation Limit Test

This test was carried out for all the batches produced. The weights of 10 tablets were determined collectively and individually on a sensitive balance (XP-300, Denver). The mean weight, percentage (%) deviation from the mean and standard deviation were calculated.

2.2.8.2 Thickness of Tablets

The thickness of the tablets was measured with the aid of micrometer screw gauge (Moore and Wright, England). Five tablets were selected randomly and the thickness for each was measured and the mean value determined.

2.2.8.3 Hardness of Tablets

The hardness of all the tablets produced was determined as the crushing strength with the aid of a Monsanto hardness tester (England).

2.2.8.4 Friability

The friability test was performed for the tablets produced by both direct and wet granulation methods in a Friabilator (TA3R. Erweka, Germany). The weight of 10 tablets was determined on a sensitive balance (XP-300, Denver).

The tablets were placed in the friabilator and set to rotate at 25 rpm. for 5 min

(1) Chloroquine Phosphate Tablets

after which the tablets were de-dusted gently and their weight determined. The weight difference was calculated and the percentage (%) loss in weight and hence the value of the friability was calculated.

2.2.8.5 Content Uniformity

The USP (2003) method was adopted. Twenty tablets (505 mg each) were weighed and finely powdered. A portion (2.02 g) of the powder equivalent to 800 mg of the chloroquine phosphate was weighed and transferred into a 200 ml volumetric flask. One hundred milliliter (100 ml) of water were added and shaken for twenty min. More water was added to make up the volume to 200 mls and then filtered. The first 50 ml filtrate were discarded (assumed to contain loose fibres from the filter paper). Fifty milliliters (50 ml) of the clear filtrates were transferred into a 250 ml separator and 5 ml of 6 N Ammonium hydroxide was added, agitated and the chloroquine content was extracted with 25 ml portions of chloroform. The combined extracts were washed with 10 ml of water and extracted with 10ml of chloroform. The combined chloroform extracts were then evaporated on a steam bath to 10 ml and then 50 ml of dilute HCl (1 in 250) was added and heated on a water bath until the odour of chloroform ceased. The solution was then transferred into a 200 ml volumetric flask; the evaporating vessel was rinsed with dilute HCl (1 in 1000) and was added to the solution in the flask. The volume was made up with the dilute HCl to 200 ml. The volume was diluted quantitatively and stepwise with the dilute HCl (1 in 1000) to a concentration of 10 µg per ml.

A reference standard solution of chloroquine phosphate USP was prepared by

(2) Metronidazole Tablet

weighing 200 mg and dissolving in 10 ml dilute HCl (1 in 1000), diluted quantitatively and stepwise to obtain a concentration of 10 µg per ml.

The absorbance of both solutions (Test and RS) was determined in 1-cm cells (polystyrene) at the wavelength of maximum absorbance at 343 nm with a U.V Spectrophotometer (160A, Shimadzu-Japan), using dilute HCl as blank.

The amount of chloroquine phosphate ($C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$) in the portion of tablet taken was then calculated using the formula:

$$\text{Amount of chloroquine in a tablet} = 80 \times C \times (A_u / A_s)$$

Where C is the concentration, in µg per ml, of chloroquine phosphate USP(RS) in the standard solution and, A_u and A_s are the absorbances of the solution from tablets and the standard solution respectively.

The USP (2003) method was adopted. A tablet (505 mg) was placed in a 250 ml volumetric flask and dissolved with 100 ml of dilute HCl (1 in 100). The mixture was shaken for 30 min. The volume was made up to 250 ml with the dil HCl (1 in 100). The solution was filtered, and the first 15 ml of the filtrate was discarded. The filtrate was then diluted quantitatively with dilute HCl (1in 100), to a solution having concentration of 0.2 mg of metronidazole per ml.

Ten millilitre (10ml) of the solution was transferred into a 100 ml volumetric flask and was diluted with the dilute HCl to make up the volume to 100 ml. A similar solution of standard metronidazole USP (RS) was prepared having concentration of 20 µg per ml. The absorbance of both solutions (Test and RS) was determined in 1-cm cells (polystyrene), at wavelength of maximum absorbance at 278 nm, with a U.V. Spectrophotometer (160A -Schimedczu- Japan) using dilute HCl (1 in 100) as the blank.

The quantity in mg, of metronidazole ($C_6H_9N_3O_3$) in the tablet taken was calculated using the formula:

$$\text{Amount of metronidazole in a tablet} = (T \times C / D) \times (A_u / A_s)$$

Where T is the labeled quantity, in mg, of the metronidazole in the tablet, C is the concentration, in µg per ml, of USP, metronidazole RS in the standard solution, D is the concentration, in µg per ml, of metronidazole in the test solution, on the basis of the labeled quantity per tablet and the extent of dilution, and A_u and A_s are the absorbances of the test solution and the standard solution respectively.

2.2.8.6 In-vitro Drug Release Studies

Drug release from the various tablets was determined using the paddle method of the U.S.P. XXIII dissolution apparatus (DT.Erweka, Germany). The tests were conducted in 900 ml 0.1N HCl medium maintained at $37.0 \text{ }^\circ\text{C} \pm 0.5 \text{ }^\circ\text{C}$ at a paddle rotation speed of 100 rpm. Ten ml (10 ml) of the sample were taken at

regular intervals analysed for chloroquine phosphate content in one experiment and metronidazole in another experiment. A 10 ml volume of filtered, fresh dissolution medium was added to make up the volume after each sample withdrawal.

2.2.9 Statistical Analysis

The drug release data of *Acacia sieberiana* gum matrix tablets containing chloroquine in the dissolution medium at the end of the dissolution rate test was compared with that of standard acacia gum matrix tablets containing Chloroquine using USP specification, F2 value, a similarity factor. A value less than 50 was considered significant value indicating dissimilarity in dissolution profiles (Rockville, 1995).

CHAPTER THREE

3 RESULTS

3.1 PURIFIED LOCAL *ACACIA SIEBERIANA* GUM

Light brown to whitish hydrocolloid was precipitated from the solution containing 1 kg of crude gum following addition of 6 liters of ethanol (95 %). The recovered hydrocolloids when dried in a Gallenkemp Oven at 60 °C for 48 h gave light brownish flakes which were easily broken.

3.1.1. Percent Yield of Gum.

The percentage yield of the gum was calculated as follows:

$$\% \text{ yield} = \text{weight of gum recovered} / \text{weight of dried gum} \times 100$$

Eight hundred and thirty grams (830 g) was recovered. Therefore, the percent yield of the crude *Acacia sieberiana* gum was calculated and found to be 83 %.

3.1.2. Particle Size (Sieve) Analysis of the Purified Gum

Fig 3.1 illustrates the particle size distribution of the gum. All passed through sieve size 1000 µm. The particle size fraction >250-500 µm and >150-250 µm constitute 51 % and 20 % respectively while the other particle size fractions (>90-125, >125-250 and >500 µm) made up the remaining percentage. The mean particle size fell within >250-500 µm.

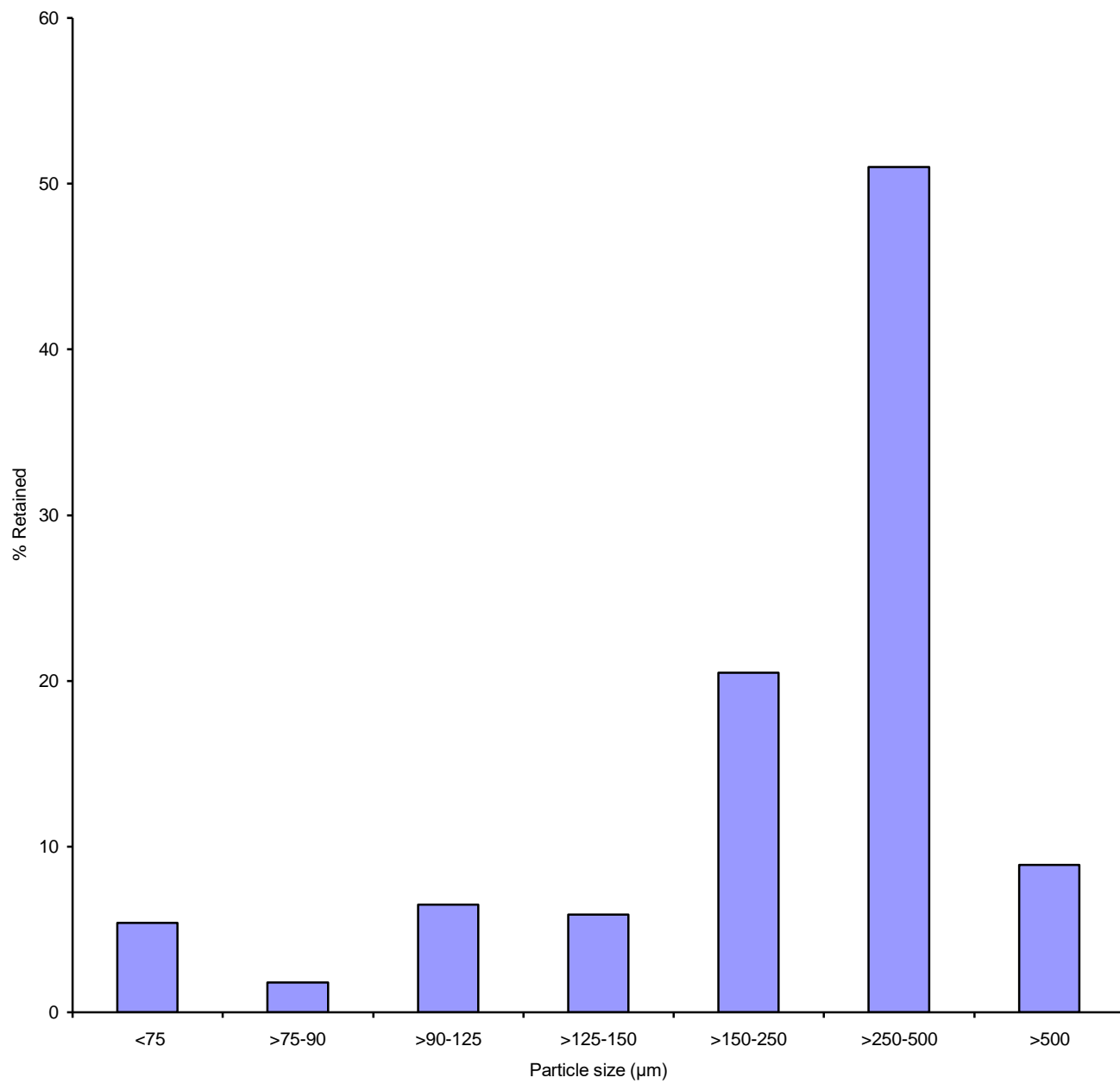


Figure 3.1: Particle size distribution of the purified gum.

3.1.3 Characteristics of the Different Particle Size Fraction of the Gum

The characteristics of the various particle size fractions of the purified *Acacia sieberiana* gum and microcrystalline cellulose (Avicel PH 101) have been determined.

The different particle size fractions of the gum exhibited far greater flow rate than the Avicel PH 101. The angle of repose of Avicel PH 101 was 50.4° while that of the purified gum, except for 90 μm -125 μm particle size fraction were below 30° indicating better flow than the avicel PH 101.

A relationship exists between the particle size and the flow rate (Fig. 3.2). There was an increase in flow rate from >90 -125 to >125 -150 μm particle size fraction, then a decline to >500 μm and a higher rate for the selected size range, (i.e. >90-500 μm powder).

Fig. 3.3 illustrates the relationship between the various particle sizes and the angle of repose. There was a linear decline in angle of repose as the particle size increased from >90-125 to >500 μm followed by elevated value for the >90-500 μm powders. A relationship was established between the particle sizes of the gum and the Carr's index (Fig.3.4). The elevated Carr's index for the >150- 250 μm particle size fraction is an indication of higher frictional force within the powder and irregular particle shape.

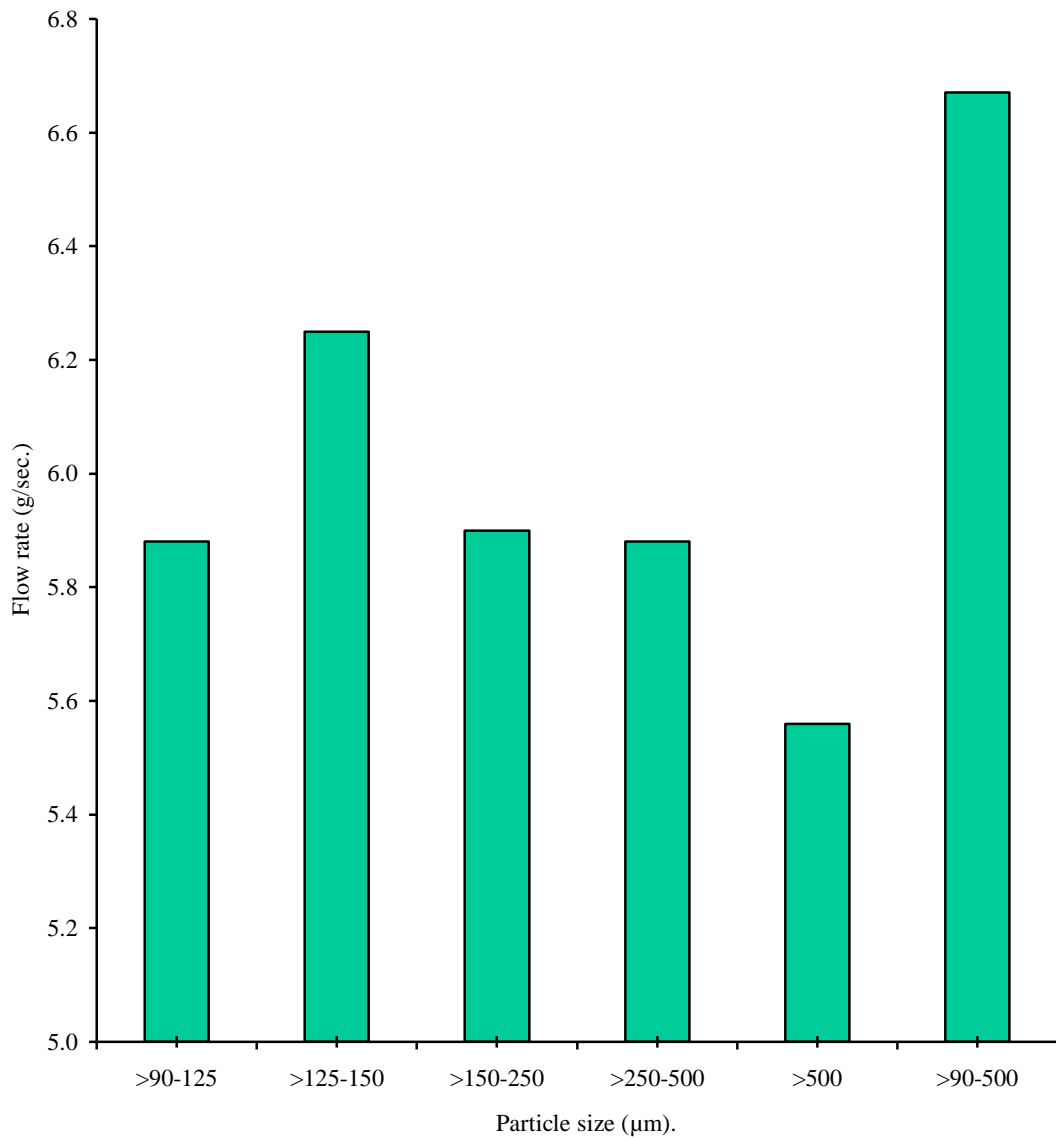


Figure 3.2: Relationship between particle size fraction of the purified gum and flow rate.

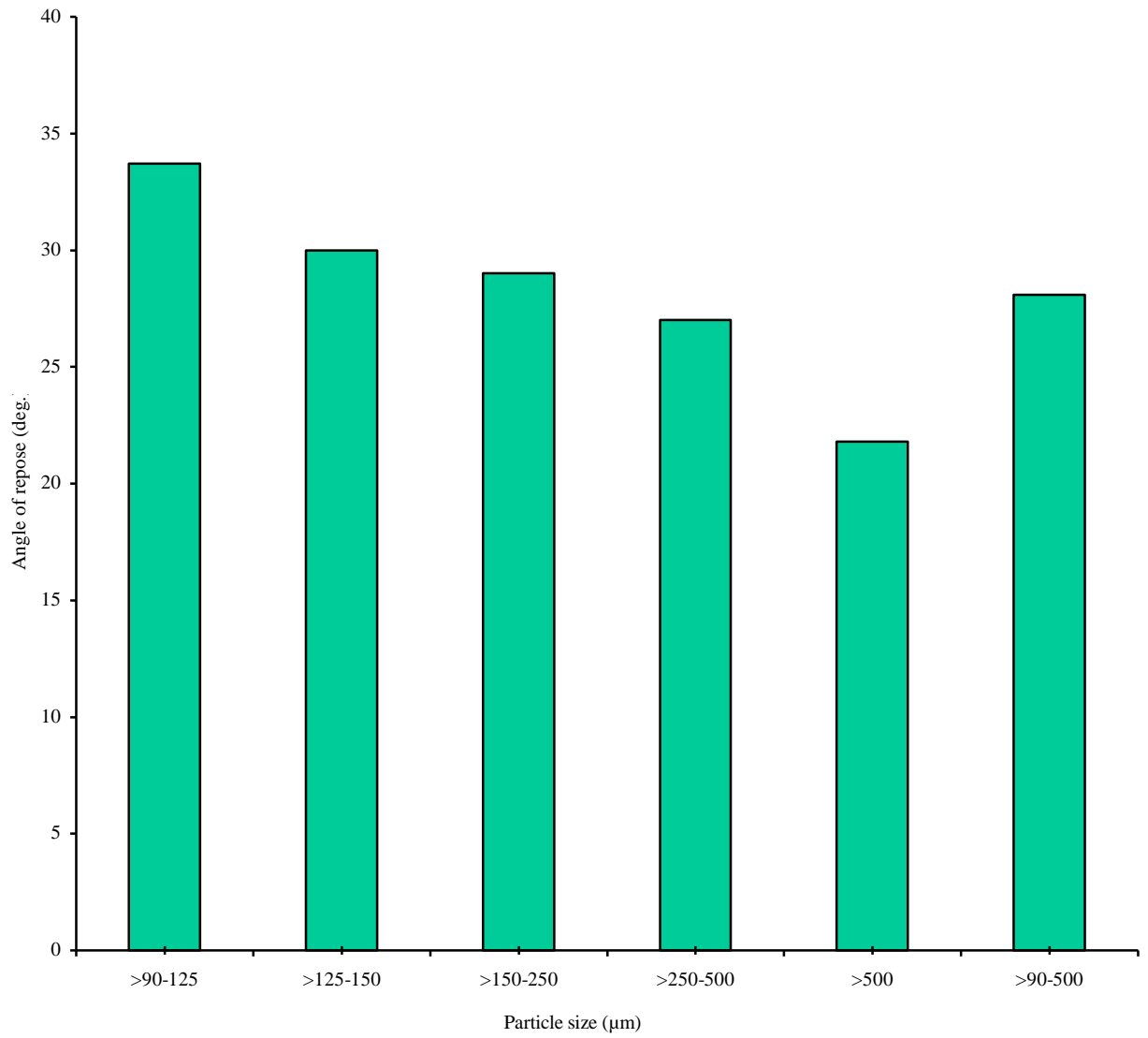


Figure 3.3: Relationship between particle size fraction of the gum and the angle of repose.

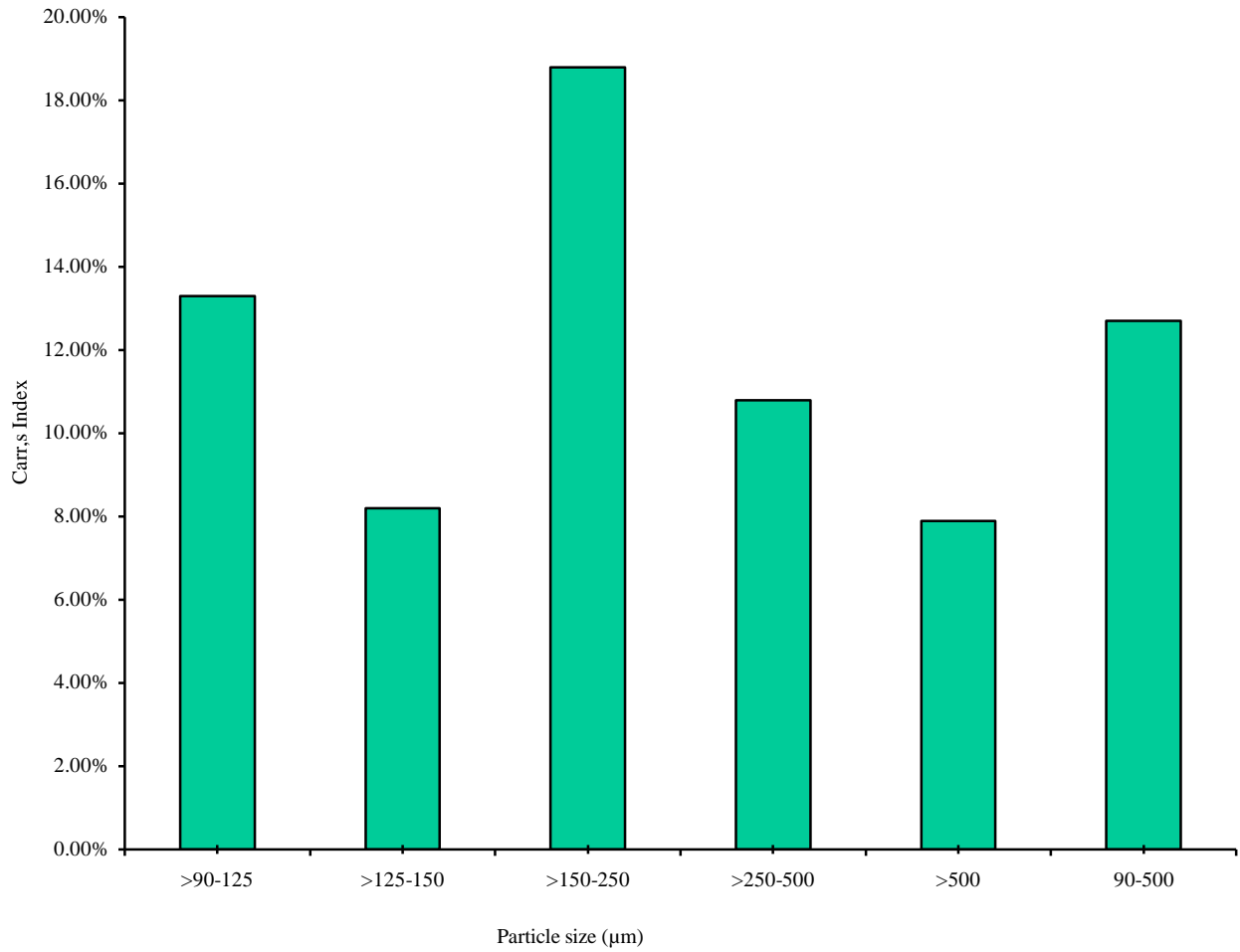


Figure 3.4: Relationship between the particle size fraction of the prified gum and the Carr's index.

3.1.4 Swelling Capacity

The final volume (V_v) was found to be 10 ml after 24 h of standing, while the initial tapped volume (V_t) was found to be 5 ml, giving the swelling capacity of 2. This indicates that the 5 g of the *Acacia sieberiana* gum measuring 5 ml as tapped volume swells over 24 h to double its initial volume. Hence, the swelling capacity of *Acacia sieberiana* gum was established as 2.

3.1.5 Hydration Capacity

The weight of dried gum powder was 1 g, while the weight of the moist powder after centrifugation was 1.66 g. Therefore, hydration capacity of the purified gum is *1.66*

3.1.6. Rheological Properties of *Acacia sieberiana* Gum.

3.1.6.1 Effect of Concentration on Viscosity of the Gum

Acacia sieberiana gum was found to exhibit shear-thinning non-Newtonian flow characteristics. An increase in concentration of the acacia mucilage led to an increase in viscosity of the system.(Table 3.1).

3.1.6.2 Effect of pH on Viscosity of the Gum

Table 3.2, shows that no changes were observed in viscosity of a 10 % solution of *Acacia sieberiana* gum with pH variation. The effect of pH on the Viscosity of acacia mucilage was insignificant.

TABLE 3.1 : Effect of concentration of the gum on viscosity, at different shear rates

Shear rate (r.p.m)	<i>Acacia sieberiana</i> mucilage (%w/v)		
	10	20	30
	Viscosity (Pa.s)		
10	6.3	8.7	9.8
20	5.1	8.1	9.1
50	4.6	7.0	8.2
100	3.8	6.4	7.8

NB:Viscosity values in Pa.s of mucilage of *Acacia sieberiana*.

Table 3.2: Effect of pH on Viscosity of 10 % *Acacia sieberiana* mucilage.

PH	Viscosity of mucilage (Pa.s)
1	5.95
3	5.87
5	5.89
7	5.85
9	5.79
11	5.79
13	5.79

3.1.6.3 Result of the Chromatographic Analysis

Acacia sieberiana gum was found to contain rhamnose, galactose, arabinose, xylose and fructose.

3.1.6.4 Moisture content

The moisture content of the purified *Acacia sieberiana* gum was found to be 6.1% at temperature of 105 °C.

3.2 COMPRESSIBILITY AND COMPACTIBILITY STUDIES

3.2.1 Compressibility

The compression of the purified gum was achieved at far lower pressure than the Avicel ($1.8 \times 10^5 \text{ N/m}^2$ to $3.10 \times 10^5 \text{ N/m}^2$) corresponding to compression force of 20 N to 40 N.

The microcrystalline cellulose (Avicel PH101) was used as standard, and compression was achieved at compression pressure from between $8.90 \times 10^5 \text{ N/m}^2$ to $10.6 \times 10^5 \text{ N/m}^2$ (corresponding to compression force 100 N to 120 N). The compression of the purified gum was achieved at far lower pressure than the Avicel ($1.8 \times 10^5 \text{ N/m}^2$ to $3.10 \times 10^5 \text{ N/m}^2$) corresponding to compression force of 20 N to 40 N.

A relationship between the compression pressure and compact density of the gum tablets of each particle size fraction was established (Fig. 3.5). There was an increase in volume reduction (densification) to certain degree for different particle fraction of the gum. The selected fraction (>90-500 μm) was marked with four segments of consolidation, >90-

125, >150-250, and >500 μm characterized by two segments, while both the >125-150 and >250-500 μm were distinct with one segment indicating slight increase in densification with increase in compression pressure. The compact density become higher as the powder bed increasingly densified. The compressibility decreases with increase in particle size (Fig. 3.5).

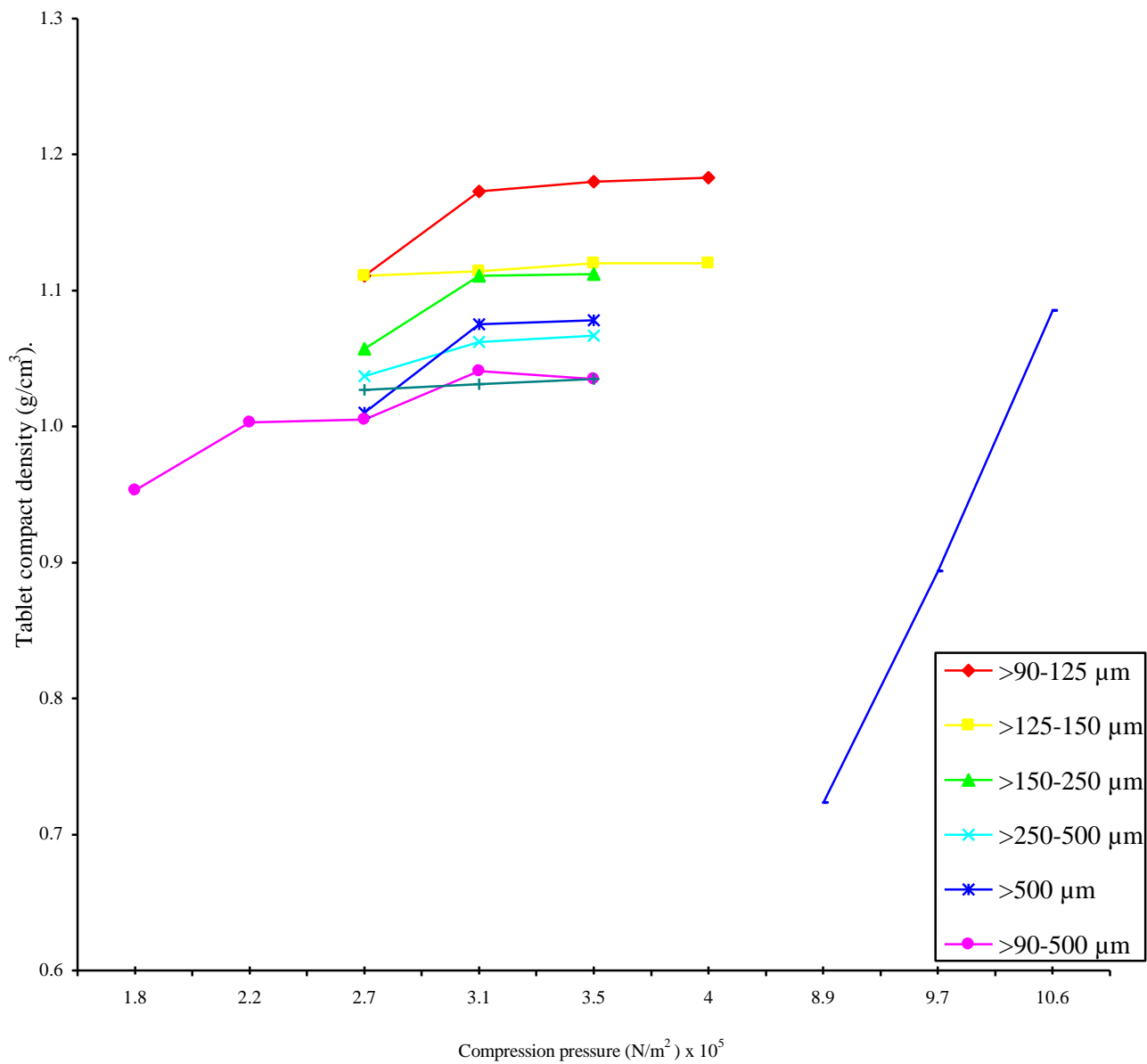


Figure 3.5: Compression characteristic of the gum: compact density versus compression pressure.

3.2.2 Compactibility of *Acacia sieberiana* Gum

The compactibility was measured as the strength of a compact tablet. The crushing strengths were determined and the radial tensile strengths were computed using the formula of Fell and Newton (1968).

The compactibility of purified *Acacia sieberiana* gum was determined from the effect of compression pressure on the tensile strength of the compact tablet (Fig 3.6). Avicel PH101 was used as reference. The tensile strength of compact produced with the particle size fractions > 90-500 μm , >150-250 μm , >125-150 μm have showed increase in tensile strength with increase in compression pressure to certain degree, while powders with particle fractions >250-500 μm and the whole powder (i.e. <90- >500 μm) showed slight increased in tensile strength with increase compression pressure. At compaction force of 35 N (compression pressure $3.1 \times 10^5 \text{ N/m}^2$) only particle size fraction >150-250 μm and >90-500 μm has acceptable tensile strength ($6.7 \times 10^5 \text{ N/m}^2$ and $11.77 \times 10^5 \text{ N/m}^2$ respectively). At compaction force of 40 N (compression pressure $3.5 \times 10^5 \text{ N/m}^2$), the particle size fraction >150-250 μm has tensile strength of $8.1 \times 10^5 \text{ N/m}^2$. These two-particle size fractions exhibited the highest compaction.

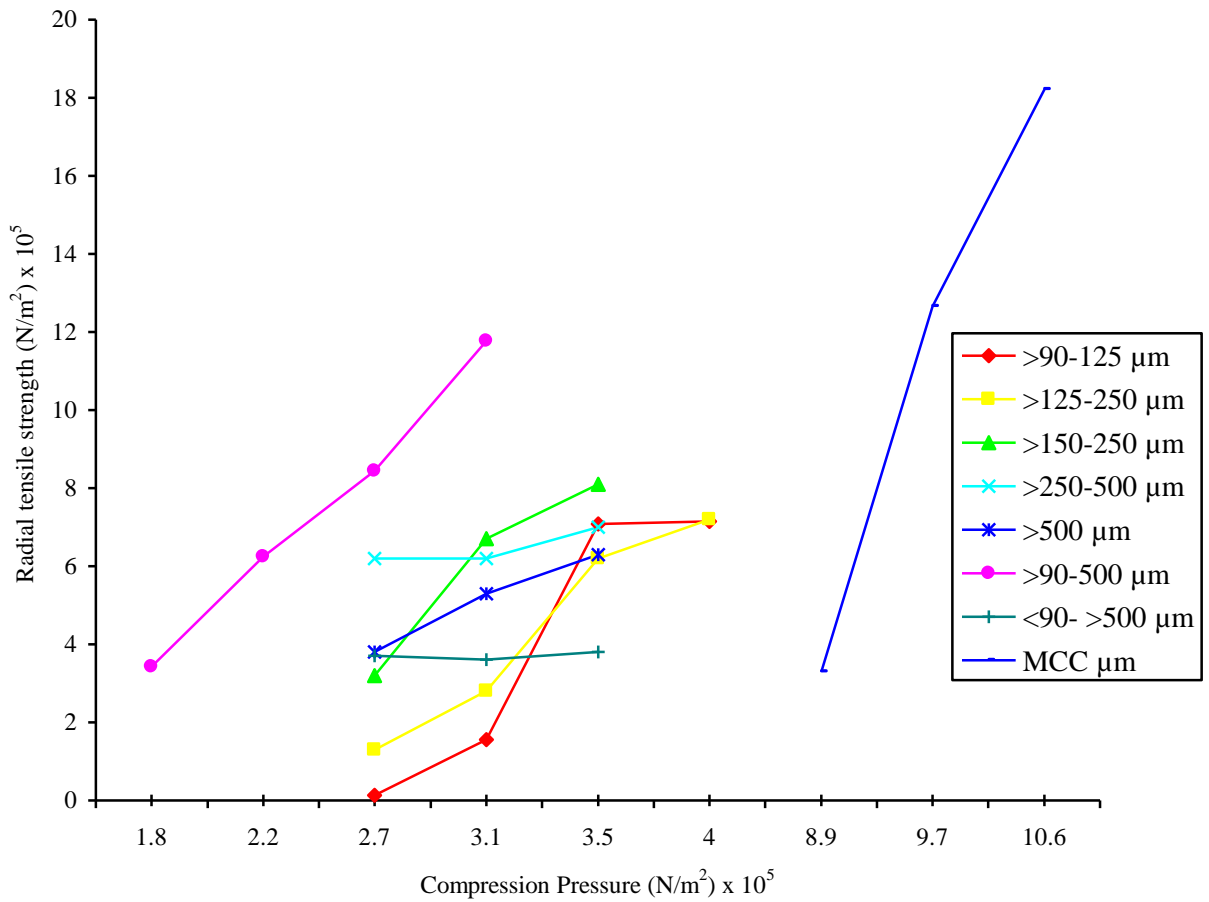


Figure 3.6: The compaction characteristics of the particle size fractions of *Acacia sieberiana* gum compressed at a range of compression pressure of $1.8 \times 10^5 \text{ N/m}^2$ to $10.6 \times 10^5 \text{ N/m}^2$, using microcrystalline cellulose (Avicel PH 101) as reference.

3.3 CHARACTERISTICS OF DIRECT COMPRESSION POWDER MIXTURE

The characteristics of the chloroquine-gum matrix powder and metronidazole - gum powder mixture (Tables 3.3 and 3.4 respectively) showed that the chloroquine phosphate-gum powder mixture exhibited greater flow rate and lower angle of repose than the metronidazole-gum powder mixture. But the densification index (Carr's index) was higher for the latter and than for the former.

TABLE 3.3: Characteristics of the Chloroquine Gum Matrix Powder for Direct Compression

PARTICLE SIZE (μm)	BATCH	FLOW RATE (g/sec)	ANGLE OF REPOSE (deg.)	BULK DENSITY (g/cm^3)	TAPPED DENSITIES (g/cm^3)	CARR'S INDEX (%)
>125-150	1	10	21.8	0.694	0.877	20.9
	2	8.3	26.6	0.667	0.877	24.0
	3	7.1	28.0	0.658	0.863	23.8
>150-250	1	10.3	23.0	0.720	0.900	20.0
	2	10.16	27.8	0.710	0.910	22.0
	3	9.1	28.50	0.670	0.930	28.0
>250-500	1	10.16	28.5	0.790	0.960	17.7
	2	10.12	27.8	0.770	1.000	23.0
	3	6.4	30.6	0.700	1.000	23.0

BATCH 1 contained 60 % gum and 40 % model drug

BATCH 2 contained 50 % gum and 40 % model drug.

BATCH 3 contained 40 % gum and 40 % model drug.

TABLE 3.4: Characteristics of the Metronidazole-Gum Matrix Powder for Direct Compression

PARTICLE SIZE (μm)	BATCH	FLOW RATE (g/sec)	ANGLE OF REPOSE (deg.)	BULK DENSITY (g/cm^3)	TAPPED DENSITIES (g/cm^3)	CAR'S INDEX (%)
>125-150	1	4.55	28.0	0.595	0.758	21.5
	2	3.85	31.2	0.556	0.807	31.1
	3	3.57	32.3	0.544	0.807	32.6
>150-250	1	5.00	26.0	0.641	0.862	25.6
	2	4.17	31.0	0.625	0.893	29.2
	3	3.85	32.3	0.568	0.926	42.6
	4	3.57	46.3	0.556	0.962	42.2
>250 -500	1	6.25	29.3	0.694	0.962	27.9
	2	5.00	31.0	0.641	1.042	38.5
	3	3.5	32.8	0.595	1.087	45.3

BATCH 1 contained 60 % gum and 40 % model drug

BATCH 2 contained 50 % gum and 40 % model drug.

BATCH 3 contained 40 % gum and 4 % model drug.

3.4 GRANULE SIZE ANALYSIS

The chloroquine phosphate matrix granules were characterized by higher percentage of $>500\ \mu\text{m}$ granules, ranging from 57 % to 75 % for the batches 1 to 6; followed by $>250\text{-}500\ \mu\text{m}$ granules, ranging from 10 % to 20 % for the same set of batches (Figs. 3.7 – 3.12). The other granule sizes made up the remaining percentage. Similar results were obtained for the metronidazole matrix granules. The granule size of $>500\ \mu\text{m}$ ranged from between 65 % to 87.9 % for the batches 1 to 6, followed by $>250\text{-}500\ \mu\text{m}$, constituting from between 1.5 % to 12 % for batches 1 to 6 (see Figs. 3.7 - 3.12). The granules of chloroquine for both test and standard showed slight decrease in granule size with decrease in concentration of the gum while granules of metronidazole showed higher decrease in granule size with decrease in concentration of the gum. The granules were irregular in shape and looked non-porous, and the average granule size fell within the granule size fraction $>500\ \mu\text{m}$ for all the batches of both soluble and insoluble drugs.

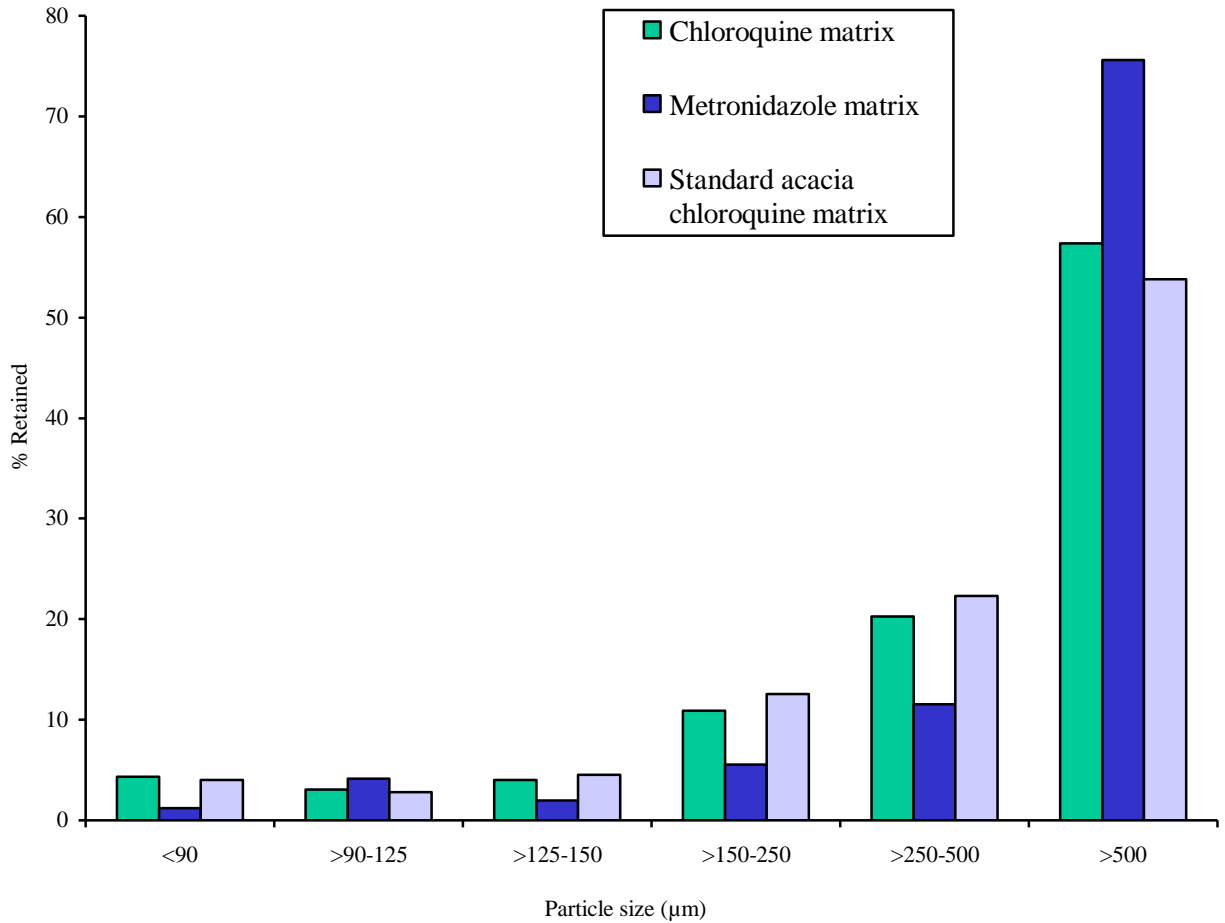


Figure 3.7: Granule size distribution of chloroquine phosphate matrix and metronidazole matrix, batch 1 contains 60 % gum.

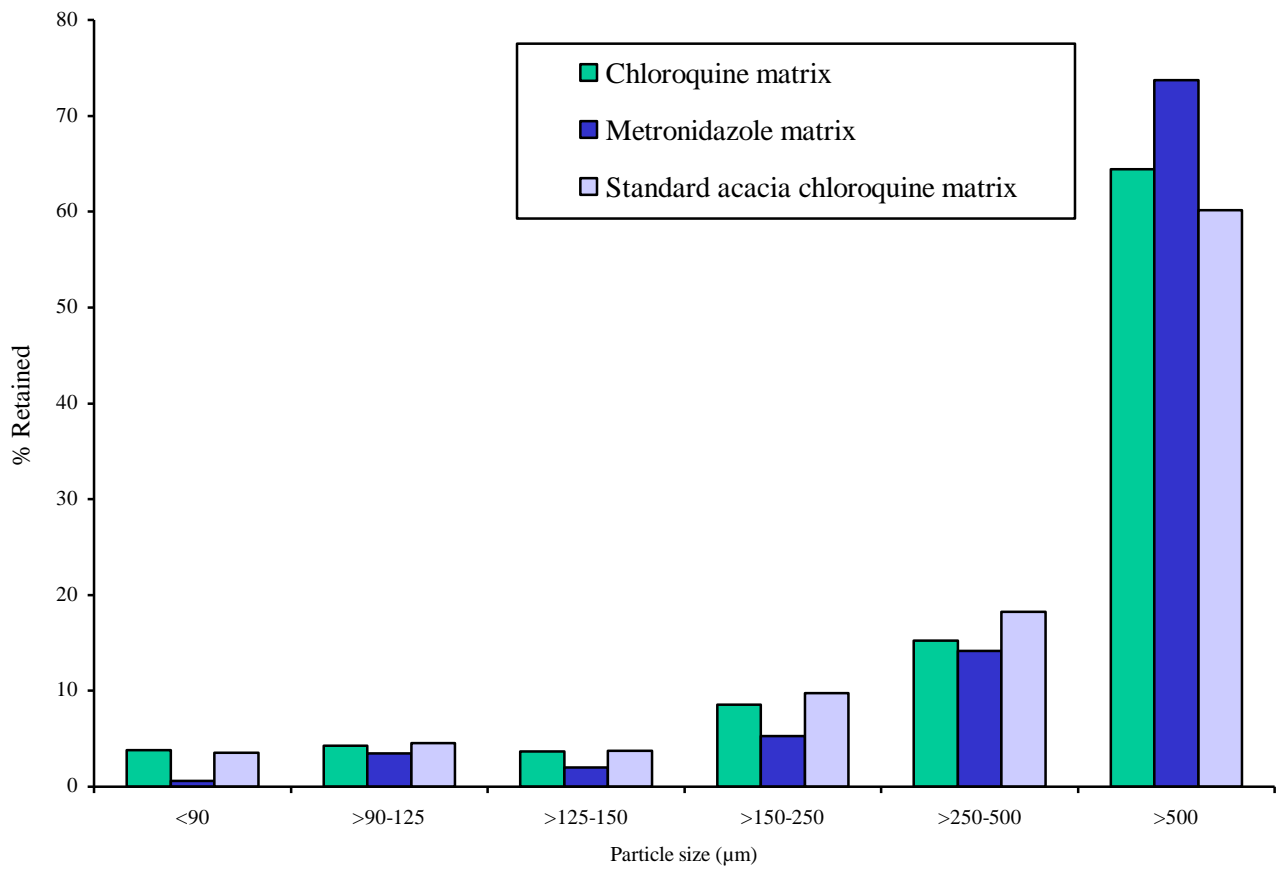


Figure 3.8: Granule size distribution of chloroquine and metronidazole matrices (batch 2) containing 50 % gum.

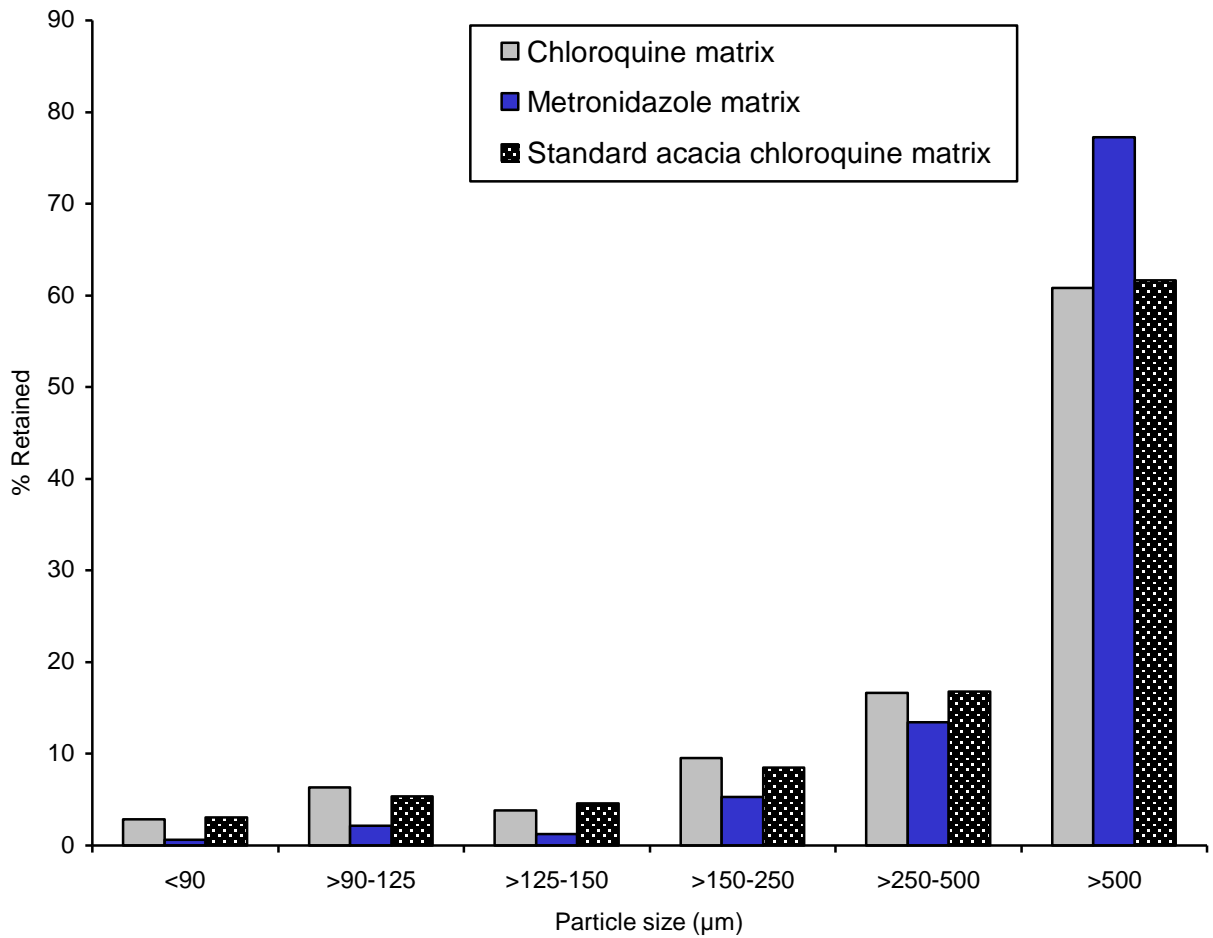


Figure 3.9: Granule size distribution of chloroquine phosphate and metronidazole matrices (batch 3) containing 40 % gum.

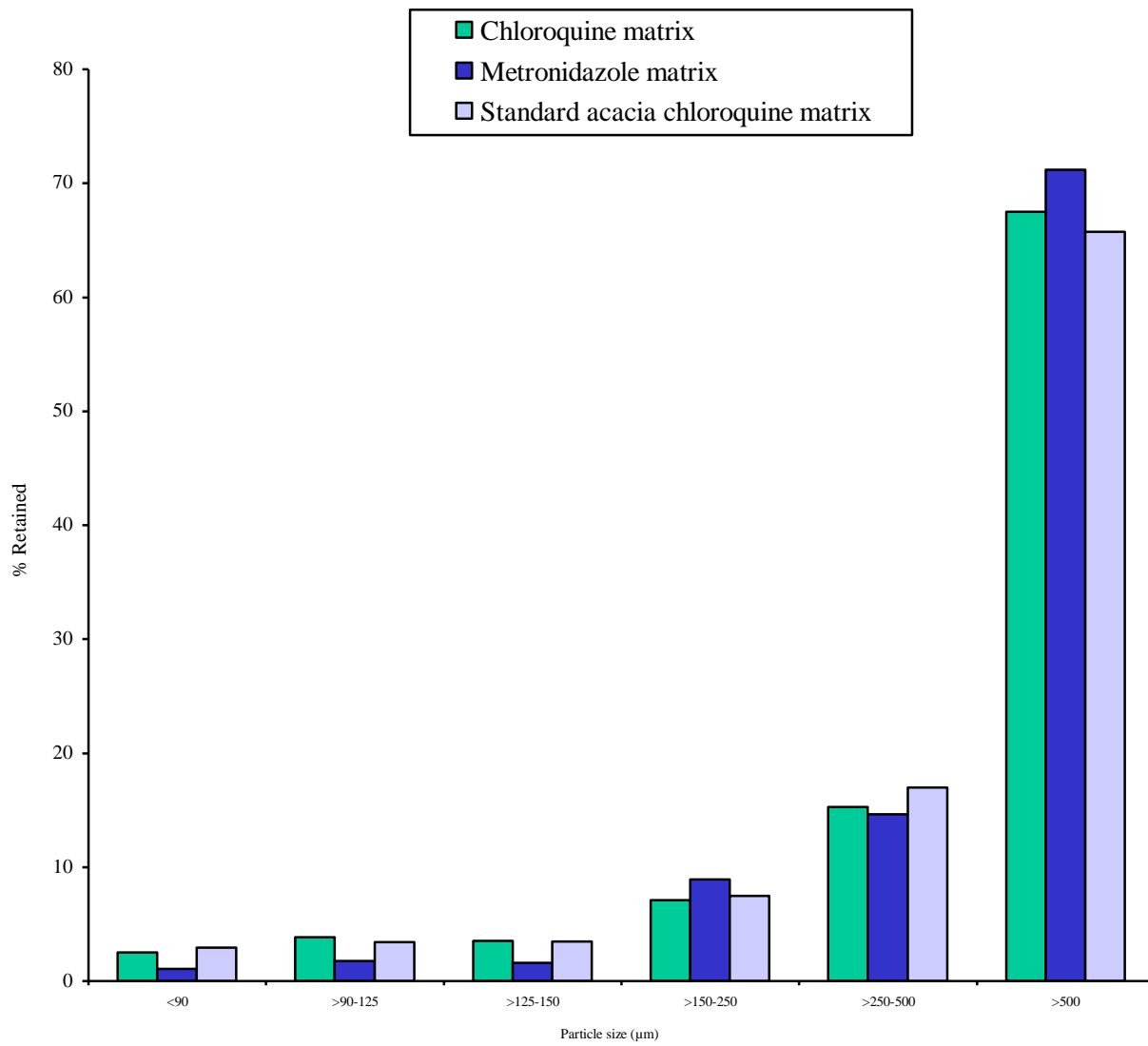


Figure 3.10: Granule size distribution of chloroquine phosphate matrix and metronidazole matrix (batch 4) containing 30 % gum.

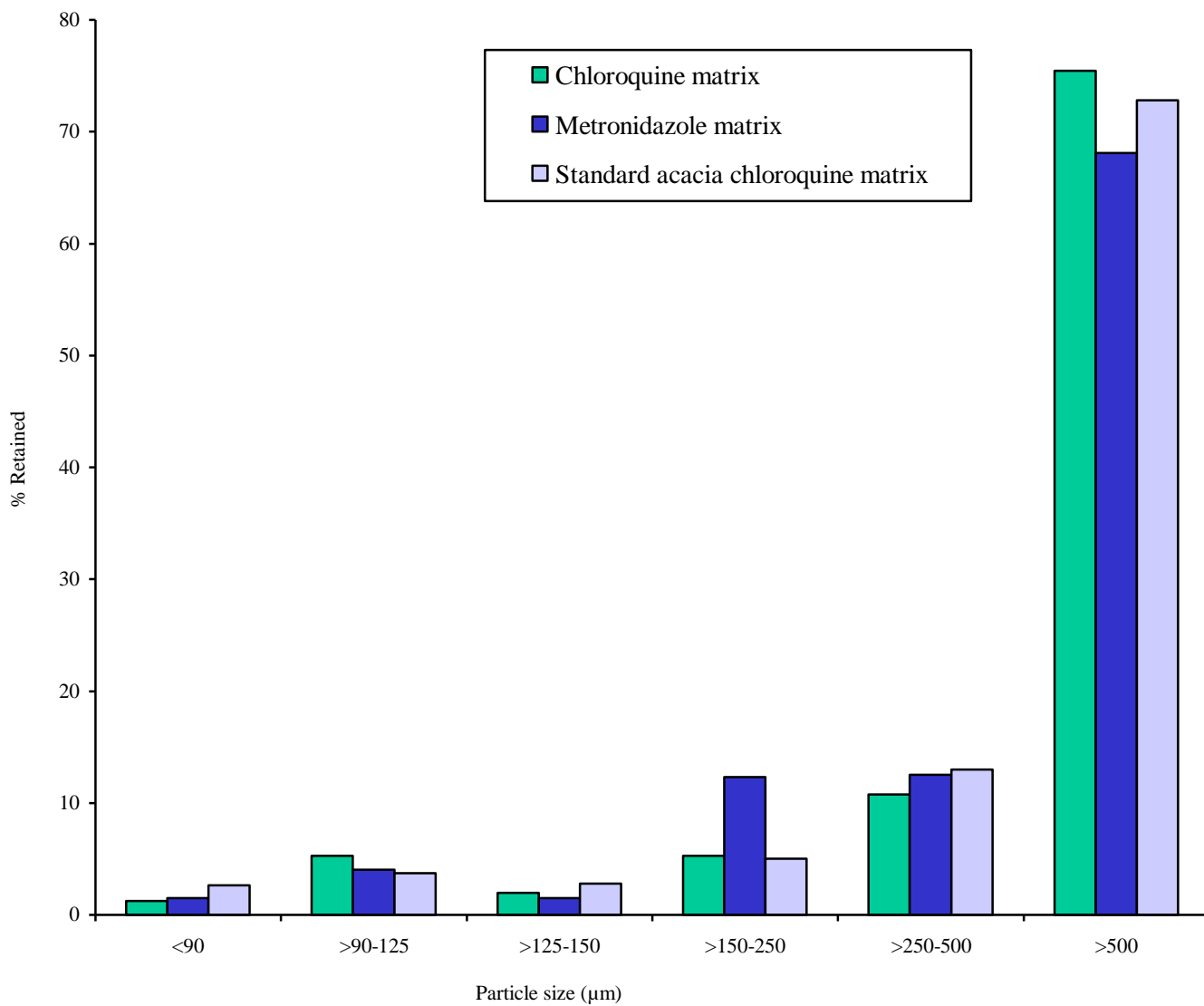


Figure 3.11: Granule size distribution of chloroquine phosphate matrix and metronidazole matrix (batch 5) containing 20 % gum.

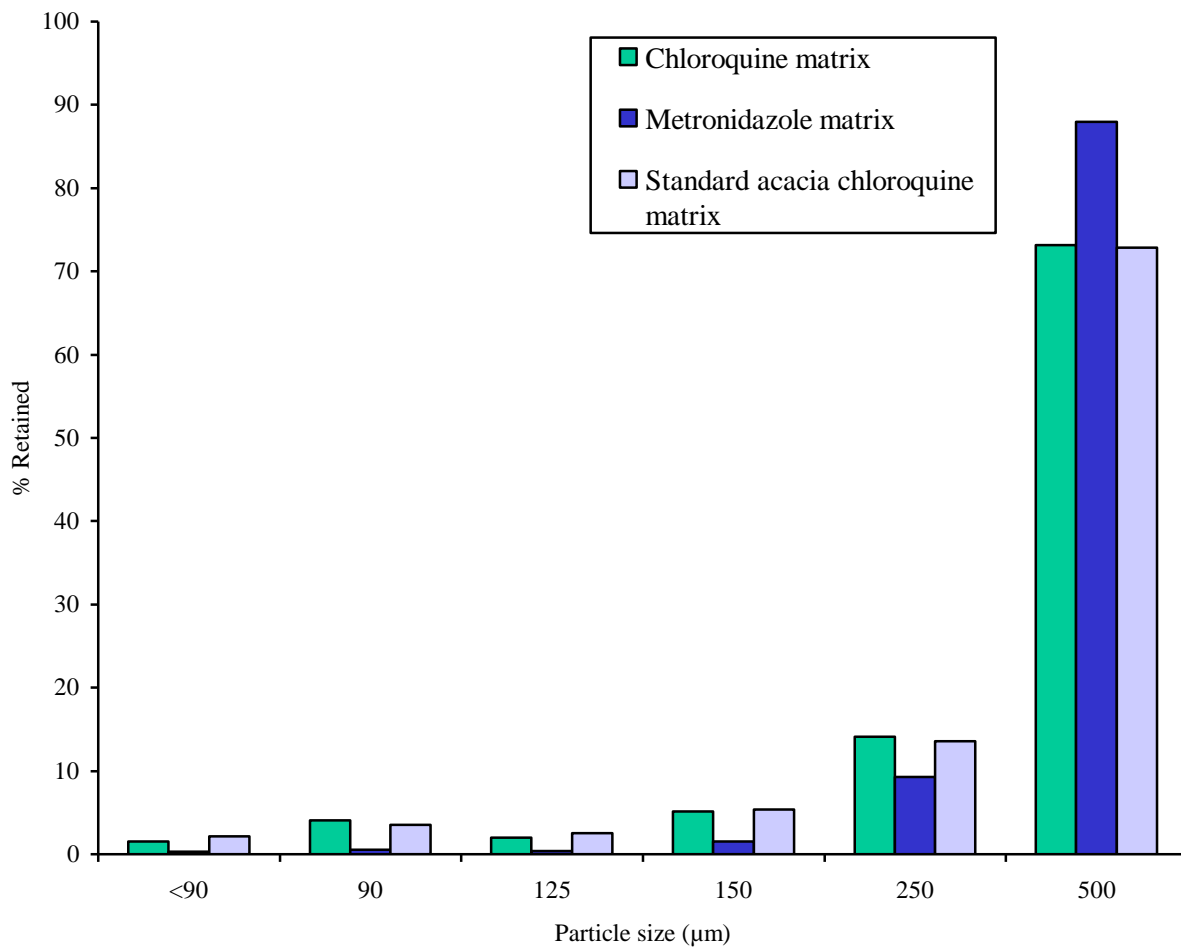


Figure 3.12: Granule size distribution of chloroquine phosphate and metronidazole matrices (batch 6) containing 10 % gum.

3.4.1 Characteristics of the Granules

The characteristics of the chloroquine phosphate and Metronidazole matrix granules are as shown in Table 3.5. The chloroquine matrix granules exhibited slightly higher flow rate while metronidazole matrix granules were characterized by lower angle of repose. The Carr's index value for the metronidazole matrix is slightly higher than that of chloroquine matrix. This result reflects higher densification index for the metronidazole matrix granules than chloroquine phosphate matrix granules. There was no significant difference between the test and the reference acacia gum.

TABLE 3.5: Characteristics of Chloroquine-Gum Matrix Granules and

Batch	Biopolymer (%)	Flow Rate (g/sec).	Angle of Repose (deg)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)
1	60	a)4.194 4.20 ^R b)3.28	29.8 28.0 ^R 24.0	0.699 0.690 ^R 0.656	0.839 0.826 ^R 0.820	16.7 19.7 20.0
2	50	a)4.08 4.13 ^R b)3.63	29.5 28.5 ^R 22.6	0.636 0.650 ^R 0.630	0.781 0.758 ^R 0.844	18.6 16.6 ^R 25.4
3	40	a)4.49 4.36 ^R b)3.66	29.2 28.8 ^R 23.4	0.641 0.563 ^R 0.600	0.816 0.752 ^R 0.819	21.5 15.0 ^R 19.4
4	30	a)3.99 4.06 ^R b)3.59	29.2 29.0 ^R 24.0	0.655 0.652 ^R 0.673	0.814 0.762 ^R 0.816	19.4 16.9 ^R 22.2
5	20	a)4.04 4.02 ^R b)3.70	24.4 26.5 ^R 26.6	0.766 0.754 ^R 0.651	0.831 0.831 ^R 0.816	7.8 10.2 ^R 20.2
6	10	a)3.76 3.97 ^R b)3.24	27.3 28.0 ^R 24.8	0.700 0.710 ^R 0.466	0.770 0.754 ^R 0.514	9.1 6.2 ^R 9.3

Metronidazole Gum Matrix Granules**Key:**

a – Chloroquine gum matrix (test gum).

a^R - Chloroquine gum matrix (standard acacia gum).

b – Metronidazole gum matrix (test gum).

3.5 EFFECT OF CONCENTRATION OF GUM ON TABLET STRENGTH

The chloroquine phosphate matrix powder was well compacted at compression pressure of $3.50 \times 10^5 \text{ N/m}^2$ (compression force 40 N). As the concentration of gum decreased, the tablet strength was found to decrease (Fig.3.13). The tablet strength was also found to be higher for the smaller particle size ($>90\text{-}125 \mu\text{m}$) than the bigger particle size. The compression of metronidazole matrix tablet was achieved at a higher compression pressure, of $4.42 \times 10^5 \text{ N/m}^2$ (compression force, 50N). Despite the higher pressure applied, the tensile strength observed were lower than that of chloroquine matrix tablets (Fig. 3.14). In chloroquine matrix compaction, only particle size fractions $>90\text{-}125 \mu\text{m}$ and $>125\text{-}150 \mu\text{m}$ revealed progressive plastic deformation; others were marked with reduction in plastic deformation.

The $>250\text{-}500\mu\text{m}$ particle fraction exhibited different behaviour in both chloroquine and metronidazole matrix compact. For the former, there was an irregular compaction; the tablet strength was higher for the Batch 2 containing 50 % gum (i.e. $15.3 \times 10^5 \text{ N/m}^2$) than Batch 1 containing 60 % gum (i.e. $14.6 \times 10^5 \text{ N/m}^2$). While for the latter, the tablet strength was found to be higher for the compact containing 40 % gum than those of the compact containing 50 % and 60 %. (Fig. 3.14).

The effect of concentration of the gum on compactness of both drugs was found to follow the same pattern (decrease in strength as the concentration of gum decreased). The soluble drug (chloroquine) compact exhibited higher strength. Although the variation in concentration of gum has more effect on compact strength of metronidazole, similar trend was observed in chloroquine phosphate compact.

3.6 EFFECT OF PARTICLE SIZE ON TABLET STRENGTH

Chloroquine matrix tablets were compacted at compression pressure of 3.5×10^5 N/m² (i.e. compression force of 40 N), while metronidazole matrix tablets were compacted at compression pressure of 4.42×10^5 N/m². The result of both soluble and poorly soluble drug compact established decreasing tablet strength with increase in particle size (figs.3.15 and 3.16).

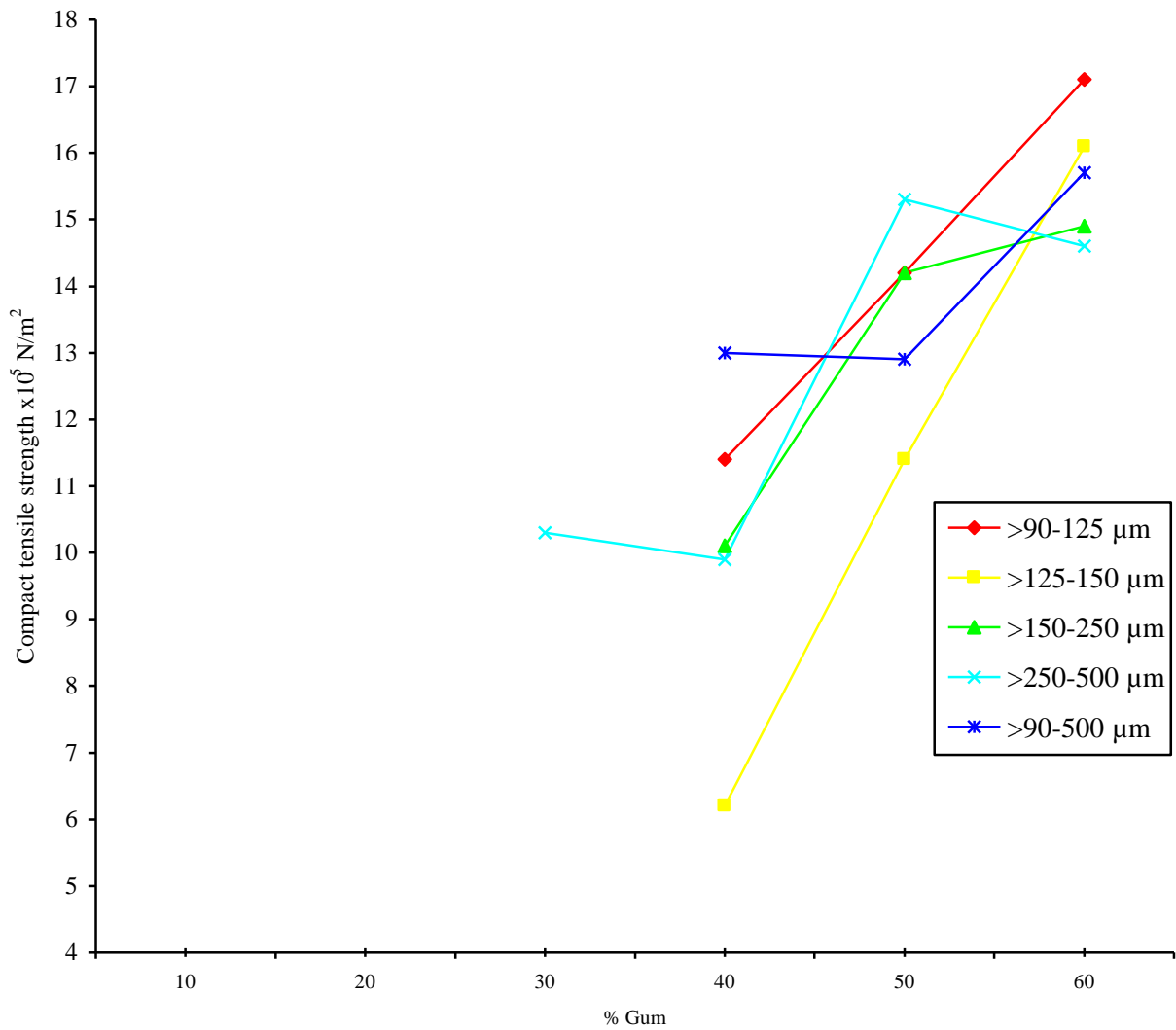


Figure 3.13: Effect of concentration of gum on tablet strength. Chloroquine phosphate matrix tablet compressed at $3.5 \times 10^5 \text{ N/m}^2$ (compaction force 40 N).

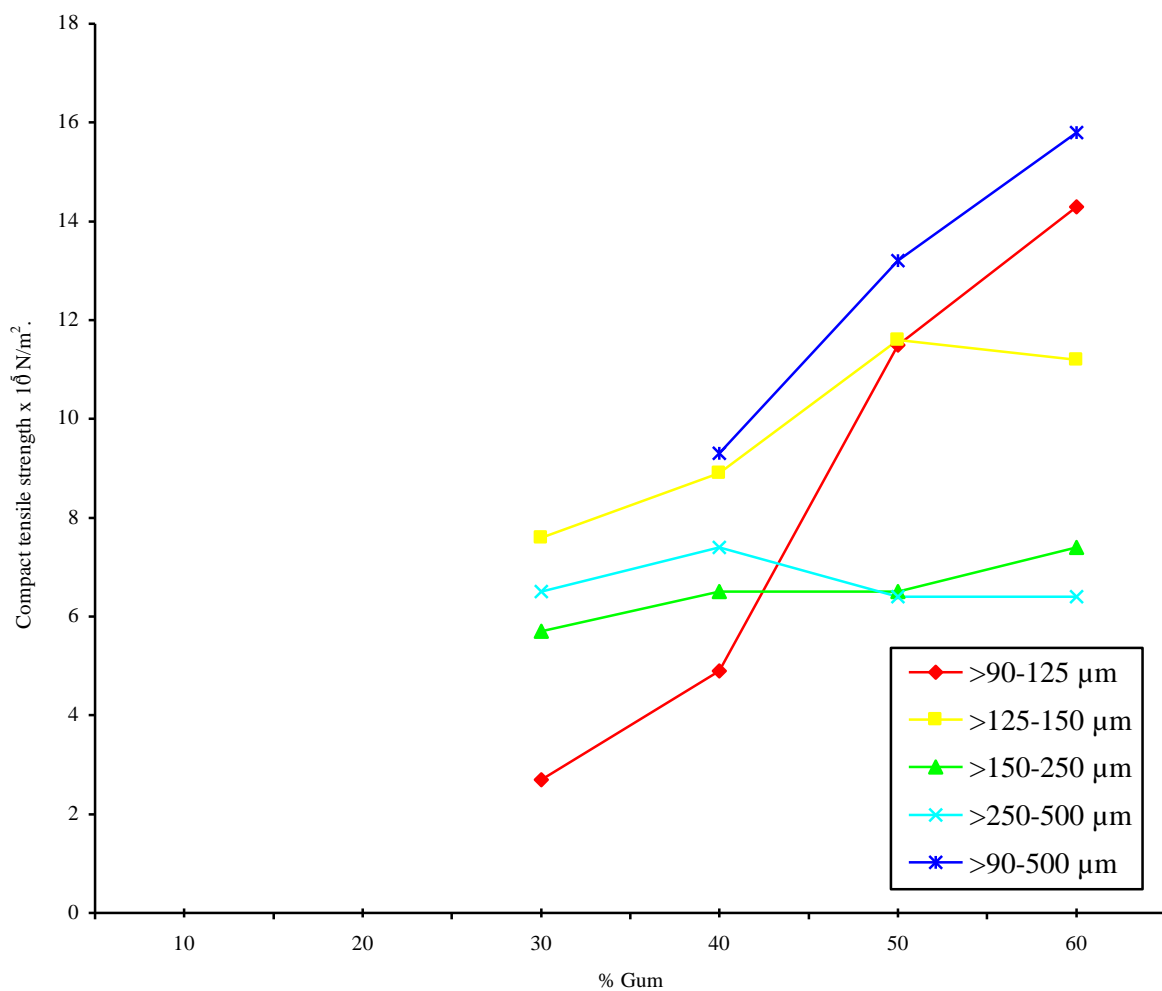


Figure 3.14: Effects of concentration of gum on metronidazole matrix tablet strength compacted at $4.42 \times 10^5 \text{ N/m}^2$

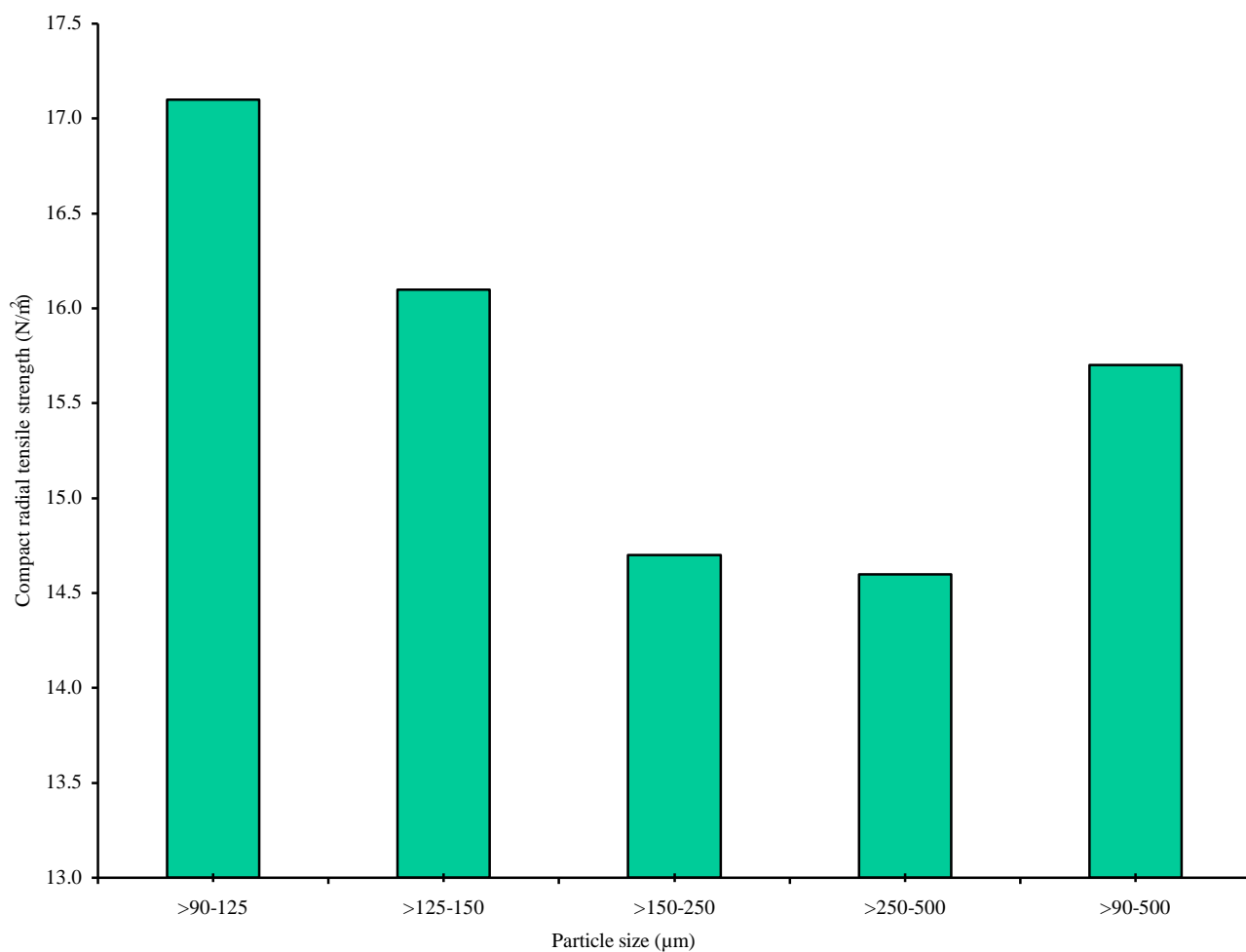


Figure 3.15: Effect of particle size of gum on matrix tablet strength of chloroquine phosphate compacted at 40 N (compression pressure $3.5 \times 10^5 \text{ N}/\text{m}^2$)

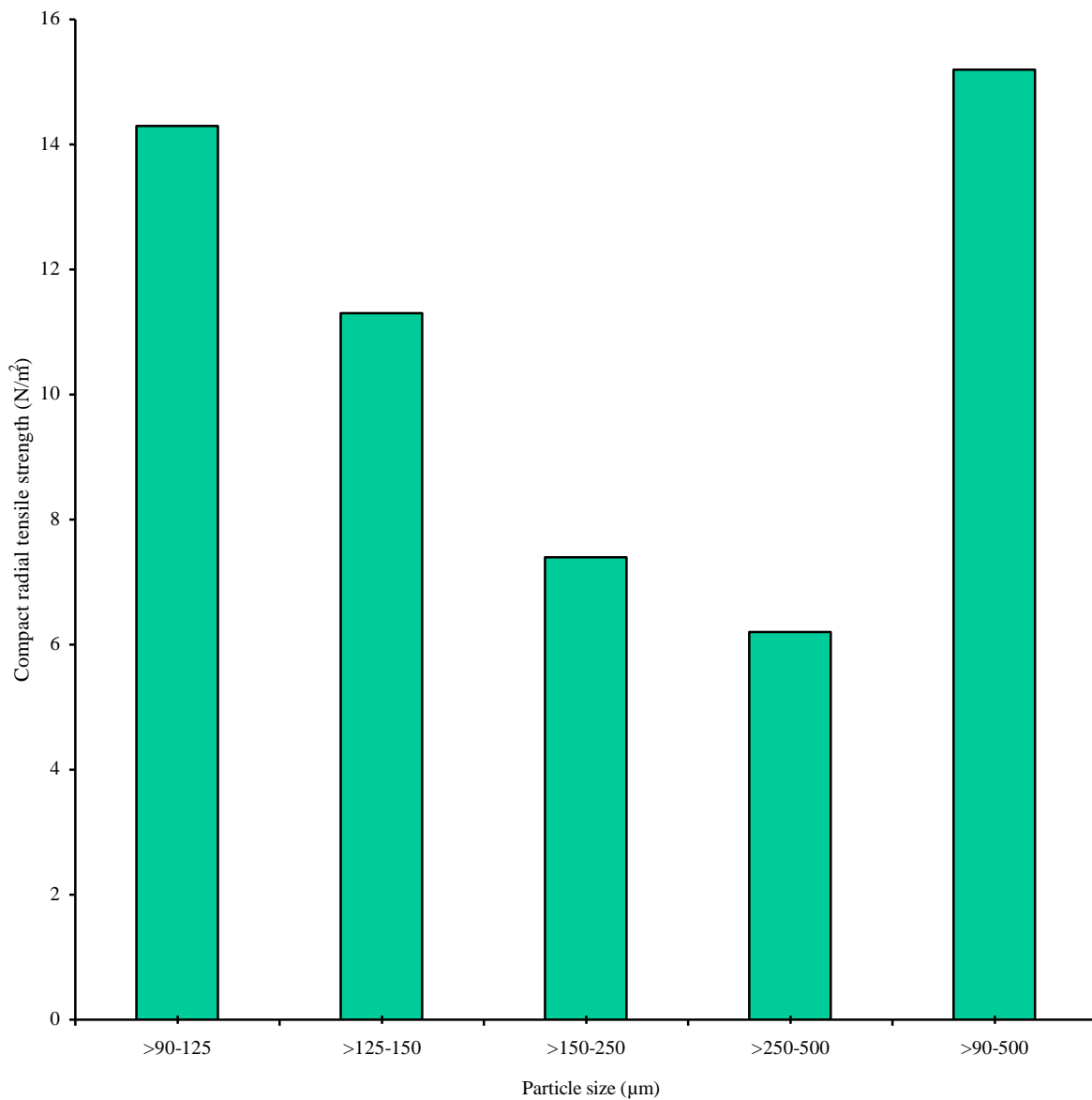


Figure 3.16: Effect of particle size on matrix tablet strength of metronidazole compacted at 50 N (compression pressure $4.43 \times 10^5 \text{ N}/\text{m}^2$)

3.7 COMPACTIBILITY AND RETARDANT EFFECT OF ACACIA SIEBERIANA GUM, BY WET GRAUNLATION PROCEDURE

The compaction characteristics of chloroquine phosphate matrix granules (test and reference acacia gum) and metronidazole matrix granules were illustrated (Fig. 3.17). The compaction processes for both soluble and insoluble drug matrix were achieved at the same compression pressure ($3.5 \times 10^5 \text{ N/m}^2$) The concentration of the gum has greater effect on the chloroquine matrix tablet strength (compactibility) than metronidazole matrix tablet strength.

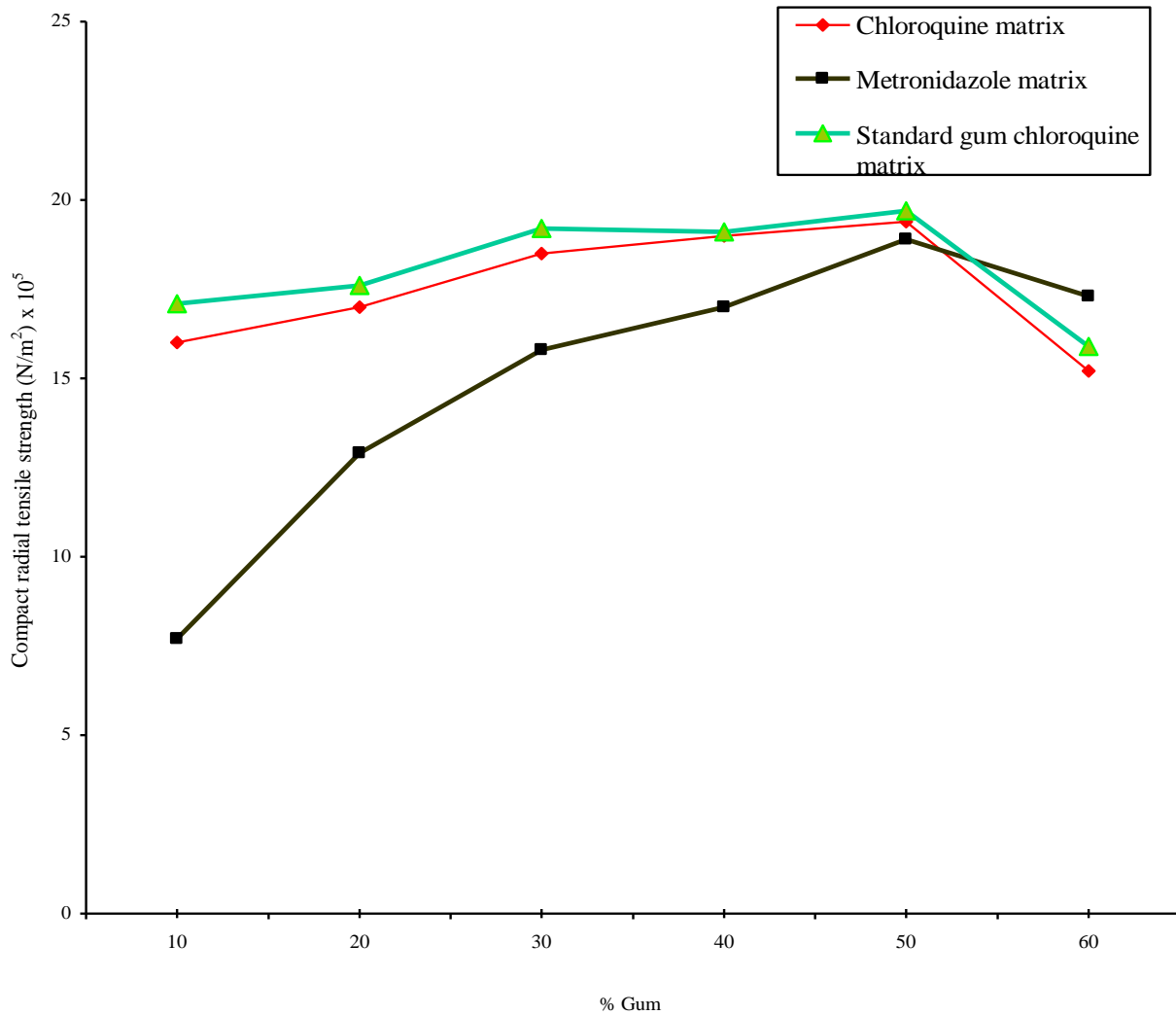


Figure 3.17: Effect of concentration of gum on tablet strength, formulated by wet granulation method at compression pressure of $3.5 \times 10^5 \text{ N/m}^2$.

3.8 TABLET ANALYSES

3.8.1 Results of the Weight Variation Test

All the batches of the tablets formulated by both direct compression and wet granulation methods were subjected to weight variation test. None of the matrix tablet weight fell outside 500 ± 25 mg. (i.e. mean weight $\pm 5\%$) for the directly compressed tablets, and none-fell outside 505 ± 25.25 mg for the tablets formulated by wet granulation method (Appendix 6).

3.8.2 Results of the Content of Dosage Unit Test

The result of content of dosage unit test carried out according to the U S P (2003), for the matrix compact tablets formulated by wet granulation method met the official standard (i.e. $100 \pm 5\%$) (Appendix 6).

3.8.3 Tablet Disintegration

All the tablets formulated by both direct compression and wet granulation method failed the disintegration test (official time of 15 min.). Even at 30 min. The tablets showed slight change in shape as a result of erosion of the surface of the tablets. The tablets formed were non-disintegrating as the erosion of the tablets continued until they eroded away completely (no swelling).

3.9 DISSOLUTION RATE TEST

3.9.1 Effect of concentration of gum (particle size >90—500 µm) on the rate of drug release from directly compressed tablet

The pattern of drug release from the matrices of batches 1, 2 and 3 containing chloroquine phosphates are illustrated in Fig.3.18. The $T_{90\%}$ for the three batches was 3 h 30 min, 1 h 45 min and 1h 40 min respectively.

The Dissolution Efficiencies (DE) at 1 h for the three batches were found to be 37 %, 72 % and 75 % respectively.

3.9.2 The effect of particle size of the gum on the rate of drug release from the directly compressed tablets

The pattern of Chloroquine phosphate release from the matrices of batch 1 formulated with gum of particle size >125-150 µm and batch 1 formulated with gum of particle size >150-250 µm is shown in Fig. 3.19.

The $T_{90\%}$ for the matrices made of >125-150 µm and >150-250 µm particle sizes were 2 h 12 min and 38 min respectively. The Dissolution Efficiencies (DE) at 1 h were found to be 76 % and 100 % respectively. The USP Food and Drug Administration (FDA) similarity factor “ f_2 ” value for difference in dissolution between the two matrix tablets was found to be less than fifty (<50). A conventional chloroquine tablet is expected to release 90% of its active ingredient in 45 min (U.S.P, 2003).

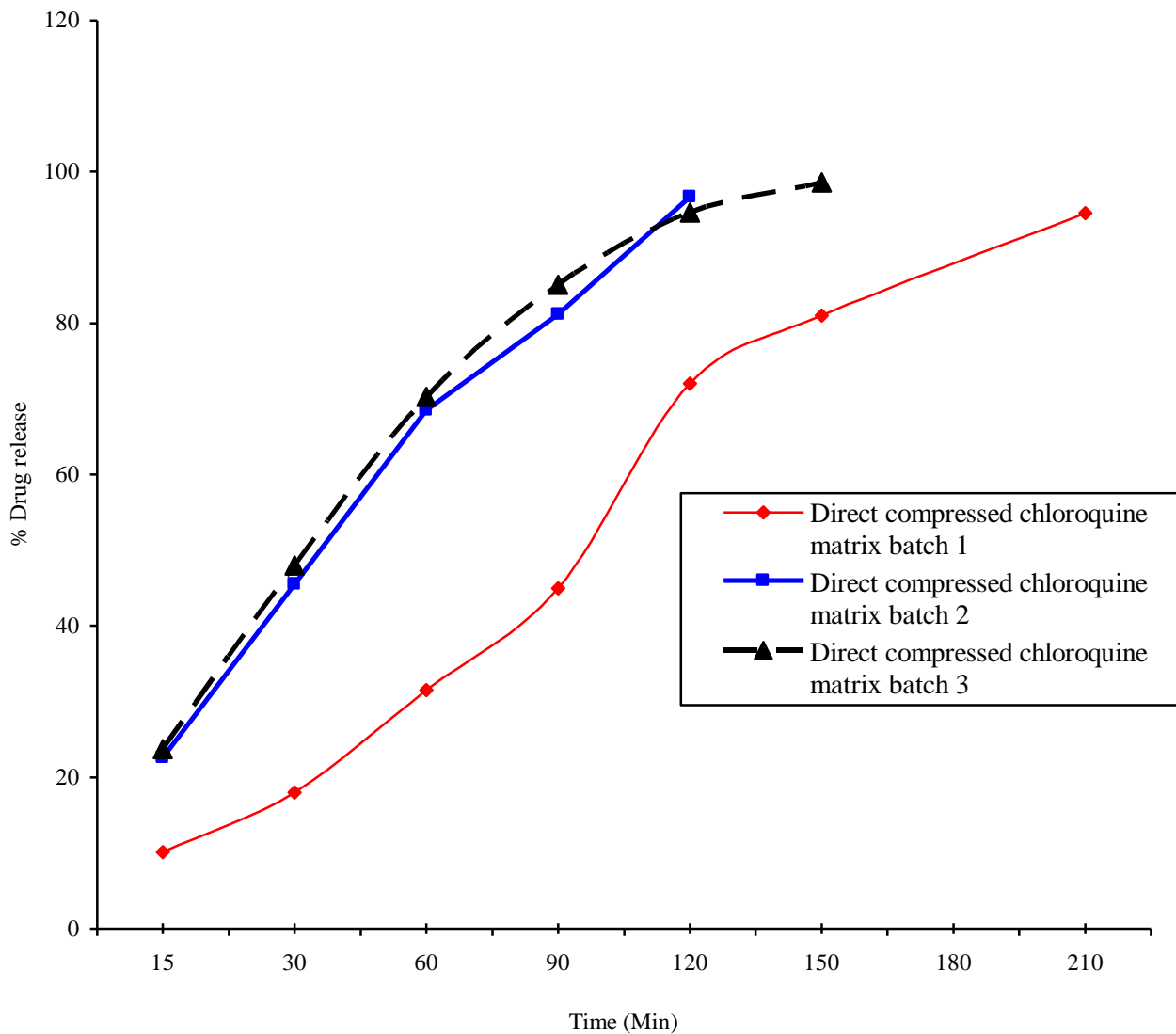


Figure 3.18: Effect of concentration of the gum on drug release from matrices of batches 1, 2 and 3 containing chloroquine and gum of particle size range >90-500 μm , formulated by direct compression method.

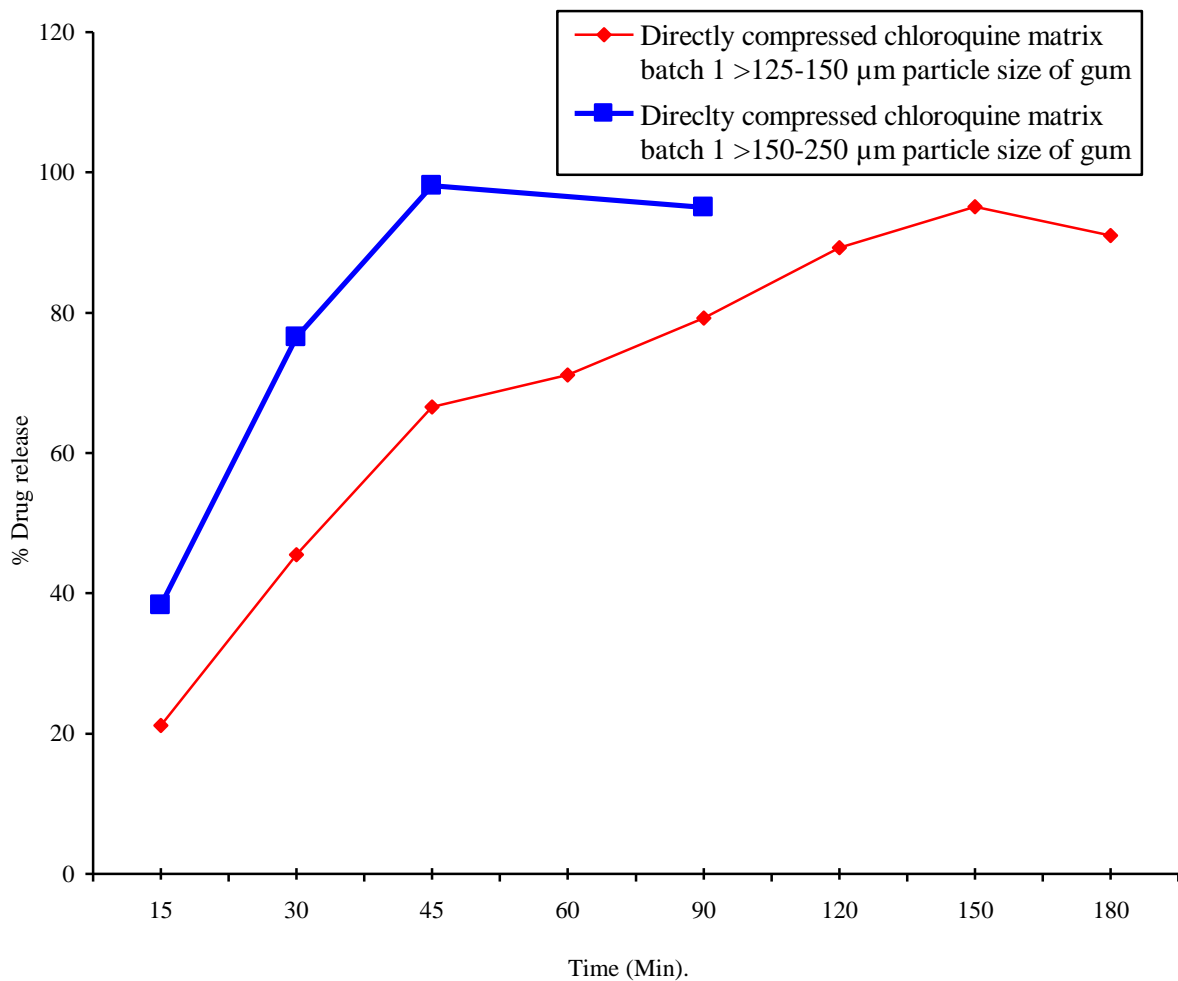


Figure 3.19: Effect of particle size on drug release from matrices of batch 1 for >125-150 μm particle size gum (test) and batch 1 for >150-250μm particle size gum respectively, formulated by direct compression method.

3.9.3 The retardant effect of *Acacia sieberiana* gum on drug release from the compact formulated by wet granulation method

The pattern of drug release from matrix compacts of batches 1 of chloroquine phosphate (made with test and standard gum) and metronidazole is illustrated in Fig. 3.20.

The matrices of chloroquine (test and standard) and metronidazole represents highly and poorly water soluble group of drugs respectively.

The DE (45 min) for the batch 1 of test matrices of test gum chloroquine, test gum metronidazole and standard gum chloroquine (SGCQ) were 88 %, 24 % and 82 % respectively. The DE (1 h) for same batch was 98 %, 34 % and 92 % respectively.

The DE (1 h) for the test and standard gum (SG) Chloroquine matrix tablets showed little but no significant difference, while the metronidazole matrix released drug at a rate much slower than the chloroquine matrix tablet.

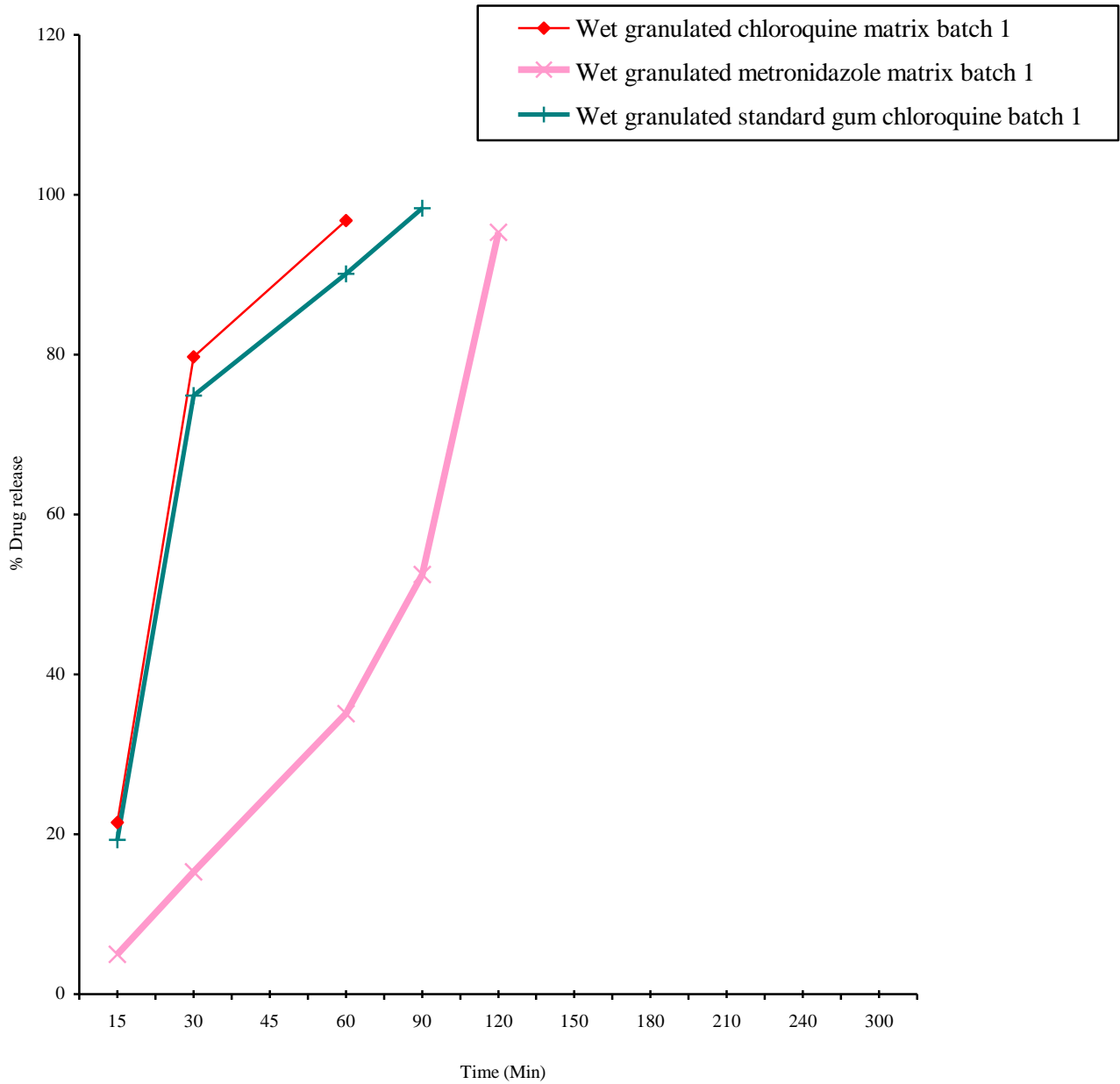


Figure 3.20: Drug release from matrices of Batch 1 formulated by wet granulation procedure compacted at compression pressure of $3.5 \times 10^5 \text{ N/m}^2$

3.10 STATISTICAL ANALYSIS

The similarity factor “ f_2 ” from FDA guideline was used to compare the dissolution profiles of reference standard and the test gum matrix compacts.

$$f_2 = 50 \log_{10} \left\{ 100 \left[1 + \frac{1}{t} \sum_{j=1}^t (R_j - T_j)^2 \right]^{-0.5} \right\} \quad (8)$$

Where R_j and T_j represent the average percent dissolved at time j for reference and test respectively, and t is the number of time points tested.

1. The results of the dissolution of matrices of batch 1 (containing, chloroquine phosphate) for both test and standard gums was compared as follow:

At, $j = 45$ min; $R_j = 88$ % and $T_j = 82$ %.

At, $j = 1$ h; $R_j = 98$ and $T_j = 92$.

Therefore: $\sum_{j=0.75, 1}^t [(88 - 82) + (98 - 92)]^2 = 144$

$$\begin{aligned} f_2 &= 50 \log_{10} \left\{ \left[100 \left(1 + \frac{1}{2} (144) \right) \right]^{-0.5} \right\} \\ &= 50 \log_{10} \left\{ 100 (73)^{0.5} \right\} \\ &= 50 \log_{10} \left\{ 100 \times 0.117 \right\} = 50 \times 1.07 \\ &= 53.5 \end{aligned}$$

Since f_2 has the value of 53.5, which is within 50 and 100. The standard and the test matrix compact dissolution data are similar.

2. The results of the dissolution of matrices of test chloroquine were compared with that of metronidazole (all batch 1 containing 60 % purified gum) as follows:

At, $j = 45$ min; $R_j = 88$ % and $T_j = 24$ %.

At, $j = 1$ h; $R_j = 98\%$ and $T_j = 34\%$.

Therefore: $\sum_{j=0.75, 1}^t [(88 - 24) + (98 - 34)]^2 = 16384$

$$f_2 = 50 \log_{10} \left\{ \left[100 \left(1 + \frac{1}{2} (16384) \right)^{-0.5} \right] \right\}$$

$$= 50 \log_{10} \{ 100 (8193)^{-0.5} \}$$

$$= 50 \log_{10} \{ 100 \times 0.011 \} = 50 \times 0.0414$$

$$= 2.07$$

Since f_2 has the value of 2.07 which is outside 50 and 100, the test and standard matrix compact dissolution data are therefore not similar.

CHAPTER FOUR

4 DISCUSSIONS

The percent yield of the *Acacia sieberiana gum* was found to be 83%. The particle size distribution of the gum follows the normal sigmoid distribution. The >250-500 μ m particle size constitute over 51 % of the bulk powder, while the >500 μ m constitute 10 % and the remaining 39 % were completed by the >75-90, >90-125, >125-150 and >150-250 μ m. This distribution imparted free flowing property to the whole powder. The different particle sizes of the purified gum exhibited far greater flow rate than the MCC (Avicel PH 101).

With the value of carr's index for Avicel PH 101 at 32 % and those of gum ranging from 7.9 % to 18.8 %, the gum has a greater chance of volume reduction than the Avicel due to the fact that a higher compressibility index value is proportional to adhesion and friction properties of a powder (Podczec, 1998). The lower Carr's index is an indication of a better flow for all the particle size fractions of the gum.

In characterizing the gum, a relationship was established between the particle size and the flow rate (Fig 3.2). There was an increase in flow rate from >90-125 to >125-150 μ m particle then a decline at >500 μ m and a higher rate for the selected size range,(i.e. >90-500 μ m powder). The reason is that, the shape of the particle plays a vital role in the flow rate, as the particle size of the gum increases; the shape becomes rougher and therefore hindering smooth flow. For the size range

>90-500 μm powders, the presence of the smaller particles might have covered the roughness of the bigger particles. There was a linear decline in angle of repose as the particle size increased from >90-125 to >500 μm followed by elevated value for the >90-500 μm powder. The reason is not far from the explanation given above for the flow rate (Fig.3.3). A relationship was established between the particle sizes of the gum and the Carr's index (Fig.3.4). The higher value of Carr's index for the >150-250 μm particle size is proportional to the detachment force (i.e., adhesion strength) (Podczeck, 1998).

The swelling capacity of *Acacia sieberiana* gum was established as 2 (swelled to twice its initial volume), which means, the gum is highly hydrophilic and will therefore release whatever drug is embedded within 24 h.

Hydration capacity of the purified gum obtained was 1.66, this shows that the gum retained 66 % of its weight of water in less than 3 h. The water penetration into the gum is therefore rapid.

Changes in pH of the acacia mucilage have no effect on the viscosity. It can therefore be used to formulate controlled release matrix tablets since the release can take place at any pH of the physiological environment.

The relationship between the compression pressure and compact density of the gum tablets of each particle fraction (Fig.3.5) was used to compare the compressibility with

that of MCC (avicel PH 101). There was an increase in volume reduction (densification) to certain degree for all the particle size fractions of the gum. The fact that the gum compressed at much lower compression pressure range $1.8 \times 10^5 \text{ N/m}^2$ to $3.1 \times 10^5 \text{ N/m}^2$ (i.e. compression force of 20 N to 40 N), and have higher compact density than those of MCC (Avicel PH 101), which compacted at much higher compression pressure, $8.90 \times 10^5 \text{ N/m}^2$ to $10.6 \times 10^5 \text{ N/m}^2$ (i.e. compression force of 100 N to 120 N) implies that the gum is more easily compressible than the MCC. The order of volume reduction within gum particle fraction is as follows: $[\gt 90-125] > [\gt 125-150] > [\gt 150-250] > [\gt 500] > [\gt 250-500] > [\gt 90-500] \mu\text{m} > \text{whole powder}$. The degree of volume reduction that a pharmaceutical powder bed undergoes depends on the mechanical properties of the powder and the volume reduction mechanism involved. Particle size and speed of compression have influence on the mechanical properties of the compact (Roberts and Rowe, 1987). For instance, reduction in particle size has been related to a decreased tendency to fragment (Alderborn and Nystrom, 1985).

The compactibility of purified *Acacia sieberiana* gum was determined from the effect of compression pressure on the tensile strength of the compact tablet (Fig 3.6). The gum with the particle size $\gt 90-500 \mu\text{m}$ compared favourably with the MCC (Avicel PH 101) in terms of pattern of deformation but at different compaction force. Fig. 3.6 shows that gum compact strength of $3.43 \times 10^5 \text{ N/m}^2$ was achieved by applying $1.8 \times 10^5 \text{ N/m}^2$ compression pressure, while for the MCC, compact strength of $3.30 \times 10^5 \text{ N/m}^2$ was achieved with 8.9

$\times 10^5$ N/m² compression pressure. The gum compact strength of 11.77×10^5 N/m² was achieved by applying 3.1×10^5 N/m² compression pressure, while for MCC, compact strength of 12.65×10^5 N/m² was achieved with 9.7×10^5 N/m² compression pressure. The purified gum with the particle range >90 - 500 μm is highly compactible.

Characteristics of direct compression powder mixture as indicated in table 3.3 and 3.4 show that, the flow rates of the chloroquine gum powder mixture has improved over that of gum alone, while for the metronidazole gum powder mixture, the flow rates were slightly reduced. The densification indices of both sets of mixtures were elevated above those of corresponding gum powder fractions. This points to the fact that the powder mixture's forces of adherence and friction properties have been increased. Furthermore, that means, chloroquine gum matrix powder mixture possessed better flow and compressibility properties than metronidazole gum powder mixture.

Granule size distribution (Figs. 3.7 - 3.12) shows that chloroquine phosphate matrix granules were characterized by higher percentage of >500 μm granules, ranging from 57 % to 75 % for the batches 1 to 6; followed by >250 - 500 μm granules, ranging from 10 % to 20 % (Figs. 3.7 – 3.12). The other granule sizes made up the remaining percentage. Similar results were obtained for the metronidazole matrix granules. The granule size of >500 μm range from between 65-87.9 % for batches 1-6, followed by >250 - 500 μm , constituting from between

1.5 % to 12 % for batches 1 to 6 (see Figure 3.7-3.12). The shape of the curve is sigmoid. The distribution of the chloroquine gum granules favoured good compaction over metronidazole gum granules. The >500 μm granule size was found to increase with decrease in the concentration of the gum for the highly water soluble drug while the other size fractions decreased. The granule size distribution of the poorly water soluble drug was found to present an opposite result with slight decrease in >500 μm size fraction and an increase in other size fraction as the concentration of the gum decreases from 60 % to 10 %.

The characteristics of the chloroquine phosphate matrix granules and metronidazole matrix granules are as shown in Table 3.5. The granules were all irregular in shape and appeared non-porous. The irregular shape makes rearrangement uneasy during volume reduction mechanisms (York, 1978). Volume reduction is mostly favoured by plastic deformation and or fragmentation of the granules (Train, 1956; Duberg and Nystrom, 1986). Irregular shaped granules also favour mechanical interlocking (hooking and twisting) of particles in bond formation during compaction (Fuherer, 1977). The chloroquine matrix granules exhibited little higher flow rate than metronidazole matrix, while the latter showed low angle of repose as an expression of better granules packing than for the former. The Carr's index values for the metronidazole matrix are a little

higher than that of chloroquine matrix. This result reflects higher densification for the chloroquine phosphate matrix granule than metronidazole matrix granules.

The effects of concentration of the gum on the tablet strength of chloroquine and metronidazole matrices investigated by direct compression method shows that chloroquine phosphate matrix powder compacted well at compression pressure of $3.50 \times 10^5 \text{ N/m}^2$ (compression force 40 N) and as the concentration of gum decreases, the tablet strength was found to decrease (Fig. 3.13). The tablet strength was also found to be higher for the smaller particle size (>90-125 μm) than the bigger particle size. This was due to the larger surface area and the fact that the smaller particle size gum presents more binding sites hence giving rise to stronger tablet (bond summation concept by Rumpf, 1962). The mechanical strength of powder mixtures were also described quantitatively as a result of the sum total of all the bonds formed between the different components of the mixtures (Leuenberger, 1982; Eriksson and Alderborn, 1995). The compression of metronidazole matrix tablet was achieved at a higher compression pressure, $4.42 \times 10^5 \text{ N/m}^2$ (compression force, 50 N). Despite the higher pressure applied, the tensile strength observed were lower than that of chloroquine matrix tablets (Fig. 3.14). The behaviour of metronidazole matrix is attributed to its inherent elastic property, surface energy or charges that also affect its water solubility. The

concentration of the gum has a greater effect on the strength of the compact for both the soluble and poorly soluble drugs

For the highly water soluble drug, the >90-125 μm gum compact gave the highest tensile strength ($17.1 \times 10^5 \text{ N/m}^2$) at 60 % concentration of gum, while at 50 % gum; the >250-500 μm gum fraction gave the highest tensile strength.

For the sparingly water soluble drug, the >90-500 μm gave the highest tensile strength at 60, 50, and 40 %. These gum fractions can be used for direct compression of both soluble and sparingly soluble drug.

The concentration of the gum has a profound effect on the strength of the compact for both the soluble and poorly soluble drugs. The effect of concentration of gum on compactness of both drugs was found to follow the same pattern (decrease in strength as the concentration of gum decreased). The soluble drug (chloroquine phosphate) compact exhibited higher strength than the sparingly soluble drugs.

Particle size of the gum was found to have effect on tablet strength (compactness) of both drugs formulated by direct compression method consisting of a fixed ratio of 60 % acacia gum to 40 % model drug (Figs.3.15 and 3.16) A direct relationship exists between the particle size and surface area and particle size and number of binding sites available. A good pharmaceutical binder possessed such relationship as inherent properties as observed with *Acacia sieberiana* gum. As the particle size

increased the number of the gum particles taking part in bond formation decreased. As a result this, the number of bonds formed decreased, hence average tensile strength reduced. A reduction in particle size is generally associated with an increase in mechanical strength (Shotton and Ganderton 1961; Alderborn and Nystrom, 1982a; McKenna and McCafferty 1982; Alderborn *et al*; 1988). It has been pointed out that the relationship between surface area and mechanical strength may be affected by particle size (Eriksson and Alderborn, 1995). The increase in mechanical strength is attributed to an increase in the surface area available for inter particulate attractions, as the particles become smaller. This is consistent with the relationships between the particle size of the powder (both pure and mixture) and the resultant tablet strength (McKenna and McCafferty, 1982). The effect of particle size on tensile strength of the compact tablets was more pronounced in chloroquine phosphate matrix than in metronidazole matrix tablet (Fig. 3.15 and 3.16). The reasons could be attributed to more hydrogen bonds associated with the highly water soluble drugs inter-particulate in nature coupled with the other bonds such as interlocking and distance attraction forces. The tablet strength observed for the gum powder fraction >90-500 μm is an indication of summation of all the bonds formed by individual particle fractions making up the resultant tablet strength.

Compactibility and retardant effect was investigated using massing and sieving method of wet granulation. The <90 µm particle size of the purified gum was used to formulate granules.. The compaction processes for both water soluble and insoluble drug matrix was achieved at the same compression pressure (3.5×10^5 N/m²). This is an indication that granulation of the powder mixture improved the compaction of the metronidazole matrix powder (physical mixture) which compacted at compression pressure of 4.42×10^5 N/m². The shape of granules in both matrices was irregular and this contributed immensely to the compaction of the granules due to an irreversible deformation process resulting in a permanent change of the particule shape (Train, 1956; Duberg and Nystrom, 1986). This was an added advantage to the increase in surface area available for both intra-particulate and inter-particulate bonding. A reduction in particle size is generally associated with an increase in mechanical strength (Shotton and Ganderton, 1961). The binding properties of the gum, the increased binding sites available (due to reduction in particle size) and the solid bridges created as a result of the granulation liquid which on drying cohered the particle together.

The tablet strengths of batches 2 to 6 were higher than batch 1 for chloroquine phosphate matrix compact, while the compact strength of batch 2 was higher than batch 1 for the metronidazole matrix compact. The batches 1 and 2 composed of

the model drug and the gum in ratios of 40 % and 60 % respectively, while in batches 2 to 6, an inert diluent (lactose) was introduced. The presence of lactose contributed additional bond to the compacts such as solid bridges. However, tablets containing these strong bonds are also associated with an extended disintegration time (Fuhrer, 1977). It has also been proposed that amorphous materials are more likely to bond with solid bridges (Fuhrer, 1977; Sebhatu *et al.*, 1997) and that the presence of moisture in a tablet increases the likelihood of solid bridges developing (Sebhatu *et al.*, 1997). Mechanical interlocking describes the hooking and twisting together of particles in a tablet. This is possible because of particle irregularities and roughness on the surface of the particles (Fuhrer, 1977). The above-mentioned bonds are likely to be responsible for the strength of the compact produced by wet granulation.

All the batches of the tablets formulated by direct compression (containing gum fractions >125-150, >150-250 and >90-500 μm) met the USP (2003) standard in terms of weight variation, friability and content uniformity.

The matrix tablets formulated by wet granulation method met the USP (2003) official standard,(i.e. $100 \pm 5\%$).

All the tablets formulated by both direct compression and wet granulation method were non-disintegrating tablets, as such all failed the disintegration test. Drug release from the

compacts was characterised by washing away of the surface of the tablets. until the entire embodiment eroded away.

Increase in concentration of gum was found to have profound effects on drug release rate from tablets formulated by direct compression method as illustrated by fig. 3.18. The matrices of batches 1, 2 and 3 containing chloroquine phosphate were subjected to dissolution test. The $T_{90\%}$ for the three batches was 3 h 30min, 1 h 45min and 1 h 40min respectively. The Dissolution Efficiency (DE) at 1 h for the three batches were found to be 37 %, 71 % and 75 % respectively. These results reflected an increase in dissolution rate as the concentration of the gum decreased.. The more the number of particles of gum present in the powder mixture, the higher the tensile strength and the better the coverage over the particles of chloroquine. Hence, as the concentration of the gum decreased, the tensile strength reduced thereby giving way to easy erosion of the matrix.

The drug release pattern of different particle sizes of the gum was investigated using the USP XXIII (2003) method of dissolution. Directly compressed tablets made of gum of particle sizes >125-150 μm and >150-250 μm were employed. The pattern of drug release from the matrices of batch 1 formulated with gum of particle size >125-150 μm and batch 1 formulated with gum of particle size >150-250 μm is shown in fig.3.19. The result obtained revealed that the reduction in particle size led to increase in surface area, number of binding sites and

compactness of the tablets. The higher tensile strength of the compact made of particle size >125-150 μm ($16.1 \times 10^5 \text{ N/m}^2$) and the nature of bonds formed must be responsible for the longer retardant effect than the compact of >150-250 μm particle size (tensile strength $14.9 \times 10^5 \text{ N/m}^2$) since both contain the same concentration of gum. The smaller particle size of the gum with multiple binding sites is very important, as more of the >125-150 μm particles will cover the surfaces of the drug than the larger particle size.

The pattern of drug release from the compact formulated by wet granulation method was investigated. The particle size less than 90 μm of both the test and reference standard acacia were employed. The fig.3.20 illustrates the pattern of drug release from matrices of compacts of batch 1. The DE (1 h) into the dissolution test for the batch 1 of test matrices of chloroquine, metronidazole and standard gum matrix of chloroquine (SGCQ) were 98 %, 34 % and 92 % respectively. The batch 1 of both test and standard containing chloroquine serve the purpose of matrix formulation by not disintegrating and secondly, by not releasing 90 % of its active ingredient in 45 min (USP, 2003). The retardant effect of the *Acacia sieberiana* gum was more profound on the poor water soluble drug. The poor water solubility of the metronidazole played a vital role by slowing down the erosion of the matrix compact. The result obtained revealed that, this

type of gum releases drug by erosion instead of swelling by water penetration and drug diffusion. The low retardant effect could be attributed to the nature of the gum, its high swellability, high hydration capacity high solubility of chloroquine and the gum to drug ratio (3:2),

Since USP FDA similarity factor “ f_2 ” value for reference standard and the test matrix-chloroquine compact dissolution data has the value of 53.5, which is between 50 and 100, drug release from the two compacts is therefore similar, while f_2 value for the test matrix-chloroquine and test matrix-metronidazole was calculated as 2.07, implying significant difference in dissolution and hence different mechanism of drug release.

CHAPTER FIVE

CONCLUSION

In conclusion, the *Acacia sieberiana* gum formed non-disintegrating tablets which releases the active ingredient by surface erosion and met the official standard requirement of a good matrix tablet. This work have shown that: *Acacia sieberiana* gum is a good directly compressible excipient, alone and in the presence of poorly compressible lactose and drug, a good material for wet granulation and a potential material for matrix tablet formulation, having more sustain release effect with poorly or sparingly soluble drugs.

Drug release from matrices of *Acacia sieberiana* can be adjusted by careful selection of particle size and concentration of the gum. Since some of the batches of the direct compression powder mixture produced compact with $t_{90\%}$ less than 1 h and acceptable quality of a good pharmaceutical tablet, further work will employ this result to design a direct compression excipient inform of composite diluent using the process of microstructuring or coprocessing that could compete favourably with the existing directly compressible excipient in commerce.

A well engineered *Acacia sieberiana* gum may make possible a number of new therapies: it may be use to deliver the complex drugs that are becoming available through genetic engineering techniques; and will be able to target drugs to specific cells.

Recommendation for further Work

Because polymers are easy to modify, the use of *Acacia sieberiana* gum as a release retardant agent may further be modified to increase its viscosity by cross – linking with a highly viscous gum such as xanthan gum and guar gum and investigated for sustained release. The cross – linked gum may also be investigated for coating purpose as colon – targeted agent for sparingly soluble drugs and in multiple layer matrix formulation. Although we are already seeing the benefit of controlled - release technology, the industry is still in its infancy. As we gain more control over the release of drugs, using a well engineered natural polymer such as *Acacia sieberiana* gum, we will see a decrease in drug side effects, as well as improved efficacy, safety, and patient convenience.

It will also be employed in composite excipients involving two or more already established excipients using: massing and sieving method of wet granulation, spray drying, flash drying or drum drying.

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APPENDICES.

Appendix 1: Acacia sieberiana Gum Powder Characteristics

Powder	Particle.Size (μm)	Flow Rate (g/sec)	Angle of repose (deg)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)
	>90-125	5.88	33.7	0.667	0.769	13.3
	>125-150	6.25	30.0	0.685	0.746	8.2
	>150-250	5.90.	29.0	0.725	0.893	18.8
	>250-500	5.88	27.0	0.769	0.862	10.8
	>500	5.56	21.8	0.794	0.862	7.9
	> 90- 500	6.67	28.1°	0.794	0.909	12.7

Appendix 2: Microcrystalline Cellulose (Avicel PH 101) Characteristics

Powder	Flow Rate (g/sec)	Angle of repose (deg)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)
	0.5	50.4	0.357	0.526	32.0

Appendix 3: Compaction Characteristics of *Acacia sieberiana* Gum Compressed at a Range of Compression Pressure $1.8 \times 10^5 \text{ N/m}^2$ to $10.6 \times 10^5 \text{ N/m}^2$ (Compression force 20 N-120 N)

Particle size (μm)	Compression force (N)	Compression pressure $\times 10^5 \text{ (N/m}^2\text{)}$	Tablet weight (g)	Crushing strength (N)	Tablet thickness (cm)	Radial Tensile Strength $\times 10^5 \text{ (N/m}^2\text{)}$	Tablet compact Density (g/cm^3)
>90-125	20	-	NC	-	-	-	-
	25	-	NC	-	-	-	-
	30	2.70	0.500	1.0	0.3980	0.13	1.111
	35	3.10	0.500	11.0	0.3770	1.55	1.173
	40	3.50	0.500	50.0	0.3750	7.09	1.180
>125-150	45	4.00	0.500	50.0	0.3740	7.14	1.183
	20	-	NC	-	-	-	-
	25	-	NC	-	-	-	-
	30	2.70	0.500	10.0	0.3980	1.30	1.111
	35	3.10	0.500	21.0	0.3970	2.80	1.114
>150-250	40	3.50	0.500	46.0	0.3960	6.20	1.120
	45	4.00	0.500	56.0	0.3960	7.50	1.120
	20	-	NC	-	-	-	-
	25	-	NC	-	-	-	-
	30	2.70	0.500	29.0	0.4180	3.20	1.057
>250-500	35	3.10	0.500	50.0	0.3980	6.70	1.111
	40	3.50	0.500	61.0	0.3960	8.10	1.112
	45	-	NC	-	-	-	-
	20	-	NC	-	-	-	-
	25	-	NC	-	-	-	-
>500	30	2.70	0.500	50.0	0.4260	6.20	1.037
	35	3.10	0.500	49.0	0.4170	6.20	1.062
	40	3.50	0.500	50.0	0.4150	7.00	1.067
	45	-	NC	-	-	-	-
	20	-	NC	-	-	-	-
>90-500	25	-	NC	-	-	-	-
	30	2.70	0.500	31.0	0.4380	3.80	1.010
	35	3.10	0.500	41.0	0.4110	5.30	1.075
	40	3.50	0.500	49.0	0.4000	6.30	1.078
	45	-	NC	-	-	-	-
Whole powder (<90->500)	20	1.80	NC	30.0	0.4640	3.43	0.953
	25	2.20	NC	52.0	0.4410	6.25	1.003
	30	2.70	0.500	70.0	0.4400	8.44	1.005
	35	3.10	0.500	95.0	0.4250	11.77	1.041
	40	-	NC	-	-	-	-
	45	-	NC	-	-	-	-
	20	-	NC	-	-	-	-
	25	-	NC	-	-	-	-
	30	2.70	0.500	30.0	0.4310	3.70	1.027
	35	3.10	0.500	29.0	0.4290	3.60	1.031
	40	3.50	0.500	30.0	0.4290	3.80	1.035
	45	-	NC	-	-	-	-

N.C signifies, no compaction.

Appendix 4a Physico-mechanical Properties of Chlorquine Phosphate Matrix Tablets (lactose as Diluent) Compacted by Direct Compression at 40N. Diameter of the die cavity is 12mm

Particle Size (µm)	Batch	Gum (%)	Average weight (mg)	Average thickness of tablet (cm)	Average crushing force (N)	Radial tensile strength X 10 ⁵ (N/m ²)	Friability (%)
>90-125	1	60	500	0.420	135	17.1	1.1
	2	50	500	0.410	110	14.2	1.2
	3	40	500	0.420	90	11.4	0.81
	4	30	-	-	-	-	Capping
>125-150	1	60	500	0.430	130	16.1	0.8
	2	50	500	0.421	90	11.4	0.5
	3	40	500	0.423	50	6.2	0.6
	4	30	-	-	-	-	Capping
>150-250	1	60	500	0.428	120	14.9	0.3
	2	50	500	0.411	110	14.2	0.5
	3	40	500	0.418	80	10.1	1.0
	4	30	500	-	-	-	Capping.
>250-500	1	60	500	0.415	114	14.6	0.64
	2	50	500	0.354	102	15.3	1.4
	3	40	500	0.484	90	9.9	1.5
	4	30	500	0.414	80	10.3	0.67
>90-500	1	60	500	0.423	125	15.7	0.8
	2	50	500	0.410	100	12.9	0.49
	3	40	500	0.409	100	13.0	0.85
	4	30	-	-	-	-	Capping

APPENDIX 4b. Physico-mechanical Properties of Metronidazole Matrix Tablets Compacted by Direct Compression at 50N. Diameter of the die cavity is 12mm

P.S (µm)	Batch	Gum (%)	Average weight (mg)	Average thickness of tablet (cm)	Average crushing force (N)	Radial tensile strength x 10 ⁵ (N/m ²)	Friability (%)
>90-125	1	60	500	0.418	113	14.3	0.9
	2	50	500	0.411	88	11.5	0.81
	3	40	500	0.425	39	4.9	0.7
	4	30	-	0.450	23	2.7	Capping
>125-150	1	60	500	0.430	91	11.2	0.9
	2	50	500	0.409	90	11.6	0.82
	3	40	500	0.419	70	8.9	0.5
	4	30	-	0.420	60	7.6	1.1
>150-250	1	60	500	0.430	60	7.4	0.8
	2	50	500	0.407	50	6.5	0.78
	3	40	500	0.404	49	6.5	0.40
	4	30	500	0.412	44	5.7	1.60.
>250-500	1	60	500	0.416	50	6.4	1.2
	2	50	500	0.417	50	6.4	1.5
	3	40	500	0.393	55	7.4	1.6
	4	30	500	0.408	50	6.5	1.3
>90-500	1	60	500	0.420	120	15.8	0.39
	2	50	500	0.416	104	13.2	0.40
	3	40	500	0.410	72	9.3	0.83
	4	30	-	-	-	-	Capping

APPENDIX 5a: Effect of particle size on tablet strength of chloroquine phosphate matrix tablet compacted at compression pressure 3.5×10^5 N/m². Each tablet weighs 500 mg. Tablet diameter was 12 mm

Gum Particle Size (µm).	Batch	Average wt (mg)	Average thickness (cm)	Average crushing force N	Radial tensile strength x 10 ⁵ (N/m ²)	Friability %
>90-125	1	500	0.420	135	17.1	1.1
>125-150	1	500	0.430	130	16.1	0.8
>150-250	1	500	0.428	118	14.7	0.3
>250-500	1	500	0.415	114	14.6	0.64
>90-500	1	500	0.423	125	15.7	0.8

Each Batch contains 40% model drug and 60% gums.

APPENDIX 5b: Effect of particle size on tablet strength of metronidazole matrix tablet compacted at compression pressure 4.42×10^5 N/m². Each tablet weighs 500 mg. Tablet diameter was 12 mm.

Gum Particle Size (µm).	Batch	Average wt (mg)	Average thickness (cm)	Average crushing force (N)	Radial tensile strength x 10 ⁵ (N/m ²)	Friability (%)
>90-125	1	500	0.418	113	14.3	0.9
>125-150	1	500	0.424	91	11.3	0.9
>150-250	1	500	0.430	60	7.1	0.8
>250-500	1	500	0.427	50	6.2	1.2
>90-500	1	500	0.420	120	15.2	0.36

Batches 1 contain 40% model drug and 60 %gums. There was no compaction at 3.5×10^5 N/m² (compression force 40 N) for all batches of metronidazole matrix powder by direct compression.

Appendix 6. Compaction Characteristics of Chloroquine Phosphate Matrix and Metronidazole Matrix Granules Both Compacted at Compression Pressure $3.5 \times 10^5 \text{ N/m}^2$ (Compression Force 40 N). Weight of each Tablet is 505 mg

Batch	Gum (%)	Average Tablet Thickness n=3 (cm)	Average crushing force n=3 (N)	Radial Tensile Strength $\times 10^5$ (N/m^2)	Friability (%)	Mean weight and standard deviation n=20 (mg)	Content of dosage n=1 (mg)
1	60	a)0.418 0.415 ^R b)0.414	125 125 ^R 135	15.2 15.9 ^R 17.3	0.65 0.50 ^R 0.00	504.5 \pm 1.0 504.6 \pm 1.2 504.3 \pm 1.3	193 (96.5%) 195 (97.5%) 190 (95.0%)
2	50	a)0.414 0.410 ^R b)0.408	150 152 ^R 145	19.4 19.7 ^R 18.9	0.64 0.60 ^R 0.65	504.6 \pm 2.5 504.3 \pm 2.8 503.7 \pm 2.3	201 (100.5%) 198 (99.0%) 198 (99.0%)
3	40	a)0.405 0.404 ^R b)0.407	145 145 ^R 130	19.0 19.1 ^R 17.0	0.65 0.50 ^R 0.65	503.9 \pm 0.5 503.5 \pm 0.8 503.7 \pm 1.6	189 (94.5%) 192 (96.0%) 196 (98.0%)
4	30	a)0.402 0.400 ^R b)0.402	140 145 ^R 120	18.5 19.2 ^R 15.8	0.66 0.60 ^R 1.25	503.2 \pm 0.5 504.5 \pm 1.2 504.7 \pm 1.7	191 (95.5%) 192 (96.0%) 197 (98.5%)
5	20	a)0.402 0.401 ^R b)0.410	130 133 ^R 100	17.0 17.6 ^R 12.9	0.65 0.70 ^R 1.28	501.0 \pm 0.2 503.2 \pm 0.8 503.7 \pm 2.3	189 (94.5%) 193 (96.5%) 196 (98.0%)
6	10	a)0.405 0.403 ^R b)0.481	128 130 ^R 70	16.0 17.1 ^R 7.7	0.71 0.70 ^R 1.31	501.0 \pm 0.8 502.5 \pm 1.8 502.0 \pm 1.0	193(96.5%) 194 (97.0%) 201 (100.5%)

NB. The values designated by “a” and “ b “ represent, values for chloroquine phosphate and metronidazole matrix compact respectively. While the values with the superscript“R “ represent the values for the Standard sigmal acacia gum- chloroquine matrix compact.

