SURFACE ACTIVITY AND RELEASE PROPERTIES OF SOME TROPICAL GUMS IN ARTEMETHER AND ARTESUNATE SODIUM TABLET FORMULATIONS

BY

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**DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY
FACULTY OF PHARMACEUTICAL SCIENCES
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MAY, 2015.

DECLARATION

I hereby declare that the work in this dissertation titled, "Surface activity and release properties of some tropical gums in artemether and artesunate sodium tablet formulations" was performed by me in the Department of Pharmaceutics and Pharmaceutical Microbiology, A.B.U. Zaria; under the supervision of Dr. P.G. Bhatia, Dr. B.A. Tytler, and Prof. M.U. Adikwu.

The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this work has been presented for any other degree or diploma in any institution.

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CERTIFICATION

This dissertation titled "Surface activity and release properties of some tropical gums in artemether and artesunate sodium tablet formulations" meets the regulation governing the award of the degree of Doctor of Philosophy of the Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

This work is dedicated to the Almighty God who gave me the endowment to carry out the work, created the tropical plants from which the gums were extracted and also created the plant *Artemisia annua* - the source of artemisinin from which artemether and artesunate were derived.

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ABSTRACT

Plant gums are natural polymers with low toxicity, high biodegradability and high compatibility with drugs making them useful as pharmaceutical excipients in solid, semi-solid and liquid formulations. This work was aimed at evaluating the surface activity and release properties of some tropical gums in artemether and artesunate sodium tablet formulations. Cashew gum (CSG) was extracted from stem bark exudates of *Anacardium occidentale L.,* khaya gum (KYG) was extracted from stem bark exudates of *Khaya senegalensis*, afzelia gum (AFG) was extracted from seeds of *Afzelia africana* while prosopis gum (PRG) was extracted from seeds of *Prosopis africana*. Acacia gum B.P (ACG) and sodium carboxymethylcellulose (SCMC) were used as standards. The gums were evaluated for their physical, chemical and thermal properties. The surface activity was studied by determining surface tension at low concentrations (0.1 to 1.0 % w/v) of gum dispersions and by determination of critical micelle concentration in respect of each gum. The hydrophile-lipophile-balance (HLB) values of the gums were also determined. Cashew gum and prosopis gum were evaluated for their release properties. Artemether and artesunate sodium tablets containing varying concentrations of the gums (1.0 – 4.0 % $^{w}/_{w}$) and those containing 3 % $^{w}/_{w}$ of ACG were formulated. Tablets containing 2 % $^{w}/_{w}$ of gum with 2 or 4 % $^{w}/_{w}$ chitosan as permeation enhancer were also formulated. The effect of the gums on the release and permeation of artemether and artesunate sodium in the presence of simulated gastric fluid and simulated intestinal fluid was determined using pig intestine as biological membrane. The yields of the gums from the different sources were: CSG (48.0% w/w), KYG (25.0% w/w), AFG (17.0% w/w) and PRG (18.2% w/w). The Hausner's ratio of the gums showed ranking of flow as ACG > KYG > CSG > AFG = PRG > SCMC. The

polymers showed comparable and moderate surface activity but different critical micelle concentrations in the order SCMC < PRG = AFG = ACG < CSG < KYG. The solubility of the gums in water was in the order CSG > ACG > KYG > SCMC > AFG > PRG. Solubility of AFG, PRG and SCMC increased significantly in 1 % $^{w}/_{v}$ solution of sodium hydroxide. The hydration and swelling capacities followed the same trend of SCMC > PRG > AFG > KYG > CSG > ACG. Cashew gum, khaya gum and acacia gum had significantly lower partition coefficient and higher HLB values while afzelia and prosopis gums had significantly higher partition coefficient and lower HLB values. Compatibility studies of CSG and PRG with artemether and artesunate sodium revealed that no new compound was formed. Artemether and artesunate sodium tablets containing cashew gum were characterized by lower crushing strength, lower friability and better release properties compared to those containing corresponding concentrations of prosopis gum. Prosopis gum showed better permeation enhancing effect on both artemether and artesunate sodium; but high concentrations of the gum were associated with poor release. Cashew gum, which is characterized by higher HLB value, can be used as a binder over a relatively wide range of concentrations to achieve a good drug release though with minimal permeation enhancement. Prosopis gum, which is characterized by lower HLB value, is capable of exerting good permeation enhancing effect on both water-soluble and poorly water-soluble drugs but must be used at low concentrations. Therefore, the suitability of gums as binders for ensuring good drug release and good permeation depends on the surface activity of the gum and the inherent properties of the drug to be formulated.

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ABBREVIATIONS

AAS	=	Atomic absorption spectrophotometry
ACG	=	Acacia gum B.P
ACG3	=	Tablets containing 3 % w/w acacia gum
AFG	=	Afzelia gum
ATM	=	Artemether
ATS	=	Artesunate sodium
BCS	=	Biopharmaceutics Classification System
CMC	=	Critical micelle concentration
CS	=	Crushing strength
CSG	=	Cashew gum
CSG1	=	Tablets containing 1 % w/w cashew gum
CSG2	=	Tablets containing 2 % w/w cashew gum
CSG2 - C2	=	Tablets containing 2 % w/w cashew gum with 2 % w/w chitosan
CSG2 - C4	=	Tablets containing 2 % w/w cashew gum with 4 % w/w chitosan
CSG3	=	Tablets containing 3 % w/w cashew gum
CSG4	=	Tablets containing 4 % w/w cashew gum
ct	=	Counts
DSC	=	Differential scanning calorimetry
$D_{30\ min}$	=	Percent drug permeated in 30 minutes
dQ	=	Change in drug permeate
DT	=	Disintegration time
dt	=	Change in time
FR	=	Friability

FTIR	=	Fourier transform infrared spectrophotometry
HLB	=	Hydrophile-lipophile balance
J	=	Steady state flow or drug flux
K	=	Partition coefficient
KYG	=	Khaya gum
K_p	=	Permeation coefficient
PI	=	Phenol index
PRG	=	Prosopis gum
PRG1	=	Tablets containing 1 % w/w prosopis gum
PRG2	=	Tablets containing 2 % w/w prosopis gum
PRG3	=	Tablets containing 3 % w/w prosopis gum
PRG4	=	Tablets containing 4 % w/w prosopis gum
PRG2 - C2	=	Tablets containing 2 % w/w prosopis gum with 2 % w/w chitosan
PRG2 - C4	=	Tablets containing 2 % w/w prosopis gum with 4 % w/w chitosan
rpm	=	revolutions per minute
SCMC	=	Sodium carboxymethylcellulose
SGF	=	Simulated gastric fluid
SIF	=	Simulated intestinal fluid
$t_{95\ \%}$	=	Time for 95 % drug permeation
t_L	=	Lag time
XRD	=	X-ray diffraction
$^0 2\Theta$	=	Degree 2Theta.

CHAPTER 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

Gums are natural polymers with low toxicity, high stability, high biodegradability and high compatibility with drugs which make them useful as pharmaceutical excipients (Mahmud, 2009). Their chemical nature is complex, but generally, they contain carbon, hydrogen and oxygen. They may also contain calcium, magnesium and potassium in the form of salts (Bleton *et al.,* 1996*).*

Tropical plants producing gum include *Acacia senegal, Anacardium occidentale L., Khaya senegalensis, Albizia zygia, Grewia occidentalis, Afzelia africana, Prosopis africana, and* numerous others. Plant families notable for gum production are *Anacardiaceae, Fabaceae, Combretaceae, Meliaceae, Rosaceae* and *Rutaceae* (Ofori-Kwakye *et al.*, 2010)*.*

Gums of natural origin are used for various purposes in pharmaceutical formulations. In tableting, they are used as binders for conventional tablets or as matrices for sustained release dosage forms (Ibezim *et al.*, 2006). In liquid dosage forms, they are used as suspending agents, emulsifying agents and solubilizing agents (Mahmud, 2009).

Surface science has opened up a new branch of chemistry called ‘‘Surface Chemistry’’. It is the study of the boundary between two phases. If one of the phases is a gas, the boundary is called a surface; if no gaseous phase is involved, it is called an interface. The contraction of a surface is termed surface tension. Surface and interfacial

phenomena can be understood as the net attractive force experienced by the surface molecules of a single component liquid towards the bulk of the liquid. The resultant inward attraction reduces the number of molecules at the surface and increases the intermolecular distance giving rise to surface tension and surface free energy (Fell, 2007).

Surface tension is the force acting parallel to the surface at right angle to a line of 1 m length anywhere in the surface and is measured in Nm^{-1}. Surface free energy is defined as the work required to increase the surface area by 1 m^2. Its unit is Jm^{-2}. Surface tension and surface free energy are dimensionally and numerically equivalent (Fell, 2007).

Amphiphiles, because of their chemical structure, have a tendency to accumulate at the boundary between two phases. They are also called surface active agents or surfactants, and are characterized by having two distinct regions, termed hydrophilic and hydrophobic regions. Surfactants are generally classified according to the nature of the hydrophilic group which can be anionic, cationic or non-ionic. As such, there are three classes of surfactants which are: anionic surfactants, cationic surfactant and non-ionic surfactants (Attwood, 2007).

The adsorption of surfactants at various interfaces results in changes in the nature of the interface making them useful for pharmaceutical formulations. They are used as emulsifying agents, wetting agents, solubilizing agents and absorption enhancers. Their adsorption at interfaces sometimes results in adhesion of one surface on the other. If either or both surfaces are of biological nature, the term "bioadhesion" is used.

Bioadhesion is a state in which two materials, at least one of which is of a biological nature are held together for an extended period of time by interfacial forces (Adikwu *et al*., 2005). For drug delivery purposes, bioadhesion refers to the attachment of drug carrier system to a biological surface. This often results in increasing drug absorption (Mortazavi and Smart, 1994).

Every surfactant has a hydrophile - lipophile balance (HLB) value which is characteristic of its relative polarity and ranges from 0 to 20. The lower the HLB value, the more hydrophobic the surfactant is; and the higher the value, the more hydrophilic is the surfactant. HLB values are used for classifying surfactants into water-in-oil emulsifiers, wetting agents, oil-in-water emulsifiers, foaming agents and solubilizing agents in order of increasing HLB values.

Drug delivery encompasses the approach, formulation, technology and system involved in transporting a drug into the body. Therefore, it includes formulation of the drug into appropriate dosage form, the release of the drug from the dosage form, its absorption and transportation to the site of action (Ashford, 2007a and Ashford, 2007b).

A tablet is solid dosage form containing the active pharmaceutical agent and excipients held together by a binding agent. There are different types of tablets meant for different applications. Examples are oral tablets, sublingual tablets, pessaries, *et cetera*. A conventional oral tablet is expected to undergo disintegration and dissolution in the stomach (Rudnic and Schwartz, 2006). Dissolution is accompanied by absorption through the gastrointestinal epithelium and then transportation to the site of action.

Internal tissues like intestines from mammals are used for permeation/absorption studies (Adikwu *et al.,* 2005). Excised skins from rats, mice, guinea pigs, rabbits, pigs and monkeys are also used as biological membranes in place of human skin during experiments. These mammalian skins vary widely in stratum cornea. Thus, it is best to obtain human skin from autopsies, amputations or cosmetic surgery (Barry, 2007).

Certain substances known as membrane permeability enhancers are capable of temporarily enhancing the permeability of membranes. According to Barry (2007), the attributes of an ideal permeation enhancer are as follows:

- It should be non-toxic, non-irritating and non-allergenic.
- It should be pharmacologically inert.
- It should be compatible with all drugs and excipients.
- The action should be immediate and the effect should be suitable and predictable.
- The membrane should immediately and fully recover its barrier property upon removal.
- It should not cause loss of body fluid, electrolytes or other endogenous materials.
- It should be a good solvent for drugs.
- It should be odourless, tasteless, colourless, and inexpensive.

No single material possesses all these desirable properties. Many substances exhibit several of these attributes. Examples of such substances are:

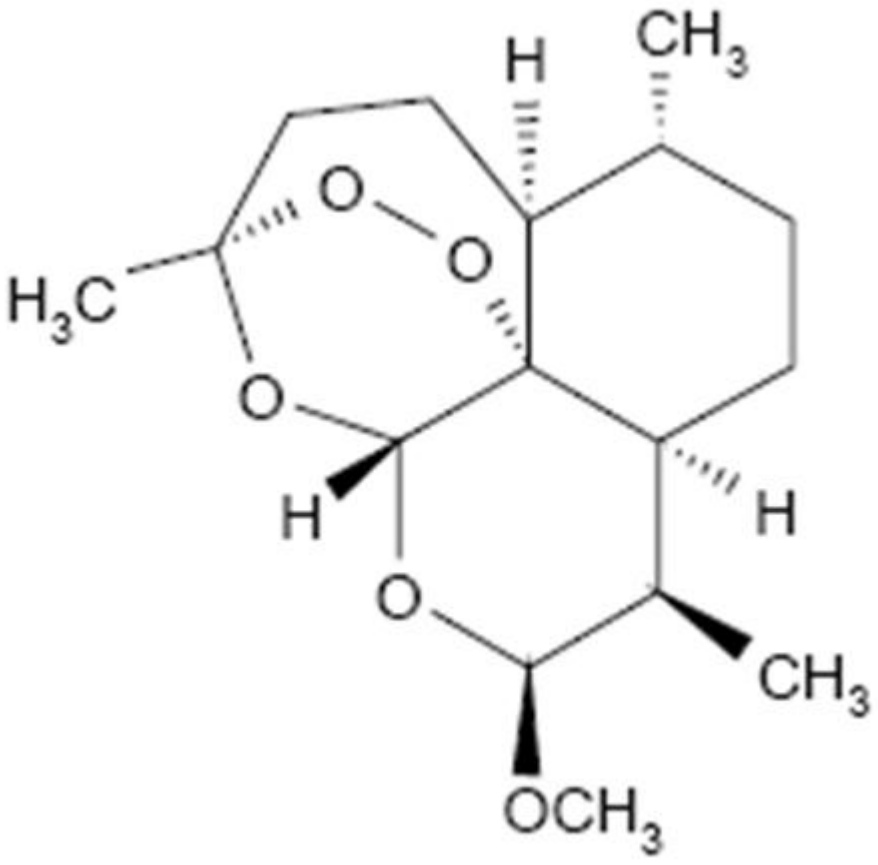
- Water
- Sulfoxides especially dimethyl sulphoxide and their analogues
- Pyrrolidones
- Fatty acids and alcohols

- Azone and its derivatives
- Surfactants: anionic, cationic and non-ionic
- Urea and its derivatives
- Alcohols and glycols
- Essential oils, terpenes and their derivatives
- Chitosan (co-polymer polysaccharide of β-1,4-linked D-glucosamine and N-acetyl-D-glucosamine units)

1.2 ARTEMETHER AND ARTESUNATE SODIUM

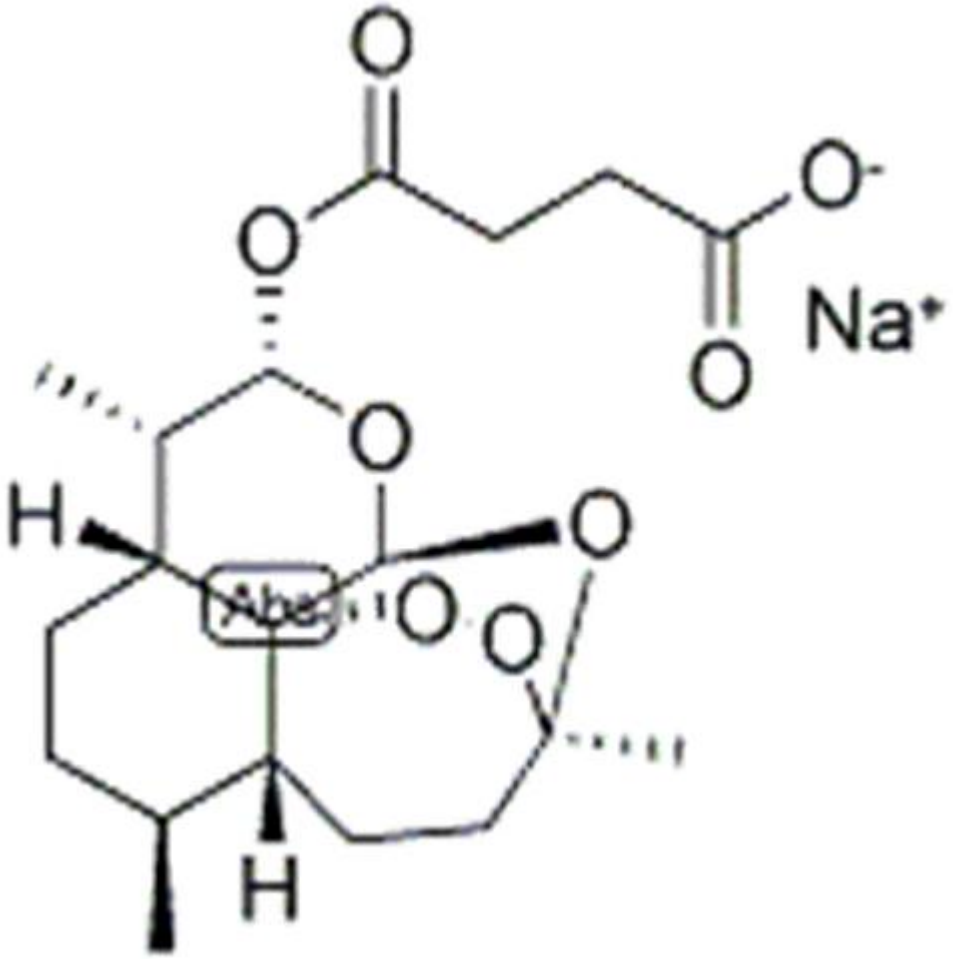
Artemether and artesunate sodium belong to the antimalarial chemical group - artemisinins. Artemisinin (*quinghaosu*) is a sesquiterpene lactone endoperoxide, the active component of an herbal medicine that has been used as an antipyretic in China for over 2000 years. Artemisinin is insoluble and can only be used orally. Analogs have been synthesized to increase solubility and to improve antimalarial efficacy. The most important of these analogs are the water-soluble artesunate sodium which is useful for oral, intravenous, intramuscular, and rectal administration; and the lipid-soluble artemether which is useful for oral, intramuscular and rectal administration (Rosenthal, 2004). The chemical structures of artemether and artesunate sodium are shown in Figure 1.1 and Figure 1.2 respectively.

Artemisinin and its analogs are rapidly absorbed, with peak plasma levels of 1 -2 hours and half-lives of 1 -3 hours after oral administration. These compounds are rapidly metabolized to the active metabolite – dihydroartemisinin and drug levels appear to decrease after a number of days of therapy (Rosenthal, 2004).



(Adapted from Pagay and Matecka, 2009)

Figure 1.1 Chemical Structure of Artemether



(Adapted from Patrick, 2013)

Figure 1.2 Chemical Structure of Artesunate Sodium

Artemisinin and analogs are very rapidly acting blood schizonticides against all human malarial parasites. They have no effect on the hepatic stages of the parasite. The antimalarial activity probably results from the production of free radicals that follows the iron-catalyzed cleavage of the artemisinin endoperoxide bridge in the parasite food vacuole.

Artemisinins, in particular artesunate sodium and artemether, are popular agents for the treatment of multidrug-resistant *P. falciparum* malaria. They are the only antimalarials reliably effective against quinine-resistant strains. In a number of studies of severe malaria, artemether and artesunate were about as effective as quinine, though mortality from severe malaria remains high (Rosenthal, 2004).

The efficacy of the artemisinins is limited somewhat by their short plasma half-lives. Recrudescence rates are high after short-course or even 7 days of therapy; and these drugs are generally best used in conjunction with another agent like lumefanthrine, pyrimethamine-sulphadoxine or amodiaquine. Also because of their short-half lives, they are not useful in chemoprophylaxis.

Artemether is a white crystalline powder that is freely soluble in acetone, quite soluble in methanol and ethanol and insoluble in water (International Pharmacopoeia, 2006). Artesunate sodium is a fine white crystalline powder slightly soluble in water, soluble in dichloromethane and freely soluble in ethanol and acetone (USP Medicines Compendium, 2013). Artemether is lipophilic while artesunate sodium is hydrophilic.

1.3 STATEMENT OF RESEARCH PROBLEM

The possible mechanisms by which surface active agents can influence drug delivery are varied and it is likely that only rarely will a single mechanism operate in isolation. Their effect on drug delivery depends on the nature of the drug especially its water solubility (Ashford, 2007b).

The release of poorly soluble drugs from tablets and capsules may be facilitated by inclusion of surfactants in their formulations. This is on account of the ability of the surfactant to reduce the solid/liquid interfacial tension and permit the gastrointestinal fluid to wet the drug. Surfactant monomers can potentially disrupt the integrity and function of biological membranes. This effect enhances drug penetration through gastrointestinal barrier.

Inhibition of absorption may occur if a drug gets incorporated into surfactant micelles. In most cases, these micelles are not absorbed resulting in a reduction in the concentration of free drugs in solution in the gastrointestinal fluid that is available for absorption. For poorly soluble drugs whose absorption is dissolution-rate limited, increase in saturation solubility by solubilization in surfactant micelles is likely to enhance dissolution and absorption.

Surfactants cannot be assumed to be inert excipients as they are capable of increasing or decreasing the rate and extent of transfer of drugs across biological membranes depending on which of the different actions is the over-riding one (Ashford, 2007b). From literature, the surface activity of cashew gum, khaya gum, afzelia gum and prosopis gum and their effect on the delivery of drugs from tablets are unknown.

1.4 JUSTIFICATION OF THE STUDY

Gums are widely used in pharmaceutical formulations (Ibezim *et al.,* 2006). They are used in solid, liquid and semi-solid dosage forms partly because of their binding properties and partly because of their surface activity (Abdulsamad *et al*., 2006; Odeku, 2005).

Gums can be obtained from some tropical plants found in Nigeria. They can be found as exudates from such plants as *Khaya senegalensis, Acacia senegal, Anacardium occidentale L.,* and from seeds like *Prosopis africana* and *Afzelia africana.* To obviate some of the problems associated with importation of purified gum to Nigeria, local gums derived from these tropical plants have been evaluated for pharmaceutical use as binders, matrices, suspending agents, emulsifying agents and solubilizing agents (Abdulsamad *et al.,* 2006; Odeku, 2005). The surface activity of these local gums and their effect on drug release from tablets has not been studied.

It is well known that the effect of surfactants on drug release and permeation depends on the nature of the drug (Ashford, 2007b). Artemether is a water-insoluble drug while artesunate sodium is a slightly water-soluble drug.

Malaria is prevalent in the tropical region where Nigeria is located. This is as a result of the significant amount of rainfall, consistently high temperature and high humidity along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding (Prothero, 1999). This factor, coupled with the World Health Organization's recommendation of artemisinin-based

combination therapy for malaria is responsible for the wide use of the artemisinins in the tropics.

The strength of the tropical gums as surfactants will be evaluated by determination of their surface tension and HLB values and subsequently their effect on the release and permeation of artemether and artesunate sodium will be studied.

1.5 HYPOTHESES

1.5.1 Null Hypothesis

Cashew, khaya, afzelia and prosopis gums do not possess surface activity and have no effect on the release of drugs from their tablet formulations.

1.5.2 Alternate Hypothesis

Cashew, khaya, afzelia and prosopis gums possess surface activity and are capable of affecting the release of drugs from their tablet formulations.

1.6 AIM AND OBJECTIVES

1.6.1 Aim

The aim of this study is to evaluate the surface activity of two exudate and two seed gums; and the effect of two of the gums with different HLB values on the release of artemether and artesunate sodium from their tablet formulations.

1.6.2 Objectives

(i) To extract and purify cashew, khaya, afzelia and prosopis gums.

(ii) To determine the physicochemical properties of the gums including their surface activity and HLB values.

(iii) To evaluate the compatibility of artemether and artesunate sodium with two gums with different HLB values.

(iv) To formulate polymer-based tablets of artemether and artesunate sodium with the two gums.

(v) To determine the quality of the tablet formulations.

(vi) To study the effect of the two gums on the release of artemether and artesunate sodium from their tablet formulations.

CHAPTER 2

LITERATURE REVIEW

2.1 PROPERTIES OF GUM

Gums are colloidal substances that are similar in appearance. They are generally non-crystalline in nature, and are water-soluble or water-dispersible hydrophilic compounds which are insoluble in alcohol and organic solvents. They are characterized by low-toxicity and high biodegradability and are compatible with many drugs (Mahmud, 2009). They are high molecular weight polysaccharides which are formed from sugars and uronic acid units. They may also contain potassium, sodium, calcium and magnesium salts (Ofori-Kwakye *et al*., 2010).

2.2 CLASSIFICATION OF GUMS

Gums are classified as natural gums, semi-synthetic gums and synthetic gums. This classification is based on their sources and mode of production (Ofori-Kwakye *et al*., 2010).

2.2.1 Natural Gums

These are gums that are obtained from living organisms (plants, animals and micro-organisms). They are formed by natural processes. The major limitation to their use as pharmaceutical excipient is their high susceptibility to microbial attack (Billany, 2007).

2.2.2 Semi-synthetic or Modified Gums

These are produced by chemical modification of natural gums. Cashew gum has been modified by carboxy - methylation using monochloroacetic acid as etherifying agent

(Maciel *et al.,* 2005). Cellulose derivatives can be made by etherification, esterification, cross-linking or graft copolymerization. Etherification yields derivatives such as hydroxypropylmethylcellulose and carboxymethylcellulose, while esterification results in derivatives which include cellulose nitrate, cellulose acetate and cellulose acetate phthalate (Ogaji *et al.*, 2012).

2.2.3 Synthetic Gums

These are chemically produced gums. Polyvinyl pyrrolidone is a typical example. They can be used at low concentrations and are less susceptible to microbial attack (Billany, 2007).

2.3 SOURCES OF NATURAL GUMS

2.3.1 Plants of Interest

A wide variety of plants are known for gum production. The gums are produced either as exudates, seed gums, seaweed gums or as pectin.

(a) Exudates

Exudates are produced by a process called "gummosis". Gummosis is the formation of patches of gluey substances on the surface of certain plant barks. It occurs as a result of wound inflicted on the plant by external stimuli, adverse weather conditions, microbial attack, insect attack or other mechanical damages. Subsequently, sap exudes from the wound as sticky substance which on exposure to air, solidifies to form amorphous translucent solids called gum (Mahmud, 2009).

Gum - producing trees do not exude gum when accidentally scorched by fire, probably due to the destruction of *Bacterium acacia* and enzymes. However, if re-infection occurs, gum is produced, implying that bacteria play a major role in gum formation (Mahmud, 2009). Some examples of plants that produce gum as exudates are acacia, cashew and khaya.

(b) Seed gums

These are extracted from seeds. Prosopis and Afzelia are examples of plants with gum-yielding seeds.

(c) Seaweed gums

These are gums that are extracted from seaweed. Examples are alginates and agar. Alginates are natural polysaccharide polymers isolated from the brown sea weed (*Phaeophyceae*). Alginic acid can be converted into its salts, of which sodium alginate is the commonest one in use. They are linear polymers consisting of D-mannuronic acid and L-glucuronic acid residues arranged in blocks in the polymer chain. They offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the biomolecules in tissue engineering applications.

Gum agar is extracted from the red-purple marine algae of the class *Rhodophyceae*. The species include *Gelidium cartilagineum* and *Gracilaria confervoides* which grow abundantly in the waters along the coast of Japan, New Zealand, South Africa, Southern California, Mexico, Chile, Morocco, and Portugal (Ogaji *et al*., 2012).

(d) Pectin

These are polysaccharides that are extracted from citrus fruits. They are predominantly linear polymers of mainly (1–4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues with a few hundreds to about one thousand building blocks per molecule (Ogaji *et al*., 2012).

2.3.1.1 Acacia senegal

The word acacia was derived from the Greek word "Akakia' referring to the pointed or spiny nature of the plant. The best quality gum is produced in Kordofan, Sudan but some Senegal and Nigerian gums are also of good quality (Mahmud, 2009). *Acacia senegal* gum is synonymous with gum Arabic, acacia gummi and gum Senegal while Acacia gum refers to all gummy exudates obtained from stems and branches of various species of Acacia (Family : *Fabaceae).*

Geographical distribution

Acacia tree is indigenous to Africa and several species have been grown in different parts of the continent. *A. senegal* and *A. seyal* are cultivated in Senegal, *A. gummifera* is found in Morocco while *A. mearnsii, A. laeta* and *A. sieberiana* are found in Nigeria (Grieve, 2006)

Plant description

All the gum-yielding Acacia trees exhibit the same habit and general appearance with technical characters being the only difference. They are thorny trees with average height of about 6 m. The trees have compound leaves with small leaflets, small white to cream coloured flowers and thin woody pods. The trees have grayish to white coloured bark.

The plant grows best in sandy or sterile regions where climatic condition is usually dry during most part of the year. About the middle of November, shortly after the rains, the gum exudes spontaneously from the trunk and principal branches, stimulated by 60 - 90 cm x 2.5 to 7.5 cm incisions in the bark of the plant. In about 15 days, it thickens and hardens on exposure to air forming amorphous translucent solids. Harvest of the gums from the various species lasts for about 5 weeks. The older trees produce better quality gums than the younger ones (Mahmud, 2009).

Gum description

Gum acacia occurs in round tears of various sizes. It is usually broken into angular fragments of glass-like fractures. It is often opaque, but transparent and almost colourless when in thin fragments. The gum is colourless to pale yellow to reddish brown. The colourless to yellow gum is of superior quality compared to the reddish brown type. It is almost insipid in taste, mucilaginous and nearly odourless. It is soluble in 50 % aqueous alcohol, acidic to litmus when dissolved in two parts of water, and gives negative result to starch and dextrin tests (Grieve, 2006).

Chemical constituents

Acacia gum consists principally of arabin, a compound of arabic acid containing a complex mixture of calcium, magnesium and potassium salts in varying amounts. *L-arabinose, L-rhamnose, D-galactose* and *D-glucuronic* acid are produced on acid hydrolysis of arabin. The backbone chain of the molecule is made up of 1,3-linked *D*-galactopyranose units while the terminal residues are mainly uronic acids. Acacia gum has a molecular weight of about 200,000 to 600,000 (Leung and Foster, 1980).

The gum contains about 12 to 17 % of moisture. It yields a total ash of 2.7 to 4 % consisting of calcium, magnesium and potassium carbonates. A small percentage of nitrogen (0.2 – 0.7 %) that does not form part of the gum molecule is also present (Frimpong-Mensah, 2000). This perhaps is because the gum is not completely free of enzymes.

2.3.1.2 Anacardium occidentale L.

Cashew, *Anacardium occidentale L.* belongs to the family *Anacardiaceae*. It is called 'Kaju' in Yoruba and 'Kashu' in Hausa, Igbo and Ibibio (Udoh *et al.*, 2005).

Geographical distribution

Cashew is native to Brazil and grows in many tropical and sub-tropical countries. India tops as the best producer, followed by Mozambique and Tanzania. Other producers are Nigeria and Ghana. It can grow on soils that are considered too poor or stony for other crops but it prefers a well drained sandy-loamy soil. The tree tolerates a wide range of soil acidity (Udoh *et al.*, 2005 and Ofori-Kwakye *et al.*, 2010).

Plant morphology

It is a perennial, evergreen spreading tree which may grow to the height of 13 m. It has a typical well-developed taproot system. It has simple, alternate leaves which may be leathery and glabrous. The plant has a terminal panicle with many flowers which may be male, female or hermaphrodite. The single ovary is locular. The fruit is kidney-shaped not covered with hard pericarp and embedded in an enlarged pedicel receptacle swollen with juice (cashew apple). The apple is shiny, red or yellow, pear-shaped, soft and juicy (Udoh *et al.*, 2005).

Gum description

Cashew gum is light to dark brown in colour. It has a pH range of 3.80 to 5.22 depending on the source and duration of storage. The unpurified gum is more stable compared to the purified form. Whether purified or unpurified, the pH increases on storage at room temperature and the instability increases with temperature. (Ofori-Kwakye *et al.*, 2010).

Chemical composition

Cashew gum contains 9.8 -13.2 % moisture, 1.9 – 4.8 % insoluble matter, 0.5 – 1.2 % total ash, 1.27 – 1.80 % protein, 9.6 – 21.0 % sugar and 0.21 – 2.26 % phenol (Gyedu-Akolo *et al.*, 2008). In terms of sugar composition, it is made up of 61 % galactose, 14 % arabinose, 7 % rhamnose, 8 % glucose, 5 % glucuronic acid and < 2 % other sugar residues. The gum has a highly branched galactan framework comprising chains of 1, 3 linked β-D-galactopyranosyl units interspersed with β-1, 6-linkages (Lima *et al.*, 2002).

2.3.1.3 Khaya senegalensis

Khaya senegalensis commonly called African mahogany in English, 'Homra' in Arabic, 'Dalehi' in Fulani, 'Madaci' in Hausa, 'Ono' in Igbo and 'Ogonwo' in Yoruba, belongs to the Family *Meliaceae.*

Geographical distribution

The plant is widely distributed in the rain forests and also scattered within the high rainfall savannah regions. In the first year of growth, the seedlings develop a strong deep tap root which makes it most drought resistant of all Khaya species. The plant can

be grown in swampy regions as it is very resistant to flooding. It remains the dominant specie in most of its range except when removed by logging (Mahmud, 2009).

Plant description

Khaya senegalensis is a plant of 15 – 30 m height and about 1 m diameter. It is recognized by its evergreen crown. The crown has dark shiny pinnate leaves and characteristic round dark grey capsules. The bark is dark grey with small reddish tinged scales.

Gum description

Khaya gum occurs in long, thin glass-like translucent fragments. The gum is colourless to light brown. The mucilage has an acidic pH of 4.2. It is insoluble in ethanol and acetone and only slightly soluble in water (Mahmud *et al.,* 2008).

Chemical constituents

Khaya gum is a polysaccharide with a galactan core in which the 1, 3-linked β-D-galactopyranosyl residues are concentrated in the inner chains. According to Edmund (1976), methylation of the gum revealed many similarities to acacia gum. The gum has been reported to contain both D-glucuronic and D-galacturonic acids. Analysis of the gum showed that approximately 50 % of the acid was in the free form while the remainder was largely as the calcium salt (Aslam *et al.,* 2006).

2.3.1.4 Afzelia africana

It is a tree belonging to the subdivision *Caesalpiniodea,* Family *Fabaceae.* It is known as 'akparata' in Igbo. *Afzelia africana* is widely distributed in the Eastern part of Nigeria,

where the seed is commonly used as a soup ingredient and as a beverage thickener (Builders *et al*., 2009).

Geographical distribution

This large tree is found growing wild in the dense evergreen forests, savannah and the coastal forests of East and West Africa (Ren *et al.,* 2005).

Plant description

It is a perennial tree growing up to a height of 10 - 20 m. The fruit is a hard shell containing 6 - 10 black seeds with an orange-coloured aril.

Gum description

Afzelia gum has been characterized as a xyloglucan (Ren *et al*., 2005). Xyloglucans are hemicelluloses or cell wall polysaccharides that are not soluble in water but can be solubilized by aqueous alkali. They are structurally related to cellulose. Afzelia gum shows close resemblance with guar gum, both being xyloglucans (Builders *et al*., 2009).

Gum composition

Afzelia gum consists of a cellulose backbone of β-glucopyranosyl residues, which are substituted at C-6. Gas liquid chromatography (GLC) of afzelia gum showed the presence of glucose, xylose, and galactose in the ratio 1.3 : 1 : 0.63 as the main monosaccharides. Small amounts of arabinose, mannose, and uronic acid were also shown to be present (Builders *et al.,* 2009).

2.3.1.5 Prosopis africana

Prosopis africana is a flowering plant in the pea family (*Fabaceae*). It is called ‘abu suruj’ in Arabic, ‘Kiriya’ in Hausa, ‘Okpei’ in Igbo, ‘Ayan’ in Yoruba and ‘Okpehe’ in Idoma (Ezike *et al.,* 2010).

Geographical distribution

It grows in Tropical America, Africa, Western and Southern Asia. It thrives in arid soil and is resistant to drought (Agboola, 2004). It is the only Prosopis specie occurring from Senegal to Ethiopia. It is native to Republic of Benin, Cameroun, Central Africa, Chad, Cote D’Ivoire, Egypt, Ethiopia, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Nigeria, Senegal, Sierra Leone, Sudan, Tanzania, Togo and Uganda. In Nigeria, it is found between latitude 7 ^{o}N and 10 ^{o}N (Agboola, 2004).

Plant description

It reaches 4 - 20 m height and has an open crown and slightly rounded buttress. The bark is dark, scaly, slash orange to red-brown with white streaks. It has a dropping foliate alternate bipinnate leaves reaching a length of 10 -15 cm with 3 – 6 pairs of opposite piannae and 9 -16 pairs of leaflets which are oblong-lanceolate. The flowers are greenish-white to yellow, fragrant, dense with 6 – 10 cm long axillary spikes. The wood is hard, dense and durable (Ezike *et al.,* 2010). The tree is a good source of firewood, the fruit is used as animal feed, while the seeds are used to make locust bean 'okpehe' - a highly proteinous condiment (Agboola, 2004).

Gum description

It is a light-brown fluffy gum, and possesses high bioadhesive strength, the value being commensurate with those of Carbopol 974-P and sodium carboxymethylcellulose (Adikwu *et al*., 2003).

Gum Composition

Prosopis gum is made up of highly branched polysaccharides with chain structure formed when monosaccharides condense with the elimination of water molecules. It is a natural polysaccharide consisting mainly of glucose, fructose, galactose and xylose as the monosaccharide units (Attama *et al*., 2000).

2.3.2 Animals

Gums derived from animal skin and bones are called gelatin. Unlike plant gums that are mostly non-ionic, gelatin has a net positive charge (Adikwu *et al.*, 2005)

2.3.3 Microbes

Microbial gums are produced by fermentation process. Xanthan gum, a complex microbial exopolysaccharide is produced from glucose fermentation by *Xanthomonas campestris*. The gum consists of *D-glucosyl*, *D-mannosyl*, and *D-glucuronyl* acid residues in a molar ratio of 2:2:1. It also contains *o-acetyl* and pyruvyl residues in variable proportions. Xanthan gum is an acidic polysaccharide gum of penta-saccharide subunits.

Gellan gum is an anionic microbial polysaccharide, secreted by *Sphingomonas elodea*, consisting of repeating tetrasaccharide units of glucose, glucuronic acid and rhamnose

residues in a 2:1:1 ratio. Pullulan is an extracellular homo-polysaccharide of glucose produced by many species of the fungus *Aureobasidium,* specifically *A. pullulans* (Ogaji *et al.,* 2012).

2.4 USES OF GUMS

2.4.1 Non-Pharmaceutical Uses of Gums

Gums have diverse industrial applications. They are used as stabilizers in soft drinks and citrus oil emulsion concentrates. They are used as thickeners in drinks and beverages (Builders *et al.,* 2009). They also have diverse applications as viscosifiers, emulsifiers and sweeteners in confectionary (Ogaji *et al.,* 2012). Acacia gum which varies from white to red in colour is used in making ink. It is also used as adhesives and fabric filling in textile industry (Mahmud, 2009).

2.4.2 Pharmaceutical Uses of Gums of Interest

Gums have found wide usage in Pharmacy due to their low cost, non-toxicity, biodegradability and several other appropriate physicochemical characteristics (Ofori-Kwakye *et al.,* 2010). They are widely applied in solid, semi-solid and liquid formulations (Ibezim *et al.,* 2006).

In solid formulations, they are used as binders in conventional tablets, and as matrices for modified-release tablets (Ibezim *et al*., 2006). In liquid dosage forms, they are useful for formulation of suspensions and emulsions. Here, they are used as suspending agents, emulsifying agents and solubilizing agents. In semi-solid formulations, they are used as emulsifying agents in creams. They are also used as gelling agents (Kumar *et al*., 2009).

A number of gums have been studied for various pharmaceutical usages. Gums which have been studied include acacia gum, cashew gum, khaya gum, afzelia gum and prosopis gum.

2.4.2.1 Acacia Gum

Researchers have focused on comparative studies of suspending and emulsifying abilities of different *Acacia species*, for example, comparative evaluation of suspending properties of gum obtained from two species of Acacia, namely, *A. senegal* and *A. sieberiana* (Mahmud, 2009). The two gums compared favourably in terms of producing suspensions with low sedimentation rate at high concentrations.

2.4.2.2 Cashew Gum

Cashew gum has been suggested for use as an agglutinant for capsules and pills in place of gum Arabic (Lima *et al*., 2002). Cashew gum utilized as a binder in paracetamol tablet formulations was reported to impart better mechanical properties to the tablets compared to povidone and gelatin (Okoye *et al*., 2009).

Cashew gum modified by carboxymethylation with monochloroaectic acid has been used to form polyelectrolyte complex with chitosan and employed as a controlled drug delivery system (Maciel *et al.,* 2005). It has also been evaluated as a gelling agent in an aceclofenac topical gel formulation. The gel containing 5 % $^{w}/_{w}$ cashew gum was found to be suitable for topical application (Kumar *et al*., 2009).

2.4.2.3 Khaya Gum

The binding properties of Khaya gum obtained from *Khaya senegalensis Juss* was studied by Mgbahurike and Igwilo (1991). It was observed that 3 % $^{w}/_{w}$ khaya gum had

binding property similar to that of 5 % $^{w}/_{w}$ acacia gum. The effect of method of preparation on the compression, mechanical and release properties of khaya gum matrices was studied by Odeku and Fell (2006). Direct compression and wet granulation methods were used in preparing the matrices. It was observed that wet granulation method produced better tablets in terms of mechanical and release properties.

Khaya gum had also been evaluated for suspending property by Mahmud (2009). Co-trimoxazole suspensions formulated with khaya gum had the highest sedimentation rate compared to *Acacia senegal* and *Acacia sieberiana* gums at 2 % $^{w}/_{w}$ gum concentration. Suspension containing 5 % $^{w}/_{w}$ khaya gum was more stable compared to suspension containing 2 % $^{w}/_{w}$ gum concentration.

2.4.2.4 Afzelia Gum

The seed gum was used for tablet formulation of 5-amino salicylic acid tablet using wet granulation method. The tablet showed better tablet properties when lactose was used as diluent than when microcrystalline cellulose was used. It was also observed that the tablet compared favourably in terms of mechanical and release properties with tablets containing acacia as binder. From the dissolution time studies, it was concluded that afzelia gum can be used as binder for conventional tablet and not as matrix for sustained release dosage form (Ibezim *et al*., 2006).

2.4.2.5 Prosopis Gum

The antidiabetic properties of prosopis gum alone and as a bioadhesive base for the delivery of metformin were evaluated by Adikwu *et al*. (2003). The gum showed moderate antidiabetic properties when used alone. The bioadhesive value of the gum

was commensurate with those of Carbopol 974-P and sodium carboxymethylcellulose (SCMC) and the release of the drug was higher from prosopis gum - based bioadhesive formulations than from those containing SCMC and Carbopol 974-P.

Prosopis gum extracted from *Prosopis africana* had also been investigated for bioadhesive delivery of theophylline. The bioadhesion of the gum dispersion was evaluated using bioadhesive granules and coated glass beads. The results showed that prosopis gum was highly bioadhesive compared to sodium carboxymethylcellulose and that it could be used to deliver theophylline in a bioadhesive dosage form (Attama *et al*., 2000).

The effect of cast films of bovine mucin and prosopis gum containing Cicatrin powder on wound healing was evaluated by Momoh *et al.* (2008). It was observed that both bovine mucin and the gum potentiated the wound healing effect of Cicatrin powder.

2.5 RHEOLOGY

Rheology is the study of changes in structure and flow of matter. It encompasses plasticity, elasticity and viscosity. Viscosity is the ability of a fluid substance to resist flow. Water is the most widely used solvent and vehicle but it is characterized by thinness and inability to hold insoluble particulates. With these shortcomings, it is expedient for formulators to modify it using viscosifiers such as gums (Mahmud, 2009).

2.5.1 Classification of Fluids

Fluids can be classified into Newtonian and Non-Newtonian systems based on their flow properties.

2.5.1.1 Newtonian fluids

Newtonian fluids are those fluids that obey Newton's law of flow. The law states that, the rate of flow (γ) is directly proportional to the applied stress (σ).

$$\gamma \ \alpha \ \sigma \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots..(1)$$

$$\gamma \ = \ \sigma/ \ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots.\ldots\ldots\ldots\ldots\ldots\ldots..\ldots(2)$$

$$= \ \sigma/\gamma \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots.\ldots\ldots\ldots\ldots\ldots\ldots..\ldots(3)$$

$\text{where} \ = \ \text{viscosity}$

An increase in the rate of shear has no effect on the viscosity of the fluid as it remains constant. A plot of shear stress (force per unit area required to effect flow) versus shear rate (γ) gives a straight line passing through the origin while the slope gives the viscosity. Examples of Newtonian fluids are water and thin motor oils (Marriot, 2007).

2.5.1.2 Non-Newtonian Fluids

A fluid material is said to be Non-Newtonian when the relationship between shear stress and shear rate is not a constant. In this system, when the shear rate is varied, the shear stress does not vary in the same proportion or even direction. This means that as shear rate increases, the viscosity of such fluid also changes (Mahmud, 2009). There are different types of non-Newtonian fluids characterized according to their flow behaviour. It has been postulated that the molecules of these fluids have different shapes and sizes which affect the flow pattern as they pass by one another. The force required to move these molecules is determined by their types of bond, shape and size.

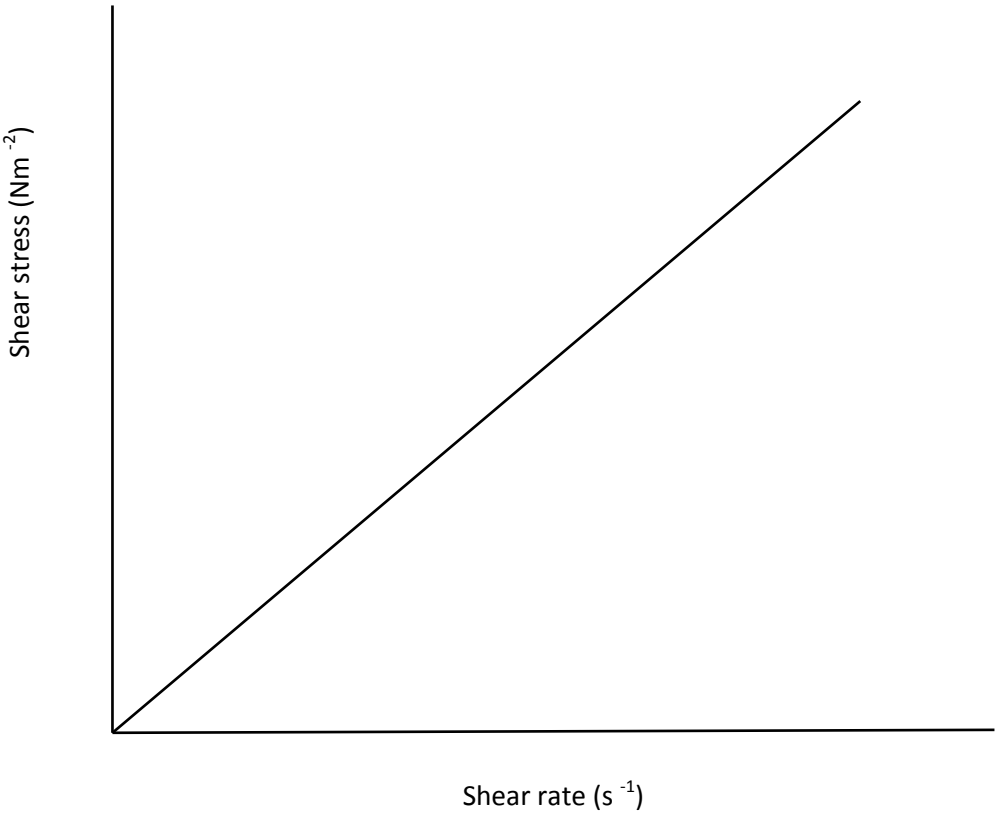


Figure 2.1 A plot of shear stress versus shear rate for Newtonian fluids

Non-Newtonian fluids are classified into:

(a) Pseudoplastic fluids

(b) Plastic fluids

(c) Dilatant fluids

(d) Thixotropic fluids

(a) Pseudo-plastic fluids

Pseudo-plastic fluids are also called 'shear-thinning" fluids. The rheogram starts from the origin and the material will flow as soon as shear stress is applied. However, when the straight line component of the rheogram is extrapolated, it intersects the shear stress axis at a point called the yield stress σ_y. The slope at each point equals the viscosity of the fluid at that shear rate (Marriot, 2007).

The structure of the molecules is temporarily changed, impacting less hindrance to the spindle as it rotates. The faster the rotation becomes, the more the structure is destroyed. The more the molecules slip and slide past one another, the lower the viscosity of the fluid material. Examples of pseudo-plastic fluids include a large number of pharmaceutical products such as natural and synthetic gums (dispersions of tragacanth, acacia, methylcellulose, polyvinyl pyrollidone *et cetera* in aqueous media), paints and emulsions (Mahmud, 2009).

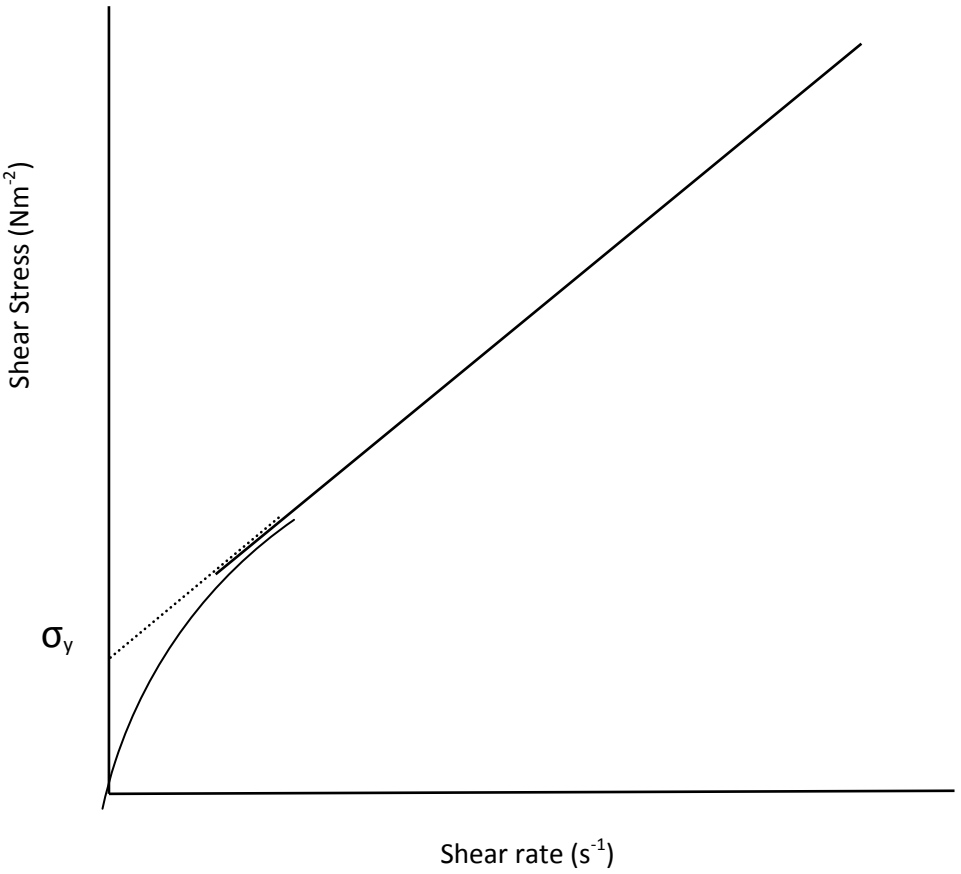


Figure 2.2 Rheogram of pseudo-plastic flow

(b) Plastic fluids

Plastic fluids behave as solids in static condition. Plastic flow exhibits a yield value, σ_y, before shearing can occur and as such the fluids are called Bingham bodies. In practice, flow occurs at a lower shear stress than σ_y and the flow curve gradually approaches the extrapolation of the linear portion of the line. Its curve does not pass through the origin but intersects the shearing stress axis. Plastic fluids require shaking or stroking before pouring due to the yield value. Tomato ketchup is an example of material that exhibits plastic flow. The flow is also exhibited by concentrated suspensions, particularly if the continuous phase is of high viscosity or if the particles are flocculated (Marriot, 2007).

(c) Dilatant fluids

In dilatant systems, viscosity increases as shear rate increases. This is also referred to as "shear thickening" behaviour. As the shear rate is increased, the particles become displaced from their uniform distribution and the clumps that are produced result in the creation of larger voids, into which liquid drains, so that the resistance to flow is increased and viscosity rises. When the material is highly sheared, it may solidify and on removal of stress, the fluid retains its original volume (Marriot, 2007).

Although rarer than pseudo-plastic and plastic flows, dilatants flow is frequently observed in fluids containing high levels of small, deflocculated solids (> 50 %). Examples of dilatant systems are clay slurries, corn starch in water and sand/water mixtures. Dilatancy can be a problem during processing of dispersions and granulation of tablet masses when high-speed mills and blenders are employed (Marriot, 2007).

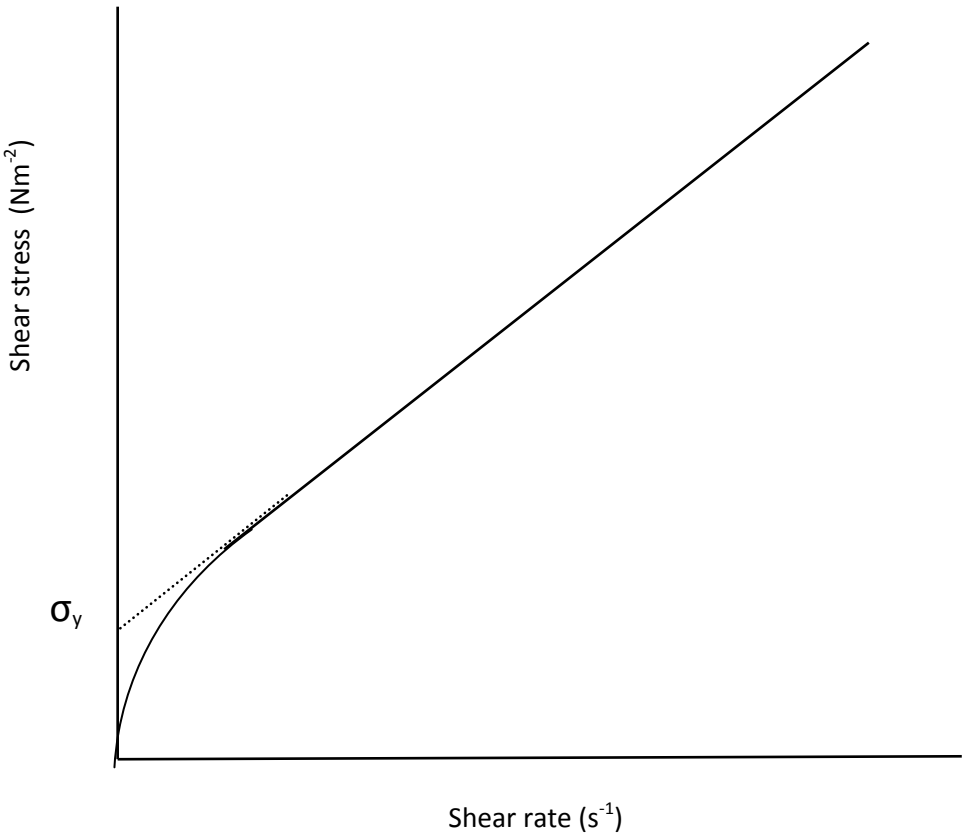


Figure 2.3 Rheogram of plastic flow.

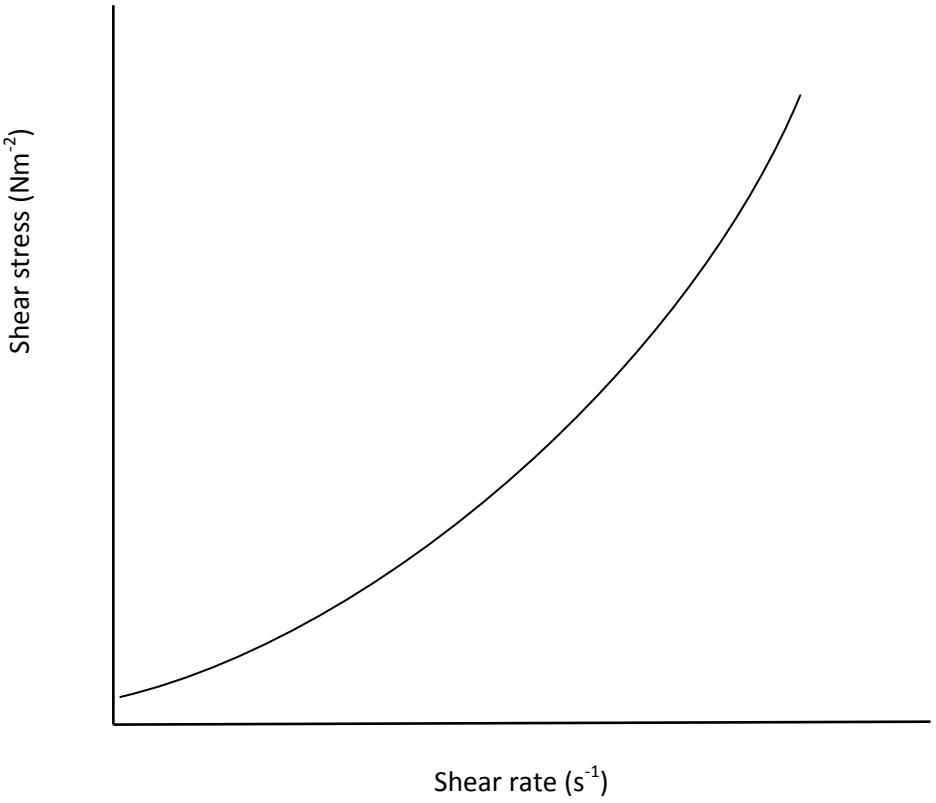


Figure 2.4 Rheogram of dilatant flow

(d) Thixotropic fluids

Thixotropic fluids show a time - dependent response to shear. When sheared at a constant shear rate, viscosity decreases or increases over time. Therefore, there are two types of thixotropic flow. These are thixotropic-pseudoplastic flow and thixotropic-dilatant flow respectively. Thixotropic materials gradually recover their viscosity on removal of shear after experiencing a change in viscosity (Marriot, 2007).

On simple shaking of thixoptropic-pseudoplastic material, it becomes fluid as a result of bond breakage; and on standing, collision of particles occur, flocculation takes place (as weak bonds form) and gel formation occurs. This gel-sol-gel non-chemical isothermal reaction is of importance in pharmaceutical suspensions such as injectables that require depot formation. The shearing force on the injection as it is pushed through the needle ensures that it is fluid when injected. However, it rapidly forms a gel preventing excessive spreading in the tissues, producing a compact depot. Stability is also improved since the material remains standing in the gel-form until it is touched. Rheograms for thixotropic materials are highly dependent on the rate at which shear is increased or decreased and the length of time a material is subjected to a particular shear (Ram, 2006). Examples of thixotropic fluid are greases, paints and heavy printing inks.

2.5.2 Factors Affecting Viscosity

(a) Temperature

Increase in temperature generally leads to decrease in viscosity. It is therefore necessary to state the temperature while stating the viscosity of fluids (Schnaare *et al*., 2005).

(b) Shear rate

The effect of shear rate on viscosity depends on the nature of the fluid. For Newtonian fluids, shear rate has no effect on the viscosity. For plastic and pseudoplastic materials, increase in shear rate leads to decrease in viscosity while for dilatant materials, increase in shear rate leads to increase in viscosity (Marriot, 2007).

(c) Duration of shear

For non-thixotropic materials, time of shear has no effect on viscosity. For thixotropic-pseudoplastic materials, viscosity decreases with time of shear while for thixotropic-dilatant materials, it increases with time of shear. In both cases, the viscosity is restored on removal of the shear (Schnaere *et al*., 2005).

2.5.3 Importance and Applications of Viscosity

The spreading of lotions and pouring from the bottle are both affected by viscosity. The lower the viscosity, the higher is the pourability and spreadability.

The viscosity of a suspension affects and controls the settling of dispersed particles. Highly viscous suspensions may prolong gastric emptying time, slow drug dissolution and decrease absorption rate. For an ideal suspension, it is best to have high viscosity during storage (preventing sedimentation) and low viscosity when sheared to ease administration (Ram, 2006). Thus, a pseudo-plastic agent and a thixotropic suspending agent could be used to maintain the suspension in flocculated form. A combination of two rheological control additives (suspending agents) will give a stronger rheological effect.

The rate of dissolution of a drug particle will be decreased as the viscosity of dissolution medium increases and usually the dissolution medium exhibits Newtonian behaviour. However, in the stomach, the presence of high molecular weight glycoproteins from mucus in acid will only be Newtonian up to a concentration of 2 % beyond which it will be non-Newtonian. The use of hydrocolloids in formulations contributes to this effect thus affecting bioavailability either positively or negatively. It is not clear whether it does this by modifying rheological properties or by affecting GI transit (Marriot, 2007).

The effect of viscosity operates at other drug delivery sites as well. For example, the absorption of drugs by the skin and from injection sites will be decreased by increasing the viscosity of the vehicle. In the case of injections, the creation of a depot with highly viscoelastic nature will result in prolonged delivery of the drug (Marriot, 2007).

2.5.4 Measurement of Viscosity

Viscosity of fluids can be measured using viscometer, of which there are different types.

(a) Ostwald viscometer

This is a U-shaped viscometer that is used in the measurement of viscosity of Newtonian fluids. It has two bulb marks (upper and lower). Liquid flow is aided by gravitational force from the upper mark to the lower mark in a vertical capillary tube. The time of flow of the liquid under test is compared with the time for a liquid of known viscosity. Water is the usual reference used.

The viscosity of the unknown liquid can be determined using the following equation:

$$\eta_1 = {}^{\rho_1 t_1 \eta_2}/_{\rho_2 t_2} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (4)$$

$where\ \eta_1 = viscosity\ of\ unknown\ liquid$

$\eta_2 = viscosity\ of\ known\ liquid$

$\rho_1 = density\ of\ unknown\ liquid$

$\rho_2 = density\ of\ known\ liquid$

$t_1 = time\ of\ flow\ of\ unknown\ liquid$

$t_2 = time\ of\ flow\ of\ known\ liquid$

Ostwald viscometer is limited to the measurement of Newtonian fluids. The viscosity value obtained using this type of viscometer is dependent on the size (diameter) of the bulb (Schnaare *et al.*, 2005).

(b) Cup and bob viscometer

It is a rotational viscometer that measures the viscosity of non-Newtonian fluids. In this viscometer, the material is sheared in the space between the outer wall of a bob and the inner wall of a cup in which the bob fits. The viscous material as a result of this shearing action causes the bob to turn. The resultant torque is proportional to the viscosity of the material (Marriot, 2007).

(c) Cone and plate viscometer

It is used for measuring viscosity of non-Newtonian fluids. In this type of viscometer, the sample is placed in the centre of the plate which is then raised into position under the cone. The cone is driven by a variable speed motor and the sample is sheared in the narrow gap between the stationary plate and the rotating cone. The rate of shear in rpm can be varied by a dial and then shear produced on the cone is read on a dial indicator.

A graph of shear rate versus shear stress can be plotted. It is used for measuring viscosity of highly viscous liquids and semisolid materials (Marriot, 2007).

(d) Digital viscometer

This type of viscometer measures viscosity of both Newtonian and non-Newtonian fluids. The instrument gives an absolute viscosity value. It measures the torque required to rotate a spindle immersed in the fluid. The spindle is driven by a motor through a calibrated spring and the deflection on the spring is indicated by a display. Several speeds can be used interchangeably to measure viscosity values. In this type to viscometer, the viscous drag is proportional to the speed of rotation, size and shape of spindle. Thus, the resistance to flow increases as rotational speed increases (Mahmud, 2009).

2.6 SURFACE ACTIVITY

Surface activity relates to the ability of a substance to alter the nature of a surface or an interface between two substances. Surfactants lower the surface tension of a liquid, the interfacial tension between two liquids or that between a liquid and a solid (Florence and Attwood, 2007).

The lowering of interfacial tension between oil and water facilitates emulsion formation, adsorption of surfactant on insoluble particles that need to be dispersed facilitates formation of suspension, adsorption of surfactants on biological membranes promotes permeation while incorporation of insoluble substance within the micelles of surfactant leads to the production of clear solution (Florence and Attwood, 2007).

2.6.1 Surface Tension, Bioadhesion and Critical Micelle Concentration

The surface activity of surfactants can be expressed with respect to surface tension, bioadhesion and critical micelle concentration.

Pure liquid surfaces have a tendency to contract as a result of surface tension forces. Packing the surface with a surfactant facilitates expansion of the surface. This reduces the surface tension of the liquid. In some cases, a negative adsorption may occur and the solute migrates away from the surface. In such cases, examples of which are solutions of sugars and electrolytes, small increases in surface tension are observed (Fell, 2007).

Surface tension is the force acting parallel to the surface at right angle to a line of 1 m length anywhere in the surface. It is expressed in terms of Nm^{-1}. Surface free energy is defined as the work required to increase the surface area by 1 m^2. The unit is Jm^{-2}. Surface tension and surface free energy are dimensionally and numerically equivalent (Fell, 2007). The surface energy thermodynamics which is a measure of work required in increasing the surface area by 1 m^2 in bioadhesion is important in establishing intimate time (Smart *et al*., 1984). This explains the physical and mechanical bonds that result in deposition and inclusion of an adhesive material in the crevices of tissues (Adikwu *et al*., 2005). The penetration of an adhesive polymer or surfactant into mucus network and the formation of secondary chemical bonds are influenced by several factors which include the ionic charge of the polymer and the strength of hydrogen bonding between the polymers (Genarro, 1995).

Bioadhesion is a state in which two materials at least one of which is of a biological nature are held together for an extended period of time by interfacial forces (Adikwu *et*

al., 2005). For drug delivery purposes, bioadhesion implies attachment of drug carrier system to a biological location resulting in an increase in drug absorption and bioavailability (Mortazavi and Smart, 1994). Bioadhesive dosage forms are targeted at particular sites such as nasal, buccal, gastrointestinal tract, cervical, vaginal and dermal regions to reduce toxic effects and increase therapeutic effects of drugs (Attama *et al*., 2003). Polymer - bioadhesion had been explained by various theories. These are: electronic, adsorption, wetting, diffusion and fracture theories (Taylor, 1986). However, due to the diversity of the mechanisms involved, no single theory can explain fully the nature of the phenomena involved.

Because of the dual structure of surfactants, it is energetically favourable for them when dissolved to adsorb at interface. The force needed to cause a detachment is referred to as force of adhesion and the force applied per unit area to cause the detachment is called adhesive strength (Lee *et al.,* 2000). Since surfactants can lower the interfacial tension between two phases, adsorb on insoluble particles, adsorb on biological membranes or form micelles to cause solubilization, the net effect observed depends on whether the critical micelle concentration is exceeded or not. The critical micelle concentration is the lowest concentration of surfactant at which micelles are formed (Florence and Attwood, 2007).

2.6.2 Evaluation of Surface Activity

The surface activity of surfactants can be evaluated in terms of surface tension, force of adhesion or critical micelle concentration.

2.6.2.1 Determination of Surface Tension

There are several methods available for the determination of surface and interfacial tension.

(a) Wilhelmy plate method

The apparatus consists of thin platinum glass or mica plate attached to a suitable balance. The plate is immersed in the liquid and the liquid container is gradually lowered to a point at which the plate lies just at the surface of the liquid and the reading is zeroed. The plate is gradually raised until it just detached from the liquid and the reading on the balance is taken.

The detachment force is equal to the surface tension multiplied by the perimeter of the surface detached (Fell, 2007).

$$F = 2(L + B) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(5)$$

F is the detachment force, L is the length of plate, B is the breadth of the plate and γ is the surface tension. For this equation to hold, the contact angle the liquid makes with the plate must be zero, that is, the plate must lie in a horizontal plane.

(b) Ring method (du Nuoy tensiometer)

This method measures the force required to detach a platinum ring from a surface or an interface. The ring must lie horizontally parallel to the surface. It is immersed into the liquid and gradually raised until it gets to the surface and the reading is zeroed. Thereafter, the ring is further raised until the meniscus of liquid raised by the ring just detaches. The force applied is then read from the tensiometer.

As the shape of the liquid supported by the ring is complex and the surface tension force does not act vertically, a correction factor is applied for accurate determination (Fell, 2007 and Adikwu *et al.,* 2005).

$$= \frac{F}{2\pi R} \cdot \emptyset \quad \text{.....(6)}$$

where ɣ is the surface tension, F is the detachment force, R is radius of the ring and ∅ is the correction factor of the instrument.

(c) Drop weight and drop volume method

Here, the volume and weight of a drop detached from a tip of known radius is determined. According to Fell (2007), the surface tension is calculated using the equation.

$$= \frac{\emptyset mg}{2\pi r} = \frac{\emptyset V \rho g}{2\pi r} \quad \text{.....(7)}$$

where ɣ is the surface tension, m is the mass of the drop, V is the volume of the drop, ρ is the density of the liquid, r is the radius of the tip, g is acceleration due to gravity and ∅ is the correction factor.

It is important that the tip is completely wetted by the liquid and the drop does not climb outside the tube. The drop should also be formed slowly to get accurate result.

(d) Capillary rise method

This is seldom used in pharmaceutical research. A capillary tube is placed in a liquid and the liquid rises in the tube to a certain length. Provided the tube is small in diameter, the meniscus can be considered to be hemispherical and the radius of curvature is calculated as:

$$r_t = r_m \cos\theta \quad \text{..... .....(8)}$$

where r_t is the radius of the capillary tube, r_m is the radius of curvature of the meniscus are θ is the contact angle (Fell, 2007).

From Laplace equation,

$$\Delta p = \frac{2\cos\theta}{r_t} \quad \text{.....(9)}$$

Δp is the pressure difference between the atmosphere and the meniscus.

$$since\ p = \rho g h \quad \text{..(10)}$$

$$\frac{2\cos\theta}{r_t} = gh(\rho_L - \rho_V) \quad \text{.....(11)}$$

where $\rho_L - \rho_V$ is the density difference between the liquid and its vapour, g is acceleration due to gravity and h is the height of liquid in the capillary tube.

Careful cleaning of the surface assures carrying out the experiment with contact angle of 0^O. Since cos 0^O = 1, the equation is therefore reduced to

$$= \frac{r_t h(\rho_L - \rho_V) g}{2} \quad \text{.....(12)}$$

2.6.2.2 Determination of Force of Adhesion

Adhesive strength of solution or dispersion of a surfactant can be measured using Wilhemy and du Nuoy methods. The material is placed at interface of two substances and the force applied per unit area to cause detachment is calculated from the reading on tensiometer and the area of contact. The basic difference between surface tension and adhesive strength is that while surface tension is force per unit length (perimeter or circumference), adhesive strength is force per unit area (Fell, 2007; Adikwu *et al.,* 2005).

2.6.2.3 Determination of Critical Micelle Concentration (CMC)

A graph of surface tension is plotted against natural logarithm of different surfactant concentrations. The surface tension decreases with increase in surfactant concentration until a point where further increase in concentration does not affect surface tension. This point is termed the critical micelle concentration of the surfactant. The implication of this is that accumulation in surface layer and adsorption at interface are favoured below CMC while micelle formation and solubilization are favoured above CMC.

2.6.3 Uses of Surfactants

Surface active agents reduce the surface tension at the interface of two substances to facilitate the interaction between the particles of the two substances. This is the basis for their wide application in pharmaceutical sciences. They are useful as emulsifiers, wetting agents, foaming agents, solubilizing agents, suspending agents and stabilizers (Mahmud, 2009).

(a) Emulsifiers

Water and oil are immiscible liquids. However, emulsification of the two liquids occurs in the presence of an emulsifier. There are two types of emulsions namely; water-in-oil emulsions and oil-in-water emulsions. In water-in-oil emulsions, the internal or discontinuous phase is water while the external or continuous phase is oil. In oil-in-water emulsions, the internal phase is oil while the continuous phase is water. Multiple emulsions of water-in-oil-in-water and oil-in-water-in-oil can also be formed.

The type of emulsion produced depends on the nature of the emulsifier and the quantities of the two liquids used. Emulsifiers with low hydrophile - lipophile balance

(HLB) values form water-in-oil emulsions while those with higher HLB values form oil-in-water emulsions. Emulsifiers can thus be classified into water-in-oil emulsifiers and oil-in-water emulsifiers.

When the quantity of oil is higher, there is greater tendency for the formation of water-in-oil emulsion. Conversely, when the quantity of water is higher there is greater tendency for the formation of oil-in-water emulsion (Attwood, 2007).

(b) Wetting agents

These are water miscible solvents that reduce liquid – air interfacial tension. They act by allowing displacement of air and permitting liquid to surround or penetrate into the pores of hydrophobic powdered particles. Non-ionic surfactants with HLB values from 7-9 are used as wetting agents. (Davies, 1957).

Hydrophilic materials are easily wetted by water while hydrophobic materials are not. However, non-polar liquids wet hydrophobic materials easily. The extent of wetting by water is dependent on the hydrophilicity of the material (Gohel *et al.,* 2005). If the material is more hydrophilic, it finds less difficulty in being wetted by water. Difficulty in wetting of particles reflects higher interfacial tension between the drug material and the vehicle. For wetting to take place, interfacial tension must be reduced so that air is displaced from the solid surface by liquid. This is often achieved by use of wetting agents. Sulphamethoxazole and trimethoprim are examples of powders with poor wettability.

(c) Foaming agents

Surfactants with HLB values of 13-15 are used as foaming agents. Concentration of surfactant used should be less than 0.5 % to avert solubilization of the medicament (Mahmud, 2009).

(d) Solubilizing agents

Surfactant with HLB values close to 20 are used as solubilizing agents. These are highly polar surfactants. They are required for formulation of poorly soluble medicaments. (Attwood, 2007).

(e) Suspending agents

They are added to suspensions to increase viscosity and density of the dispersion and to reduce the settling of dispersed particles.

(f) Stabilizers

They are added to suspensions and emulsions to enhance stability. For suspensions, the rate of separation of the dispersed phase and the dispersing medium is reduced by incorporation of surfactants. For emulsions, phase separation and cracking are reduced by incorporation of surfactants (Mdhlovu, 2005).

2.6.4 Pharmaceutical Applications of Surface Activity

Interfacial phenomenon, though a subject of physical pharmaceutics is widely applied in various other branches of pharmaceutical sciences too. These branches include Pharmaceutical Technology, Pharmaceutical Microbiology, Biopharmaceutics/ Pharmacokinetics, Pharmaceutical Analysis/Chromatography, Pharmacology and Toxicology (Fell, 2007).

(a) Pharmaceutical Technology

(i) Formulation of emulsions

This is based on the surface activity of the emulgent. The emulgent reduces the interfacial tension between oil and water enabling the two substances to be formulated together. Simple emulsion can exist as oil-in-water or water-in-oil. Multiple emulsions are more complicated forms of emulsions. These can be water-in-oil-in-water (w/o/w) or oil-in-water-in-oil (o/w/o) emulsions. Two emulgents are used for the formulation of such emulsions (Attwood, 2007).

For instance, to prepare w/o/w emulsion, two emulgents are required; a w/o emulgent and an o/w emulgent. The w/o emulgent, e.g. sorbitan mono-oleate, is first mixed thoroughly with the oily phase such as liquid paraffin in a mixer. This is followed by the slow addition of the aqueous phase (containing the drug) to the oil/emulgent mixture with vigorous mixing to form a w/o emulsion. With the aid of a homogenizer or a colloid mill, the w/o emulsion is dispersed in an aqueous solution of an o/w emulgent such as tween (polysorbate) 80. This leads to the production of the desired w/o/w emulsion.

Multiple emulsions are mainly useful in parenteral therapy to effect drug localization and prolongation of drug action. The drug in the innermost phase diffuses slowly through the other phases to provide sustained release. They are used in delayed action drug delivery (Attwood, 2007).

(ii) Formulation of muco-adhesive granules, gels and tablets

This unique dosage system utilizes both the adhesive and gel-forming properties of some water-soluble polymers in which the drug is dispersed. Snail mucin had been used

as bioadhesive agent for gastrointestinal delivery of chlorpropamide (Adikwu *et al*., 2005).

Muco-adhesive delivery system (MADS) is used in the treatment of both topical and systemic ailments by application to the appropriate mucosa. It can adhere to oral mucosa and in this way, insulin has been administered successfully. Ibuprofen ointments intended for topical and systemic delivery were also formulated by Aukunuru *et al*. (2007).

The polymers used in MADS are bioadhesive, that is, they adhere well to mucosal surfaces. The drug in the polymer matrix slowly diffuses after dissolution from the dosage form into systemic circulation (Adikwu *et al*., 2005).

(b) Pharmaceutical Microbiology

Quaternary ammonium compounds (cationic surface active compounds) are used as disinfectants, antiseptics and preservatives in ophthalmic, topical and some injectable products. The use for these purposes is based on their surface activity. They interfere with cell permeability of susceptible bacteria (mainly Gram-positive group) causing leakages of cell content and eventually cell lysis occurs. They are less active against Gram-negative organisms. Their activity is favoured by alkaline conditions and increases with increase in pH. They are inactivated by foreign organic matters and grease (Moore and Payne, 2004).

(c) Biopharmaceutics / Pharmacokinetics

All surface-active agents (anionic, cationic as well as nonionic) reversibly interfere with biological membranes and cause increase in their permeability. Therefore, they are

incorporated as permeation enhancers in pharmaceutical formulations (solids, liquids and semi-solids) to promote drug absorption. Examples of such surfactants are sodium taurocholate and sodium thioglycollate (Barry, 2007). Adsorption may be put to a positive use in the enhancement of dissolution of hydrophobic drug by adsorption of surface active agents unto the surface of the drug particles (Fell, 2007).

(d) Pharmaceutical analysis / Chromatography

The phenomenon of adsorption from solution finds practical application of pharmaceutical interest in chromatographic techniques. Successive adsorption and desorption forms the basis for both TLC and HPLC chromatographic analyses (Fell, 2007).

(e) Pharmacology and Toxicology

Materials such as activated charcoal can be given in cases of orally taken poisons to adsorb the toxic materials. Adsorbents may be used also in dialysis for removing the product of dialysis from dialyzing solution, so that the solution can be recycled. Water-insoluble polymers are used for dialysis and filtration because of their very low rate of dissolution (Adikwu *et al*., 2005). The adsorptive and surface active properties of these materials are responsible for this indication.

2.7 HYDROPHILE-LIPOPHILE BALANCE (HLB)

HLB is the relative hydrophilicity or lipophilicity of a surfactant. It is characteristic of the relative polarity of the surfactant and ranges from 0 to 20. The lower the HLB value, the higher hydrophobic character and the higher the HLB value, the more hydrophilic is the substance (de Schaefer *et al*., 2002).

2.7.1 Significance of HLB Value

(a) Classification of surfactants

HLB value is used for classifying surfactants. Surfactants have been classified into water-in-oil emulsifiers, wetting agents, oil-in-water emulsifiers, foaming agents and solubilizing agents in order of increasing HLB values (Davies, 1957).

- Water-in-oil emulsifiers (surfactants having HLB values of 4-6)
- Wetting agents (surfactants having HLB value of 7-9)
- Oil-in-water emulsifiers (surfactants having HLB values of 8-18)
- Foaming agents (surfactants having HLB values of 13-15)
- Solubilizing agents (surfactants having HLB values of (15-18).

(a) Calculation of quantity of emulgent

HLB value of an emulsifier is used for estimating the quantity of emulgent that may be required for emulsification of particular oil. When a mixture of emulsifiers is to be used, the individual HLB values are used for calculating the proportion of each emulsifier required.

2.7.2 Determination of HLB Value

There are many methods for determining HLB values. These include;

(a) Water solubility method

The solubility of non-ionic surfactant can be used as a guide in approximating HLB value. The values are as illustrated in the Table 2.1.

Table 2.1 Water Solubility – HLB Relationship

Solubility	HLB Range
No dispersability	1 – 4
Poor dispersability	3 – 6
Milky dispersion after agitaton	6 – 8
Stable milky dispersion	8 – 10
Transluscent to clear dispersion	10 – 13
Clear solution	>13

Adapted from Davies (1957)

According to Kruglioaokor (2000), HLB can be calculated using the equation:

$$HLB = 54\left(\frac{\delta - 8.2}{\delta - 6.0}\right) \quad \text{.....(13)}$$

where $\delta = Hilderbrand\ solubility$

(b) Calculation of HLB from functional groups

The HLB values can be calculated from the chemical formulae using group numbers (Davies, 1957). It is calculated as:

$$HLB = \sum(hydrophilic\ grp.no.) - (no.of\ CH_2) + 7 \ldots \quad (14)$$

(c) Bancroft rule (oil-water partitioning method)

The HLB value is calculated from the distribution of non-ionic emulsifier between oil and water (Kruglioaokor, 2000).

$$HLB = 0.36\ In\ {}^{1}/_{k} + 7 \quad \text{.....(15)}$$

Or

$$HLB = 0.36\ In\left({}^{C_w}/_{C_o}\right) + 7 \quad \text{.....(16)}$$

where C_w = amount of emulgent in the aqueous phase

and C_o =amount of emulgent in the oily phase.

(d) Griffin's method

Griffin (1949) determined HLB by using molar ratio of the hydrophilic entity in the molecule.

$$HLB = 20\ x\ {}^{Mh}/_{M} \quad \text{.....(17)}$$

where Mh = molecular mass of the hydrophilic portion

and M = molecular mass of the whole molecule.

(e) Nuclear magnetic resonance

The emulsifier is subjected to NMR analysis and the HLB is calculated using the Ben-Et and Tatarsky (1972) formula.

$$HLB = \frac{AH}{5(AH+BL)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(18)$$

A = 15

B = 10

H = relative integration value of hydrophilic proton

L = relative integration value of lipophilic proton.

(f) Micro-emultocrit technique (Spontaneous emulsification method)

Here, series of emulsions are produced using binary mixtures of emulsifying agents one of whose HLB value is known. The emulsion is subjected to stability studies to determine the series of emulsifying agents that produced most stable emulsion. The HLB value of the surfactant under evaluation is extrapolated from the HLB value of the known surfactant and that of the oil (Macedo *et al.*, 2005).

(g) Titration method

A 50 ml aqueous solution of 2 % $^{w}/_{v}$ surfactant is titrated with 5 % $^{w}/_{v}$ solution of phenol until clouding becomes visible. The volume of phenol solution (known as phenol index) required to produce clouding is noted and the HLB value is calculated (Kruglioaokor, 2000).

$$HLB = 0.89(Ph.I) + 1.11 \ldots\ldots\ldots\ldots\ldots\ldots (19)$$

(h) Gas Liquid Chromatography

The partition measurement is carried out by placing 100 ml of oil (iso-octane or cyclohexane) containing the required amount of surfactant in a separating funnel,

adding 100 ml of water and allowing equilibrium to occur by diffusion at 25 ^{o}C. The two phases are separated and each concentrated by evaporation and then chromatograms for both phases are determined by gas-liquid chromatography. Thereafter, the partition coefficient is calculated and the HLB value is determined (Harusawa *et al.*, 1982) using equation 15.

2.8 DRUG TRANSPORT

The term describes the transport of drug across biological membranes. Biological membranes normally serve as barriers to the outside world. However, they are not impenetrable. They do allow entrance of nutrients and other useful materials and exit of waste materials and are selectively permeable.

2.8.1 Mechanisms of Drug Transport

The mechanisms of drug transport across biological membranes have been found to include passive transport, active transport, carrier-mediated transport and phagocytosis (Ashford, 2007a).

2.8.1.1 Passive Transport

This is the transport of drugs and nutrients along concentration gradient, that is, from an area of higher concentration to an area of low concentration. This mechanism does not involve expenditure of energy, hence the name passive transport. Passive transport can take place as lipid diffusion and aqueous diffusion (Katzung, 2004).

(a) Lipid diffusion (passive diffusion)

Since membranes are held together by weak forces, drug molecules slip between the lipid in the bilayer and cross from one side to the other. These forces allow molecules

that are small and lipophilic including most drugs to pass easily. The rate of transport is determined by the physicochemical properties of the drug, the nature of the membrane and the concentration gradient of the drug across the membrane (Oh *et al*., 1999).

Passive diffusion of drugs across the gastrointestinal – blood barrier has been described mathematically by Fick's law of diffusion. When considered in the context of bioavailability, the rate of diffusion ($^{dc}/_{dt}$) is proportional to the difference in concentration on each side of the membrane (Ashford, 2007a).

The rate of appearance of drug in the blood at the absorption site is given by the equation:

$$^{dc}/_{dt} = k\left(C_g - C_b\right). \quad \text{.....(20)}$$

$^{dc}/_{dt}$ is the rate of appearance of drug in the blood, k is proportionality constant, C_g is concentration of drug at gastrointestinal fluid and C_b is concentration of drug in the blood at absorption. The proportionality constant k incorporates the diffusion coefficient of the drug in the gastrointestinal membrane (D), the thickness (h) and the surface area of the membrane (A).

$$In\ k = \frac{DA}{h} \quad \text{.....(21)}$$

$$^{dc}/_{dt} = \frac{DAC_g}{h} \text{.....(22)}$$

(b) Aqueous diffusion

Water-soluble substances and large hydrophobic molecules do not easily pass through biological membranes. They normally require the action of channel proteins. These proteins form a pore through which these materials can pass. They carry out passive

transport by allowing materials to travel spontaneously down their concentration gradient. In some cases, carrier proteins may be involved. In such cases, the transport is called facilitated diffusion (Katzung, 2004).

It is assumed that drugs exist solely in single absorbable species which make them amenable to passive diffusion. Many drugs are weak electrolytes and exist in unionized and ionized species in solution. The unionized form of a weak electrolyte drug exhibits greater lipid solubility and the gastrointestinal tract is more permeable to the unionized form. The rate of passive absorption is dependent on the fraction of the drug that exists in the unionized form (Ashford, 2007a).

The fraction of drug in the unionized form is determined by the dissociation constant of the drug (pKa) and by the pH of the aqueous environment in accordance with Henderson-Hasselbalch equations for weak acids and bases. The gastrointestinal absorption of a weak electrolyte is enhanced when the pH at the site of absorption favours the formation of large fraction of the drug in the unionized form (Ashford, 2007a).

2.8.1.2 Active Transport

This is the transport of drug against concentration gradient. It requires energy, hence the name active transport. It is an energy consuming process. The energy is derived from hydrolysis of ATP or from trans-membranous sodium gradient and/or electrical potential (Ashford, 2007a).

2.8.1.3 Carrier-mediated Transport

This process is often explained by a shuttling process across the epithelial membrane. The drug molecule forms a complex with a carrier in the surface of apical cell membrane. The drug-carrier complex then moves across the membrane and liberates the drug at the other side of the membrane. The free-carrier then returns to its original position to pick another drug molecule (Tsuji and Tamia, 1996). Many peptide-like drugs such as penicillins, cephalosporins and ACE inhibitors rely on peptide transporters for their absorption. Nucleoside and analogues used as antivirals and anticancers depend on nucleoside transporters. L-dopa is transported by amino acid transporter (Yang *et al*., 1999).

Unlike passive transport, carrier-mediated system becomes saturated at high concentrations of the drug. It proceeds at a rate proportional to drug concentration only at low concentrations. Unlike non-carrier mediated transport, the extent of transport depends on the availability of carrier/transporter (Ashford, 2007a).

2.8.1.4 Phagocytosis/Transcytosis

Large macromolecules > 500 nm (for example, proteins and lipoproteins) follow more complex mechanisms of transport that enable them to transverse biological membranes, something akin to the process of phagocytosis. Phagocytosis has two components namely endocytosis and exocytosis. Materials are transported into the cell via endocytosis and transported out of the cell by exocytosis. This process explains absorption of polio and some other vaccines (Katzung, 2004).

Out of all the mechanisms described above, Katzung (2004) holds that lipid diffusion and carrier-mediated transport are the commonest mechanisms of drug transport. This is because of the lipophilic nature of many drugs and the abundance of carriers at the surface of apical cell membranes.

2.8.2 Factors Affecting Drug Permeation

According to Ashford (2007a), the factors affecting drug permeation include:

(a) Molecular size of the drug: the smaller the size, the easier it is to be transported.

(b) The degree of hydrophobicity: the higher the hydrophobicity, the greater the ease of transportation.

(c) Degree of ionization of the drug: the lower the degree of ionization, the more the availability of unionized form of the drug and faster the rate of permeation.

(d) Drug concentration gradient across the membrane: decrease in concentration gradient leads to decrease in the rate of drug permeation and vice versa.

(e) Surface area of the membrane: the larger the surface area the more the permeability to the drug.

Drug permeation usually follows Fick's law of diffusion given as equation 20.

2.8.3 Drug Permeation Studies

There are three methods of carrying out permeation studies. These are *in-vitro*, *ex-vivo* and *in-vivo* studies.

(a) In-vitro study

In this mode of study, the physiological condition is simulated and an artificial membrane is used as the absorption barrier. Examples of such artificial membranes are cellulose acetate, silicone rubber, and lamellar systems (Barry, 2007).

(b) Ex-vivo study

In this mode of study, the physiological condition is simulated and excised animal tissues are used. Examples of such tissues are skin, intestine and nasal mucosa from animals like rats, mice, pigs and monkey (Adikwu *et al*., 2005).

(c) In-vivo study

In this mode of study, a live animal model is used (Adikwu *et al*., 2003). In some instances, human volunteers are used, but rarely because of ethical issues. The drug formulation under study is administered and blood samples are taken at designated time intervals for analysis (Adikwu *et al*., 2003).

CHAPTER 3

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Chemicals

Acetone (Merck, Germany)

Artemether powder (Afrab Chem. Ltd., Lagos, Nigeria)

Artesunate sodium powder (IPCA Laboratory, India)

Chitosan derived from shell wastes of crab prepared using the method described by Sonia and Sharma (2011)

Chloroform (BDH Chemicals, Poole, England)

Diethyl ether (Sigma – Aldrich Lab Germany)

Ethanol (BDH Chemicals, Poole, England)

Lactose (Surechem Products Ltd., England)

Magnesium stearate (Riedel-De Haen, Germany)

Maize starch B.P (BDH Chemicals, Poole, England)

n-Hexane (BDH Chemicals, Poole, England)

Phenol (BDH Chemicals, Poole, England)

Potassium dihydrogen phosphate (Guangdong Chemical Reagent Centre, China)

Sodium carboxymethylcellulose (BDH Chemicals, Poole, England)

Sodium chloride (BDH Chemicals, Poole, England)

Sodium hydroxide pellet (BDH Chemicals, Poole, England)

Sodium metabisulphite (BDH Chemicals, Poole, England)

Standard *Acacia senegal* gum (BDH Chemicals, Poole, England)

Talc (BDH Chemicals, Poole, England)

Xylene (May and Baker, Nigeria)

3.1.2 Plant Materials

Crude cashew gum exudates from *Anacardium occidentale* trees (Abuja, Nigeria)

Crude khaya gum exudates from *Khaya senegalensis* trees (Abuja, Nigeria)

Afzelia seeds from *Afzelia africana* trees (Abuja, Nigeria)

Prosopis seeds from *Prosopis africana* trees (Abuja, Nigeria).

3.1.3 Animal Material

A section of small intestine of a freshly sacrificed pig was used for permeation studies. The animal, housed in a cross-ventilated room (temperature of 25 ± 2.5 ^{O}C) was sacrificed in accordance with internationally accepted laboratory animal use and the guidelines and rules for animal experimentation.

3.2 METHODS

3.2.1 Collection and Identification of Exudates and Seeds.

The four experimental gums were sourced from Abuja, Nigeria. Bark exudates were obtained from the stem of *Anacardium occidentale L.* and *Khaya senegalensis* trees grown in Gwagwalada, Abuja. Also, seeds of *Prosopis africana* and *Afzelia africana* trees were purchased from Gwagwalada and Gwagwa markets respectively, both in Abuja.

These plant materials were authenticated by the Taxonomist in the Herbarium unit of the Department of Biological Sciences, University of Abuja, Abuja, Nigeria and were assigned the following voucher numbers:

Cashew exudates from *Anacardium occidentale L.*- UNIABUJA I50

Khaya exudates from *Khaya senegalensis* - UNIABUJA I52

Afzelia seeds from *Afzelia africana* - UNIABUJA I51

Prosopis seeds from *Prosopis africana* - UNIABUJA I53.

3.2.2 Extraction and Purification of the Gums

(a) Cashew gum

The bark and other extraneous materials were removed from the exudates by hand. The gum was purified using the method described by Ofori-Kwakye *et al*. (2010). A 500 g quantity of the exudate was added to 1 L of distilled water. The mixture was homogenized using a laboratory blender and left for 24 h to ensure complete dissolution. The mucilage was screened through a muslin cloth to obtain particulate-free slurry. The gum was precipitated using 2 L of absolute ethanol and defatted using 200 ml of diethyl ether. It was air-dried for 3 h, then at 50 ^{O}C in a hot air oven (Gallenkamp, Germany) for 24 h. It was then pulverized using laboratory blender (Christison, United Kingdom).

(b) Khaya gum

The gum exudate was cleaned by removing extraneous materials by hand. A 500 g quantity of the exudate was purified using the method described in 3.2.2(a). However, 2 L of distilled water was used and time period of 48 h was allowed for dissolution of the gum. The mucilage was screened through a muslin cloth and the gum was

precipitated with twice the volume of acetone and defatted using 200 ml of diethyl ether. The precipitated and defatted gum was dried and pulverized as in 3.2.2(a).

(c) Afzelia gum

The method of Builders *et al*. (2009) was used for the extraction and purification of the gum. The seeds of *Afzelia africana* were washed and adhering dirt was removed. The washed seeds were soaked in water for 1 h to remove the aril and boiled for 3 h to soften the seed coat which was thereafter removed from the swollen tegument.

A 500 g quantity of the hydrated tegument was rinsed with distilled water and chopped into small pieces with knife. A 500 ml volume of distilled water was added and the mixture was homogenized using a laboratory blender. The mixture was boiled in ethanol for 1 h to denature protein and inactivate enzymes and then treated with several aliquots of diethyl ether to remove lipids. The defatted granules were air-dried for 6 h so as to remove the residual diethyl ether. It was thereafter soaked in 1 L of distilled water with intermittent agitation for 18 h. The viscous material was filtered using a muslin cloth and the gum was precipitated using double portion of acetone. The precipitated gum was dried in air for 3 h, then in a hot air oven (Gallenkamp, Germany) at 50 ^{O}C for 24 h and pulverized using a laboratory blender (Christison, United Kingdom).

(d) Prosopis gum

The extraction and purification of the prosopis gum were carried out using the method described by Adikwu *et al*. (2003). The seeds were soaked in water for 24 h and then boiled on a hot metal plate for 4 h. The softened seed coats were manually separated from the swollen tegument. A 500 g quantity of the swollen tegument was soaked in

1 L of aqueous solution of 0.1 % w/v sodium metabisulphite for 24 h. The material was homogenized using a laboratory blender (Christison, United Kingdom).

The resulting viscous material was passed through a muslin cloth to remove gritty particles and the gum in the filtrate was precipitated using acetone. The gum was air dried for 3 h then at 50 ^{O}C for 24 h after which it was pulverized using a laboratory blender (Christison, United Kingdom). The gum was screened through a 0.25 mm mesh sieve to obtain uniformly sized particles.

3.2.3 Determination of Percentage Yield of the Purified Gums

The dried, precipitated and purified gums obtained from the exudates and seeds were weighed and the percentage yields were expressed relative to the initial weight of the crude gum source.

3.2.4 Determination of Physicochemical Properties of the Different Gums

a. Organoleptic properties

The taste, colour, odour and texture of the gums were determined using five human volunteers.

b. Ash value

The ash value was determined by measuring the mass of ashes left after combustion of 1 g sample of the gum in a muffle furnace (Model 5300A30, Thomas Scientific Co., U.S.A.). The percentage of the ash relative to the initial weight of the gum was thereafter calculated.

c. pH

The pH of 2 % w/v dispersion of the gum was determined, 24 h after preparation, using a pH meter (model PHH 103B, Omega Engineering, Singapore).

d. Metal ion content

The method described by Ofori-Kwakye *et al*. (2010) was used. One gram of powdered gum was weighed, transferred into a 250 ml beaker and 25 ml of concentrated nitric acid was added. The sample was digested on a hot plate in a fume chamber, cooled and 1 ml of 70 % perchloric acid added. A 30 ml portion of deionized water was added to the digest and the mixture was boiled for 10 min and filtered hot into a 100 ml volumetric flask through a Whatman No. 4 filter paper. The solution was made to the mark with more deionized water.

One millilitre of the solution was used to determine the content of lead, magnesium, copper and calcium at wavelengths of 283.30 nm, 285.21 nm, 324.75 nm and 422.67 nm respectively using Atomic Absorption Spectrophotometer (Perkin Elmer Analyst 400, Perkin Elmer, USA) fitted with an acetylene flame. Also, 2 ml of the solution was used for the determination of sodium and potassium content using a flame photometer (Jenway Model PFP7, United Kingdom) operated on methane gas.

e. Solubility

The solubility of the gum in water and in 1 % w/v sodium hydroxide solution was determined using the method described by Olorunsola *et al*. (2011). A 2 g sample was dispersed in 20 ml solvent and left overnight. The dispersion was filtered and 5 ml of the filtrate was heated to dryness over a water bath. The residue obtained was weighed and the solubility was calculated as % w/v.

f. Hydration and swelling characteristics

Compacts of 500 mg weight (W_d) of the powdered gums were prepared by compressing the powder using a tableting machine (Shanghai Tiaxiang and Chenta Pharmaceutical Machinery Co., China) fitted with a 12 mm flat faced punch and die. The thickness 'h' and diameter '2r' of the compacts were measured with the aid of micrometer screw gauge.

The compacts were placed on glass plates and transferred into a beaker containing 60 ml of distilled water. At 5 min, 10 min and subsequently 10 min intervals, the glass plates with the hydrated compacts were removed, dried by blotting with tissue paper and then weighed (W_t) using the method of Builders *et al*. (2009) with slight modification. The process was continued until a constant weight of the hydrated mass was obtained

The hydration ratio (HR) was determined using equation 23. When the hydrated compacts reached a constant weight (W_e), the hydration ratio was considered to be the equilibrium hydration ratio, also called hydration capacity (HC) and was determined using equation 24.

$$HR = W_t / W_d \quad \text{..... (23).}$$

$$HC = W_e / W_d \quad \text{.....(24).}$$

The thickness 'h' and diameter '2r' of the hydrated mass at equilibrium were also measured. The swelling capacity (SC) was calculated as the ratio of the volume of swollen mass at equilibrium to the initial volume of the compact. The volume of compact was calculated using equation 25.

$$V = \pi r^2 h \quad \text{..... (25)}$$

The mean swelling time (MST) of the polymer compacts was taken as the time when there was no further increase in volume with time. Equation 26 (Builders *et al*., 2009) was used to determine the parameters 'n' and 'K' (swelling constant and kinetic constant respectively).

$$W_t / W_d = Kt^n \quad \text{..... (26).}$$

$$Log \frac{W_t}{W_d} = LogK + nLogt \quad \text{..... (27).}$$

The values of n and K were obtained from the plot of $Log \frac{W_t}{W_d}$ vs Log t. Values of n and K are the slope and antilog of y-intercept respectively (Builders *et al*., 2009).

g. Moisture sorption capacity (MSC)

The moisture sorption capacity was determined by gravimetric method. A 2 g sample of the gum was placed in a desiccator containing distilled water (relative humidity 100 %) for 5 days after which it was reweighed. The percentage moisture uptake was determined using equation 28 (Beristain *et al*., 2006).

$$MSC = M_m / M_d \times 100\ \% \quad \text{..... (28)}$$

where M_m is the mass of moisture absorbed and M_d is the mass of the dry gum.

h. Moisture content

The percentage moisture content of 2 g sample of the gum was analyzed using electronic moisture analyzer (Type MB 35, OHAUS, Switzerland).

i. Flow properties

For the angle of repose, 20 g of gum was poured inside a funnel of orifice diameter 0.75 cm clamped at height 10 cm from the table surface. The gum was allowed to flow freely and the angle of repose, Θ, was calculated using the equation:

$$\Theta = \text{Tan}^{-1} (2h/D) \text{……..(29)}$$

where h = height of heap and D is the diameter.

Also, 20 g of sample was placed in a flow rate machine (Erweka GMBH, Germany). The time of flow was determined and the flow rate was calculated.

j. Bulk and tapped densities

A 10 g sample was placed in a 50 ml measuring cylinder and the bulk volume was taken. The system was tapped 500 times after which the volume was retaken. The bulk density (BD) and tapped density (TD) were calculated as the ratio of mass to the corresponding volume. The Carr's index (CI) and Hausner's ratio (HR) were calculated using Wells and Aulton (2007) equations:-

$$CI = \frac{TD - BD}{TD} \; X \; 100\,\% \text{.....(30)}$$

$$HR = \frac{TD}{BD} \text{.....(31)}$$

k. Relative density of the gum mucilage

The relative density of a 2 % w/v dispersion of gum in water was determined as a ratio of the weight of 10 ml volume of the gum dispersion to the weight of a similar volume of distilled water.

l. Apparent viscosity of the gum mucilage

The viscosity of a 2 % w/v gum dispersion was measured with a DV1 prime viscometer (Brookfield Engineering, U.S.A.) at room temperature and 10 rpm. About 70 ml of the gum dispersion was placed in the cup of the viscometer and the reading was taken.

m. Microscopy

A 0.5 g gum sample was mounted on a slide. The surface morphology was taken as a photomicrograph using a compound microscope (LW Scientific Inc., U.S.A.) having a camera fitted to the eyepiece.

n. Differential scanning calorimetry (DSC)

DSC analysis was carried out on 3 mg sample in an A1 40 µL crucible using a DSC – 204FI machine (NETZSCH Co., Germany). The scanning was done at 20 ^{o}C/min heating rate over a temperature range of 0 – 500 ^{O}C under nitrogen environment.

o. Fourier transform infrared (FTIR) spectroscopy

Samples of each gum were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. FTIR spectra of these prepared samples were recorded at scanning range of 350 to 5,000 cm^{-1} using a spectrophotometer (model 8400S, Shimadzu Corporation, Kyoto - Japan).

p. X-ray diffraction (XRD)

Powder X-ray diffraction pattern of the samples was recorded on an X-ray diffractometer (PANalytical Spectris Pvt. Ltd., Singapore) using a copper target at voltage of 40 KV and a current of 30 mA over scanning range of 10 to 120 $^{0}2\Theta$.

3.2.5 Microbial Limit Test

The nutrient agar was prepared by dissolving 28 g of the solid agar in 1000 ml of sterile water. This growth medium was autoclaved for 20 min. A 20 ml volume of the cooled medium was transferred into each of 20 sterilized bottles.

The microbial limit test was carried out using the pour plate method described in the B.P (2002). One gramme sample of gum was dispersed in 10 ml of sterile water from which 1 ml was taken and diluted with 9 ml of sterile water to give a 1 in 100 dilution (10^{-2}). One millilitre of the resulting solution was aseptically transferred to a bottle containing 20 ml of the nutrient agar using seeding method. The bottle was shaken and the content poured into a labeled sterilized Petri dish. The preparation was done in triplicates for each of the gums. A positive control and negative control were also set up. The preparations were incubated at 37 ^{O}C for 48 h after which the number of growth in each plate was counted. The total viable aerobic count per gram of gum was calculated as the ratio of number of colonies to the dilution factor.

3.2.6 Surface Activity of the Gums

a. Surface tension

Dispersions (100 ml) of different gum concentrations (0.0, 0.1, 0.25, 0.5, 0.75 and 1.0 % w/v) were prepared, stirred and left for 24 h for hydration and dissolution. A Searls tensiometer (Philip Harris P23660/9, England) was used for the determination of surface tension. The circular plate was submerged below the surface of the gum dispersion and then gradually raised upward. The equipment was zeroed when the plate was just at the surface of the gum dispersion. The plate was subsequently raised until it just detached from the surface of the liquid. The reading was taken from the scale and converted to kg (10 mm being equivalent to 10^{-3} kg as specified on the instrument).

The surface tension of the liquid was calculated using the modified form of the equation of Fell (2007) :

$$= \frac{F}{2\pi R} \cdot \emptyset \quad \text{.....(32)}$$

where γ is the surface tension, F is the detachment force, R is radius of the circular plate and Ø is the correction factor of the instrument.

$$F = mg \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(33)$$

where m is the mass causing detachment and g is acceleration due to gravity.

***b*. Critical micelle concentration**

A graph of surface tension was plotted against gum concentration for the range 0.0 to 1.0 % w/v. The critical micelle concentration was determined as the point when increase in concentration did not lead to further decrease in surface tension.

3.2.7 Hydrophile – Lipophile Balance

Two methods were used for the determination of HLB values of the gums.

a. Distribution or partition coefficient method

The partition coefficient of the surfactant (gum) was determined using n-hexane and water (Schulte *et al.*, 1998). Both water and n-hexane were mutually saturated before performing the experiment. A 50 mg portion of the gum was dissolved in 10 ml of distilled water to give a 5 mg/ml solution. Thereafter, 10 ml of saturated n-hexane was added to the flask. The mixture was stirred on a mechanical shaker for 10 min and then left for 24 h.

The aqueous phase was isolated and evaporated to dryness to get the amount of gum partitioned to the aqueous phase. Amount of gum in the non-aqueous phase was obtained by calculating the difference between total gum and the gum in the aqueous

phase. The partition coefficient was calculated as the ratio of amount of gum in n-hexane to the amount of gum in the aqueous phase.

b. Phenol index (Titration method)

A 50 ml volume of 2 % w/v gum was titrated with a 5 % w/v of phenol until clouding just became visible. The volume of phenol solution used (known as phenol index, PI) was noted and the HLB value was calculated using equation 34 (Kruglioaokor, 2000)

$$HLB = 0.89\ (PI) + 1.11 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (34)$$

3.2.8 Compatibility of Gums with Artemether and Artesunate Sodium

Cashew gum and prosopis gum having different HLB values were chosen for the evaluation of effect of gums on the release and permeation of artemether and artesunate sodium. The compatibility of each gum with each of the drugs was evaluated using the following methods:

a. Different scanning calorimetry (DSC)

The DSC analysis of pure drug, pure gum and drug/gum mixtures were carried out using the method described in 3.2.4 (n).

b. Fourier transform infrared (FTIR) spectroscopy

Samples of each drug, each gum and drug/gum mixtures were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. FTIR spectra of these prepared samples were obtained as in 3.2.4 (o).

c. ***X-ray diffraction (XRD)***

Powder X-ray diffraction patterns of each drug, each gum and drug/gum mixtures were obtained using the method described in 3.2.4 (p).

3.2.9 Formulation of Artemether and Artesunate Sodium Tablets

a. Preparation of granules

Cashew gum and prosopis gum were used as binders for the preparation of granules of batch sizes of 50 tablets. Artemether granules containing varying gum concentrations (1.0, 2.0, 3.0 and 4.0 % w/w) were prepared by wet granulation. Two other batches containing 2.0 % w/w gum and 2.0 or 4.0 % w/w chitosan were also prepared (Table 3.1). A batch containing 3 % w/w of standard acacia gum was also produced. The preparations were such that 275 mg tablet contained 20 mg of artemether and varying concentrations of binder with or without chitosan (permeation enhancer).

Artesunate sodium granules containing similar gum and chitosan concentrations were also prepared by wet granulation based on the formula in Table 3.2. The preparations were such that 275 mg tablet contained 50 mg of artesunate sodium and varying concentrations of binder with or without chitosan.

Table 3.1 Formula of Artemether Tablets

Ingredient	I	II	III	IV	V	VI
Artemether (%)	7.3	7.3	7.3	7.3	7.3	7.3
Maize starch B.P (%)	10.0	10.0	10.0	10.0	10.0	10.0
Lactose (%)	79.7	78.7	77.7	76.7	76.7	74.7
***Binder (%)**	1.0	2.0	3.0	4.0	2.0	2.0
Chitosan	-	-	-	-	2.0	4.0
Talc (%)	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5
Total weight of tablet(mg)	**275**	**275**	**275**	**275**	**275**	**275**

Table 3.2 Formula of Artesunate Sodium Tablets

Ingredient	I	II	III	IV	V	VI
Artesunate sodium (%)	18.2	18.2	18.2	18.2	18.2	18.2
Maize starch B.P (%)	10.0	10.0	10.0	10.0	10.0	10.0
Lactose (%)	68.8	67.8	66.8	65.8	65.8	63.8
***Binder (%)**	1.0	2.0	3.0	4.0	2.0	2.0
Chitosan	-	-	-	-	2.0	4.0
Talc (%)	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5
Total weight of tablet (mg)	**275**	**275**	**275**	**275**	**275**	**275**

The weighed quantities of active ingredient (artemether or artesunate sodium), maize starch B.P and lactose were dry-mixed for 5 min and then moistened with 2.5 ml mucilage of the binder (ACG, CSG or PRG). The wet mass was screened through a 2.0 mm mesh and dried in a hot air oven (Gallenkamp, Germany) at 60 ^{o}C for 1 h. It was then screened through a 1.0 mm mesh.

b. Determination of granule micromeritics

The dried granules were evaluated for angle of repose, flow rate, bulk and tapped densities using the methods described in section 3.2.4.

c. Preparation of tablets

The weighed quantity of chitosan was added to appropriate batches of granules. Talc and magnesium stearate were also weighed and gently blended with the dried granules. The resulting granules were compacted at compaction pressure of 60 KN using a single punch tableting machine (Erweka, Germany) fitted with 8.0 mm punches.

3.2.10 Evaluation of Tablet Quality

A period of 24 h was allowed for all the batches of tablet produced to undergo stress relaxation before subjecting them to quality control tests (Alebiowu and Itiola, 2003). The various tests carried out included: uniformity of weight, thickness and diameter measurement, crushing strength, friability, disintegration and dissolution tests.

a. ***Uniformity of weight***

Twenty tablets were weighed individually and collectively from each batch using an analytical balance (Mettler, Germany). The mean weight was computed as total weight divided by 20. The standard error of the mean was also calculated.

b. ***Thickness and diameter***

The thickness and diameter of tablets were measured using digital caliper (Z 540 – 1, U.S.A.) 24 h after the tablets were produced. The thickness and diameter of 5 tablets were determined for each batch. The mean and standard error of the mean were subsequently calculated.

c. Crushing strength

The crushing strength of five tablets selected at random from each batch was determined using Monsanto hardness tester (Laboratory Tree Co., India). It was done by holding tablet between a fixed anvil and a moving jaw. The load was gradually increased until the tablet just fractured. The value of the load gives a measure of the crushing strength.

d. Friability

Ten tablets were dusted, weighed together and then subjected to abrasion test in Roche frabilator (model Tar 10, Erweka, Germany) operated at 25 rpm for 4 min. The tablets were then dedusted properly and weighed again collectively. The difference in weight was determined and the friability value was calculated as the ratio of difference in weight to the initial weight expressed as percentage.

e. Disintegration time

The disintegration times of the tablets were determined using disintegration tester (Type ZT3, Erweka, Germany). Distilled water thermostatically maintained at 37 ^{0}C was used as the disintegration medium. One tablet was placed in each of the six tubes and the disintegration machine was set to operate at thirty cycles per minute. The time for each

of the six tablets to disintegrate and pass through the mesh of the gauze disc was determined using a stop clock (Smith Clock, Britain).

f. Dissolution test

Different concentrations of artemether (0.05, 0.10, 0.15, 0.20 and 0.25% w/v) were prepared and the absorbance was taken at 210 nm. Different concentrations of artesunate sodium (0.10, 0.20, 0.30, 0.40 and 0.50% w/v) were also prepared and the absorbance was taken at 216 nm (USP Medicines Compendium, 2013). The Beer-Lamberts plots of the two drugs were thereafter constructed.

Dissolution test was carried out using U.S.P. dissolution apparatus (Panomex Inc., India). A tablet was placed inside the dry basket of the apparatus and lowered inside the beaker containing 900 ml of 0.1 M hydrochloric acid thermostatically maintained at 37.0 ± 0.5 ^{O}C. The apparatus was set to a rotational speed of 100 rpm for 1 h. At 10 min intervals, 10 ml samples were taken with subsequent replacement with equal volume of the dissolution medium. Each withdrawn sample was filtered and diluted with pure dissolution medium. The absorbance was taken at 210 nm for artemether and 216 nm for artesunate sodium (USP Medicines Compendium, 2013) using UV spectrophotometer (UNICO Shanghai Instrument, China). Amount of drug release at a given time was obtained by relating the absorbance of the solution to the Beer-Lambert's plot. A graph of cumulative percent drug released was plotted against time.

3.2.11 Permeation Studies

(a) Preparation of simulated gastric fluid (SGF)

The method of Adikwu *et al*. (2005) was used for this preparation. A 2.0 g quantity of sodium chloride was dissolved in 100 ml of distilled water and 7.0 ml of 14 M

hydrochloric acid was added. The solution was made up to 1,000 ml and the pH was adjusted to 1.2 using a pH meter (model PHH103B, Omega Engineering, Singapore).

(b) Preparation of simulated intestinal fluid (SIF)

The method described by Adikwu *et al*. (2005) was used. A 6.8 g quantity of potassium dihydrogen phosphate was dissolved in 250 ml of water and 190 ml of 0.2 N sodium hydroxide and 400 ml of distilled water were added. The resulting solution was adjusted to pH of 6.8 with 0.2 N sodium hydroxide and subsequently diluted with distilled water to 1,000 ml.

(c) Preparation of 1.0 M ethanolic hydrochloric acid solution

An 85 ml of concentrated hydrochloric acid was diluted to 1,000 ml with dehydrated ethanol (International Pharmacopoeia, 2006).

(d) Evaluation of permeation properties

Drug permeation study was carried out with U.S.P. dissolution apparatus using the modified method of Sharma *et al*. (2013). A segment of the intestine of freshly sacrificed pig was cut and used as the donor compartment. It was tied at one end and filled with 5 ml of simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 6.8). The tablet to be studied was introduced into the donor compartment and then tied at the other end.

The donor chamber was immersed into a dissolution apparatus containing 1,000 ml of the receptor medium. For artemether, 1.0 M ethanolic hydrochloric acid solution was used as the receptor medium, while for artesunate sodium, pH 1.2 HCl solution and pH

6.8 phosphate buffer solution were used as the receptor media. The temperature was maintained at 37 ± 0.5 ^{o}C and the apparatus was set to operate for 5 h.

Aliquots of 10 ml were withdrawn at 30 min intervals from the dissolution medium with replacement using pure medium. Each sample was filtered and 5 ml of the filtrate was diluted with 5 ml of pure medium. The resulting solution was analyzed using a UV spectrophotometer (UNICO Shanghai Instrument, China) at 210 nm for artemether and 216 nm for artesunate sodium (USP Medicines Compendium, 2013). A graph of cumulative percent drug permeated was plotted against time. The time for 95% drug permeation ($t_{95\%}$) was read from the plot. The amount of drug permeated in 30 min ($D_{30\ min}$) was also read from the plot. Value of steady state drug flux (J) and permeation coefficient (K_p) were calculated using equations 35 and 36.

$$J = \frac{dQ}{dt\,A} \quad \text{……..……..(35)}$$

where dQ is the change in the quantity of drug absorbed (µg) through the membrane of surface area A (cm^2) within time dt (min).

The value of dQ/dt was estimated from the slope of the straight line portion of graph of percentage drug permeated versus time.

$$Kp = \frac{J}{C} \text{……(36)}$$

where J is the drug flux and C is initial concentration of the drug in the donor compartment.

3.3 STATISTICAL ANALYSIS

Data obtained from evaluations were expressed as mean values ± standard error of the mean. Statistical analysis was done using one-way analysis of variance (ANOVA) followed by Turkey-Kramer multiple comparison test using GraphPad Instat-3 software. Significance of difference was taken at *p - values* less than 0.05. Graphical illustrations were carried out using Microsoft Excel.

CHAPTER 4

RESULTS

4.1 PERCENTAGE YIELD OF GUMS

Cashew exudates gave a gum yield of 48.0% w/w while Khaya exudates gave a yield of 25.0% w/w. Seeds of *Afzelia africana* gave a gum yield of 17.0% w/w while those of *Prosopis africana* gave a yield of 18.2% w/w. The exudates thus gave higher yields of gums compared to the seeds.

4.2 PHYSICAL, CHEMICAL AND THERMAL PROPERTIES

4.2.1 Some Physicochemical Properties

Some physicochemical properties of the four gums and those of acacia gum and sodium carboxymethylcellulose are shown in Table 4.1.

Cashew gum (CSG), khaya gum (KYG) and acacia gum (ACG) were tightly packed while Afzelia gum (AFG), prosopis gum (PRG) and sodium carboxymethylcellulose (SCMC) were fluffy in nature.

There was no significant difference in the moisture content of the experimental gums (CSG, KYG, AFG and PRG). However, the seed gums contained slightly higher amount of moisture compared to the exudate gums. SCMC had significantly higher moisture content.

Table 4.1 Some Physicochemical Properties of the Gums

Parameter	CSG	KYG	ACG	AFG	PRG	SCMC
Taste	Mild-sour	Mild-sour	Mild-sour	Mild-sour	Bland	Bland
Colour	Ash-brown	Golden	Light brown	Yellowish brown	Light brown	White
Odour	Odourless	Odourless	Aromatic	Odourless	Odourless	Odourless
Texture	Moderately coarse	Coarse	Fine	Fluffy	Fluffy	Fine and fluffy
Moisture content (%)	6.59 ± 0.26	6.62 ± 0.41	6.52 ± 1.38	6.81 ± 0.21	8.38 ± 0.03	11.38 ± 36
Ash value	1.00 ± 0.00	4.50 ± 1.50	4.00 ± 1.00	8.00 ± 1.00	1.50 ± 0.50	4.00 ± 2.00
pH (2 % w/v dispersion)	4.04 ± 0.01	3.38 ± 0.00	4.61 ± 0.01	4.50 ± 0.01	4.84 ± 0.01	5.29 ± 0.01
Relative density	1.017 ± 0.00	1.020 ± 0.00	1.018 ± 0.00	1.016 ± 0.00	1.015 ± 0.00	1.086 ± 0.00
Viscosity (mPa-s)	108 – 126	117 – 135	117 – 126	144 – 171	306 – 375	5040 – 5160
Angle of repose (^{O})	33.22 ± 1.14	24.23 ± 0.22	30.69 ± 0.22	42.60 ± 0.29	41.37 ± 0.99	50.56 ± 0.25
Flow rate (g/s)	2.55 ± 0.03	4.22 ± 0.24	2.72 ± 0.05	1.55 ± 0.01	1.16 ± 0.01	0.15 ± 0.00
Bulk density (g/cm^3)	0.63 ± 0.01	0.64 ± 0.01	0.72 ± 0.01	0.32 ± 0.00	0.29 ± 0.00	0.19 ± 0.00
Tapped density (g/cm^3)	0.78 ± 0.01	0.76 ± 0.01	0.82 ± 0.01	0.46 ± 0.01	0.41 ± 0.00	0.30 ± 0.00
Carr's index (%)	19.70 ± 1.00	16.10 ± 1.00	12.00 ± 1.05	29.50 ± 1.50	29.70 ± 0.00	36.30 ± 0.50
Hausner's ratio	1.25 ± 0.01	1.19 ± 0.01	1.13 ± 0.01	1.42 ± 0.01	1.42 ± 0.00	1.57 ± 0.00

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

There was no significant difference between the ash value of KYG and ACG. Their values were significantly higher than that of CSG ($P < 0.001$). Also, there was a significant difference between the ash value of AFG and that of PRG ($P < 0.001$). The ash value was in the order CSG < PRG < SCMC = ACG < KYG < AFG.

The pH of 2 % w/v dispersion of the gums was in the order KYG < CSG < AFG < ACG < PRG < SCMC. The relative density was found to be in the order PRG < AFG < CSG < ACG < KYG < SCMC while the viscosity was in the order CSG < ACG < KYG < AFG < PRG < SCMC.

Khaya gum had the lowest angle of repose and the highest flow rate while sodium carboxymethylcellulose had the highest angle of repose and the lowest flow rate. The bulk density was in the order ACG > KYG > CSG > AFG > PRG > SCMC. Acacia gum had the lowest Carr's index and Hausner's ratio while SCMC had the highest values for both parameters. The Carr's index and Hausner's ratio for the two extracted exudate gums (CSG and KYG) were significantly lower than those of the seed gums.

4.2.2 Metal Ion Content.

The metal ion contents of the different gums are shown in Table 4.2. SCMC had the highest level of sodium ion while KYG had the lowest. AFG had the highest potassium ion content followed by PRG while SCMC had the lowest value followed by ACG and CSG. Potassium was the predominant ion in khaya gum. PRG had the highest magnesium ion content followed by AFG while KYG had the lowest value. Calcium ion was the predominant ion in CSG. Afzelia gum had the highest amount of copper ion. Lead ion was absent in all the gums.

Table 4.2 Metal Ion Content of the Gums

Ion	Concentration (mg/Kg)					
	CSG	**KYG**	**ACG**	**AFG**	**PRG**	**SCMC**
Na^{+}	1,500±0.20	300±0.11	900±0.32	400±0.08	1,000±0.35	71,000±2.5
K^{+}	550±0.25	1,600±0.5	140±0.17	2,100±1.00	1,800±0.60	100±0.05
Mg^{2+}	1,375±0.19	285±0.15	441±0.15	2,045±0.07	2,359±0.30	268±0.34
Ca^{2+}	2,397±0.26	18±0.22	705±0.15	2,489±0.19	967±0.35	204±0.06
Cu^{2+}	3.1±0.04	9.0±0.09	0.00±0.0	20.9±0.08	0.02±0.1	2.1±0.03
Pb^{2+}	0.00±0.00	0.00±0.00	0.00±0.0	0.00±0.00	0.00±0.00	0.00±0.00

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

4.2.3 Microscopy

The surface morphology of the gums are shown in Figure 4.1. The particles of cashew gum, khaya gum and acacia gum are spherical in shape. Khaya gum had more of large particles compared to cashew and acacia gums. The particles of afzelia gum are spherical to rod-like in shape while those of prosopis gum and sodium carboxymethylcellulose are rod-like.

4.2.4 Differential Scanning Calorimetry (DSC) Thermograms

The DSC thermograms of CSG, KYG and ACG are shown in Figure 4.2 (i) while those of AFG, PRG and SCMC are shown in Figure 4.2 (ii). The thermogram of CSG showed a sharp endothermic transition between 20 and 100 ^{O}C with the peak at 70 ^{O}C followed by a diffuse endotherm which peaked at 305 ^{O}C. There was an endothermic transition having peak at 90 ^{O}C immediately followed by a diffuse exotherm which peaked at 275 ^{O}C in the thermogram of KYG. In the thermogram of ACG, an endotherm was observed between 20 and 200 ^{O}C. This was immediately followed by a sharp exotherm between 275 and 335 ^{O}C. The endotherm peaked at 85 ^{O}C while the exotherm peaked at 310 ^{O}C.

An endotherm which peaked at 77 ^{O}C was observed between 20 and 150 ^{O}C in the thermogram of AFG. No other clear transition was observed until at 300 ^{O}C when an exotherm which peaked at 325 ^{O}C but extended to 345 ^{O}C was observed. The thermogram of PRG showed two endotherms. The first one peaked at 62 ^{O}C while the second peaked at about 300 ^{O}C. An endotherm ranging from 20 to 150 ^{O}C with the peak at 70 ^{O}C was observed in the thermogram of SCMC. The second transition which was a diffuse exotherm was observed after 250 ^{O}C and peaked at 295 ^{O}C.

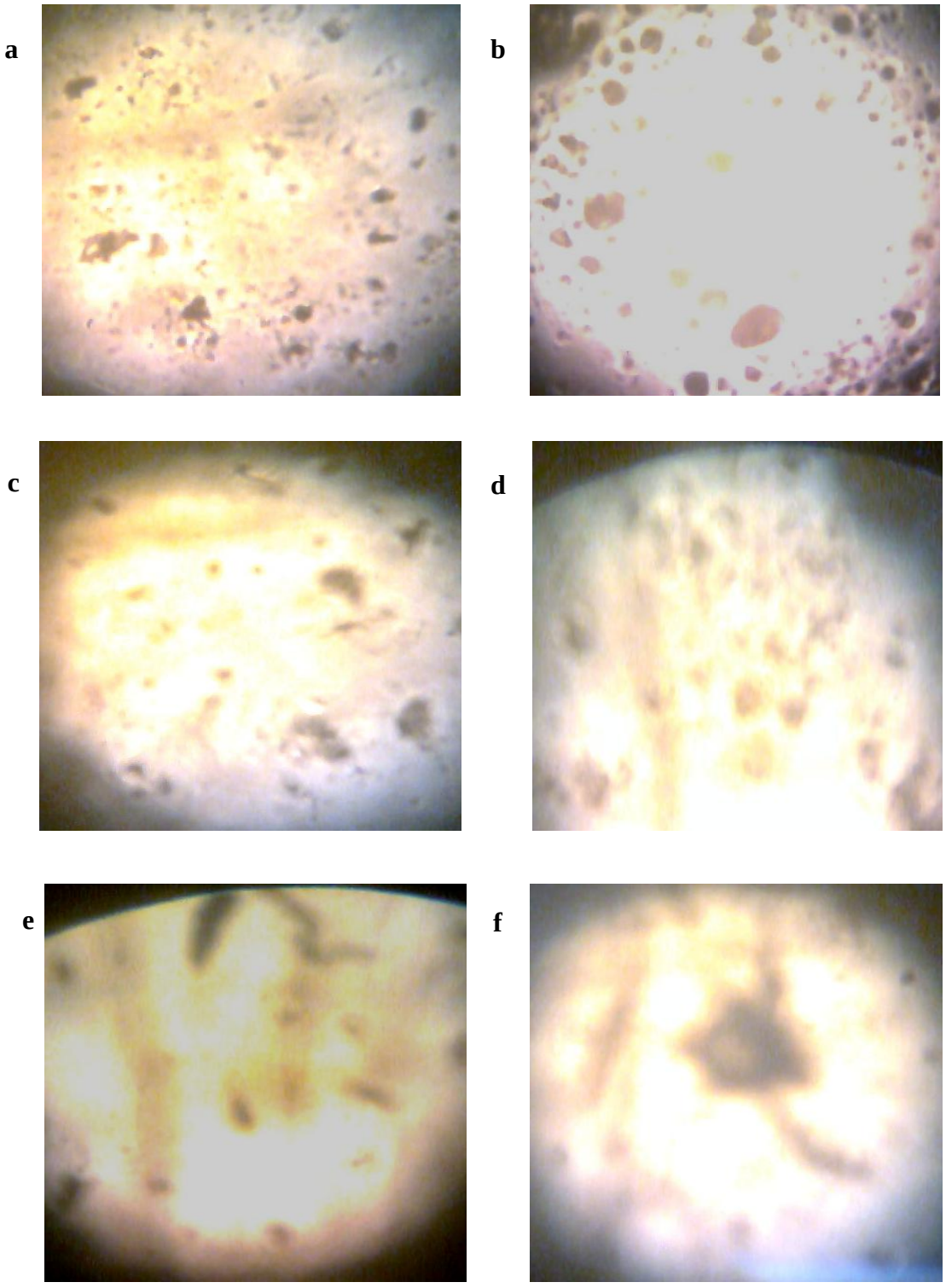


Figure 4.1 Photomicrographs of (a) Cashew Gum (b) Khaya Gum (c) Acacia Gum (d) Afzelia Gum (e) Prosopis Gum (f) Sodium Carboxymethylcellulose Mag. X 400

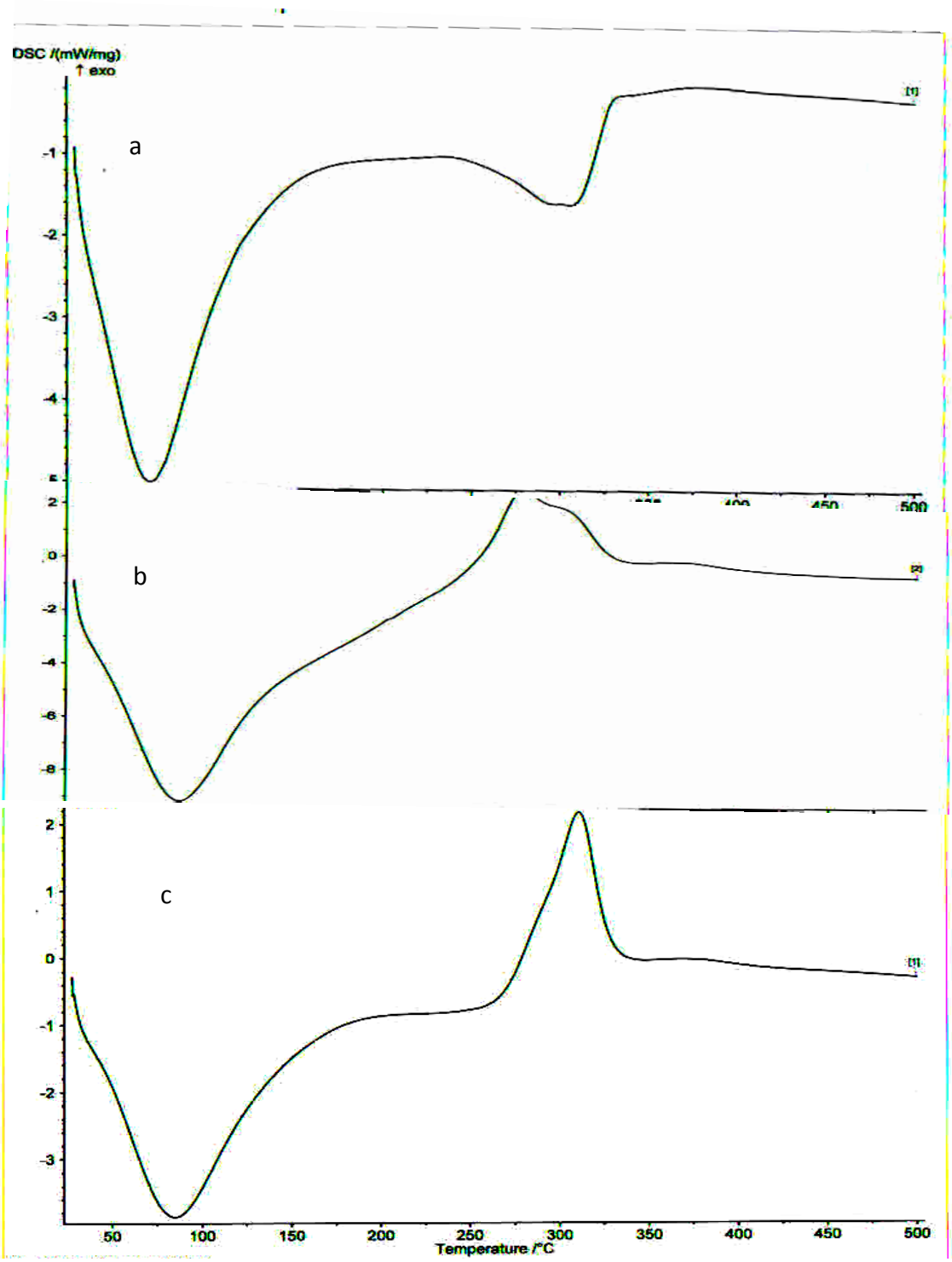


Figure 4.2 (i) Differential Scanning Thermograms of (a) Cashew Gum (b) Khaya Gum (c) Acacia Gum.

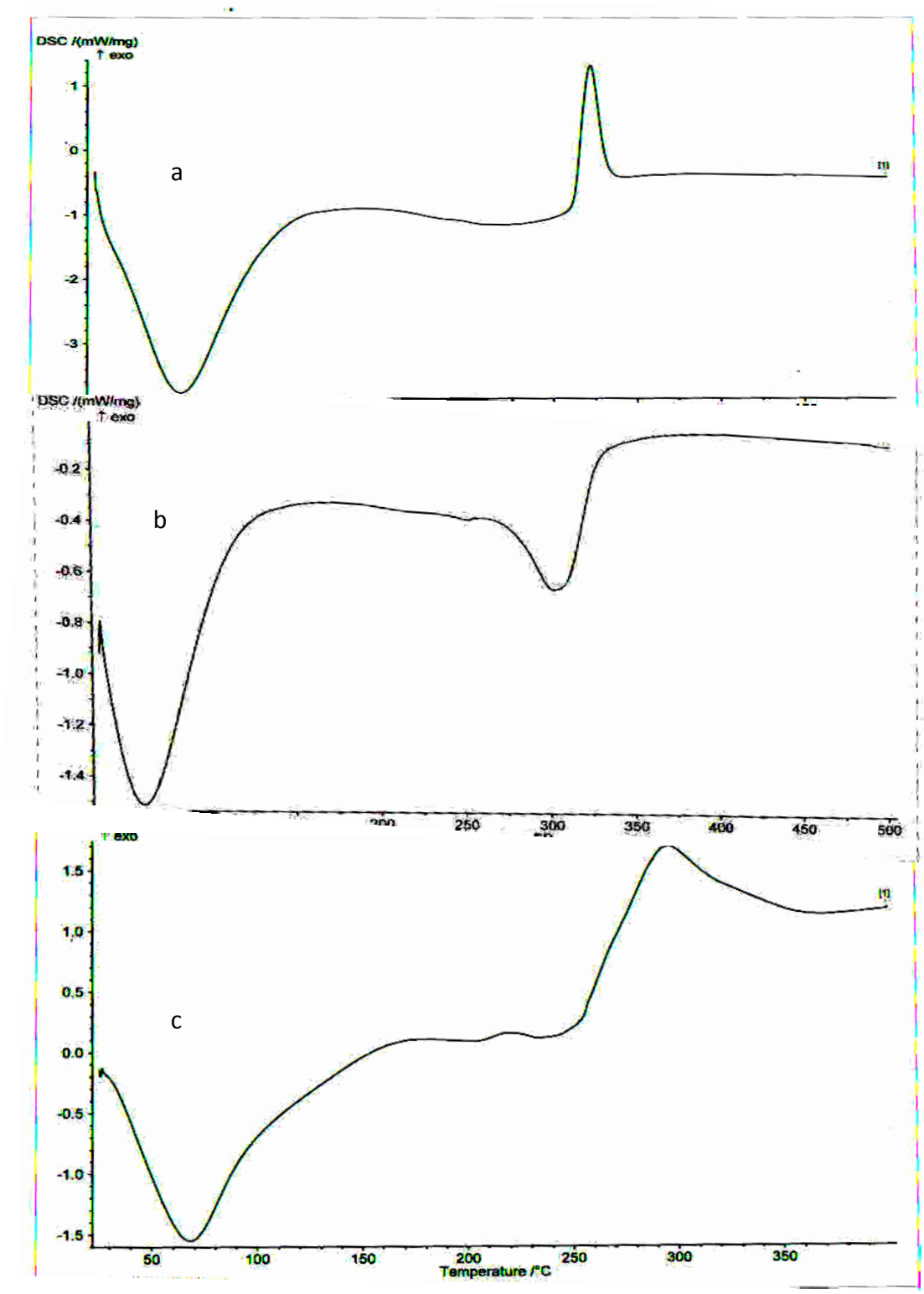


Figure 4.2 (ii) Differential Scanning Thermograms of (a) Afzelia Gum

(b) Prosopis Gum (c) Sodium Carboxymethylcellulose.

4.2.5 Fourier Transform Infra-Red (FTIR) Spectra

The FTIR spectra of the different gums are shown in Figures 4.3 (i) and (ii). Those of the exudate gums are presented in Figure 4.3 (i) while those of the seed gums and SCMC are in Figure 4.3 (ii).

The spectra of cashew gum and khaya gum were similar; the peak of highest intensity being 4,550.23 cm^{-1} for cashew gum and 4,568.55 cm^{-1} for khaya gum. The first absorption peak was 761.91 cm^{-1} for CSG while it was 757.09 cm^{-1} for KYG [Figure 4.3 (i)]. The absorption pattern for CSG and KYG were more diffuse and different from that of ACG. The first peak for ACG was noticed at 597.95 cm^{-1} and the peak at 4,301.4 cm^{-1} had the highest intensity.

The absorption pattern of PRG and SCMC were similar and were different from that of AFG [Figure 4.3 (ii)]. AFG had peak of minimum intensity at 1,390.72 cm^{-1} and that of maximum intensity at 4,384.34 cm^{-1}. PRG had distinct absorptions at 1,643.41cm^{-1} and 2,176.74 cm^{-1} while SCMC had its own at 1,611.58 cm^{-1} and 2,160 cm^{-1}.

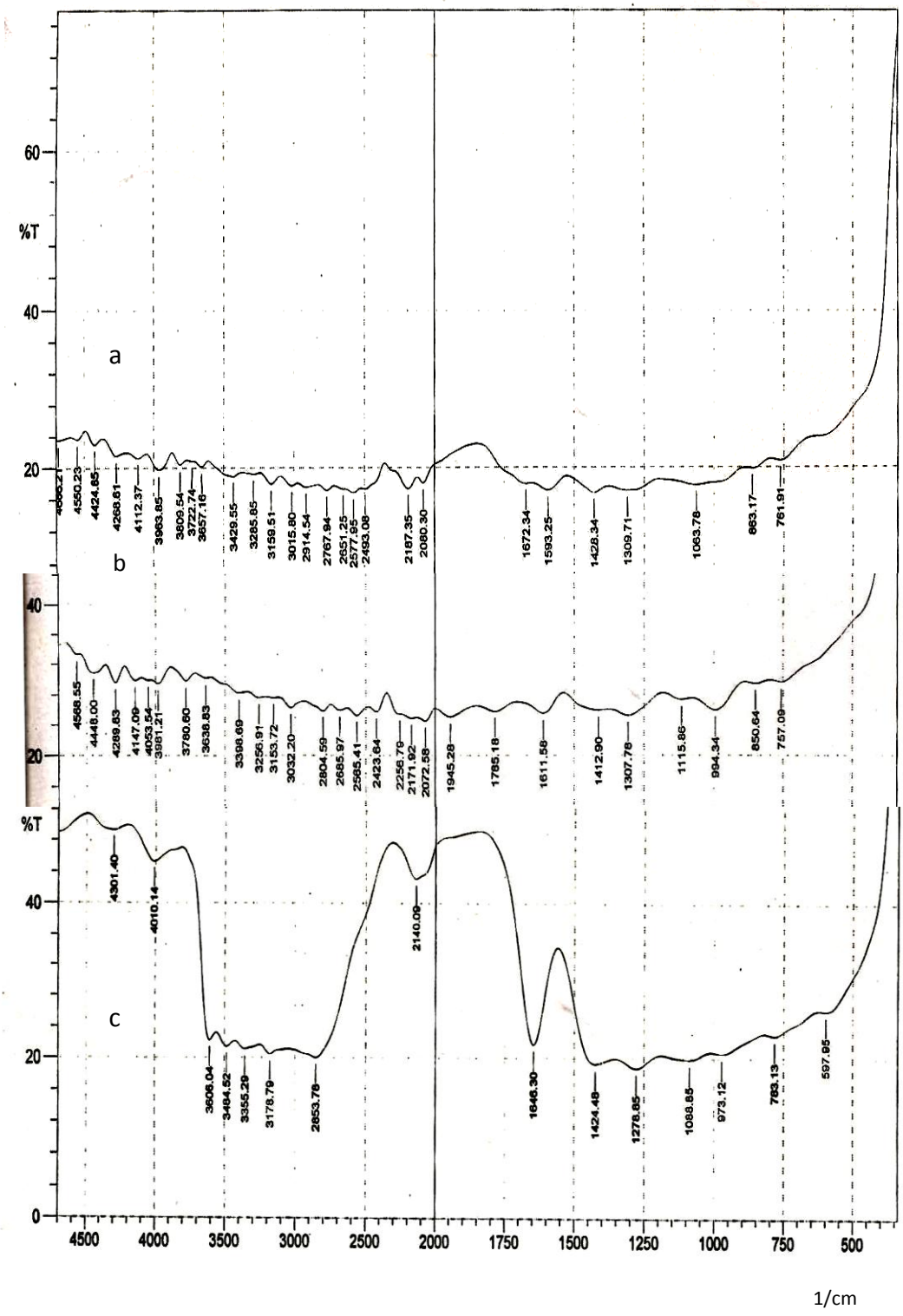


Figure 4.3 (i) Fourier Transform Infrared Spectra of (a) Cashew Gum

(b) Khaya Gum (c) Acacia Gum

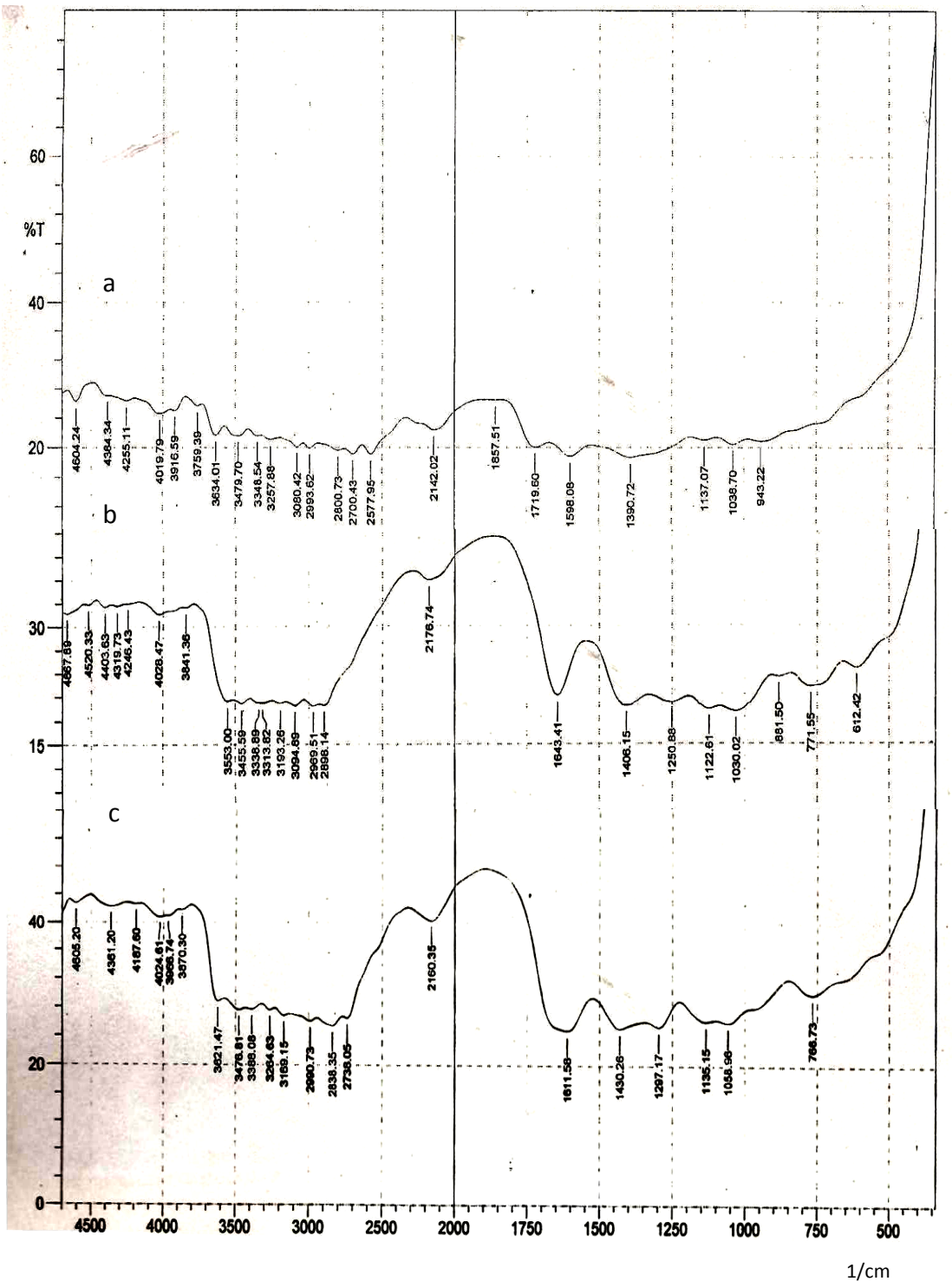


Figure 4.3 (ii) Fourier Transform Infrared Spectra of (a) Afzelia Gum (b) Prosopis Gum (c) Sodium Carboxymethylcellulose

4.2.6 X-Ray Diffraction Spectra

The XRD spectra of the different gums are shown in Figures 4.4 (i) and (ii). The patterns of the exudate gums are presented in Figure 4.4 (i), while those of the seed gums and SCMC are illustrated in Figure 4.4 (ii).

The three exudate gums (CSG, KYG and ACG) had major peak of intensity > 6,400 ct lying between 20 and 22 $^{0}2\Theta$. The cashew gum had two other peaks at 26.50 and 42.34 $^{0}2\Theta$ corresponding to calcium ion. The peak of KYG spectrum is shorter than those of CSG and ACG.

PRG had peak of intensity 6,400 ct at 20.09 $^{0}2\Theta$. AFG had a single major peak of intensity 6,400 ct at 20.00 $^{0}2\Theta$ while SCMC had its major peak of intensity 2,630.42 ct at 19.89 $^{0}2\Theta$.

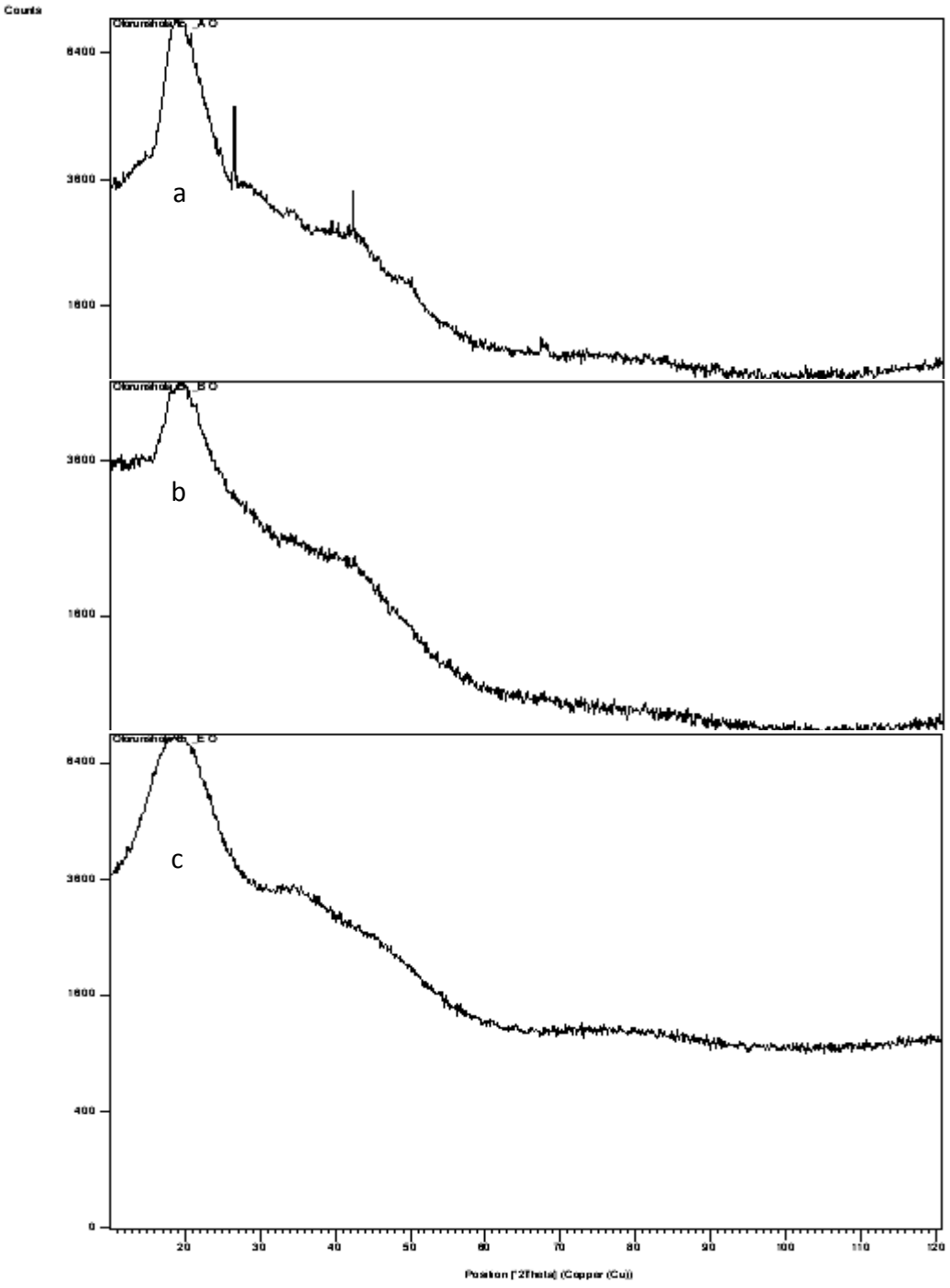


Figure 4.4 (i) X-ray Diffraction Patterns of (a) Cashew Gum (b) Khaya Gum (c) Acacia Gum

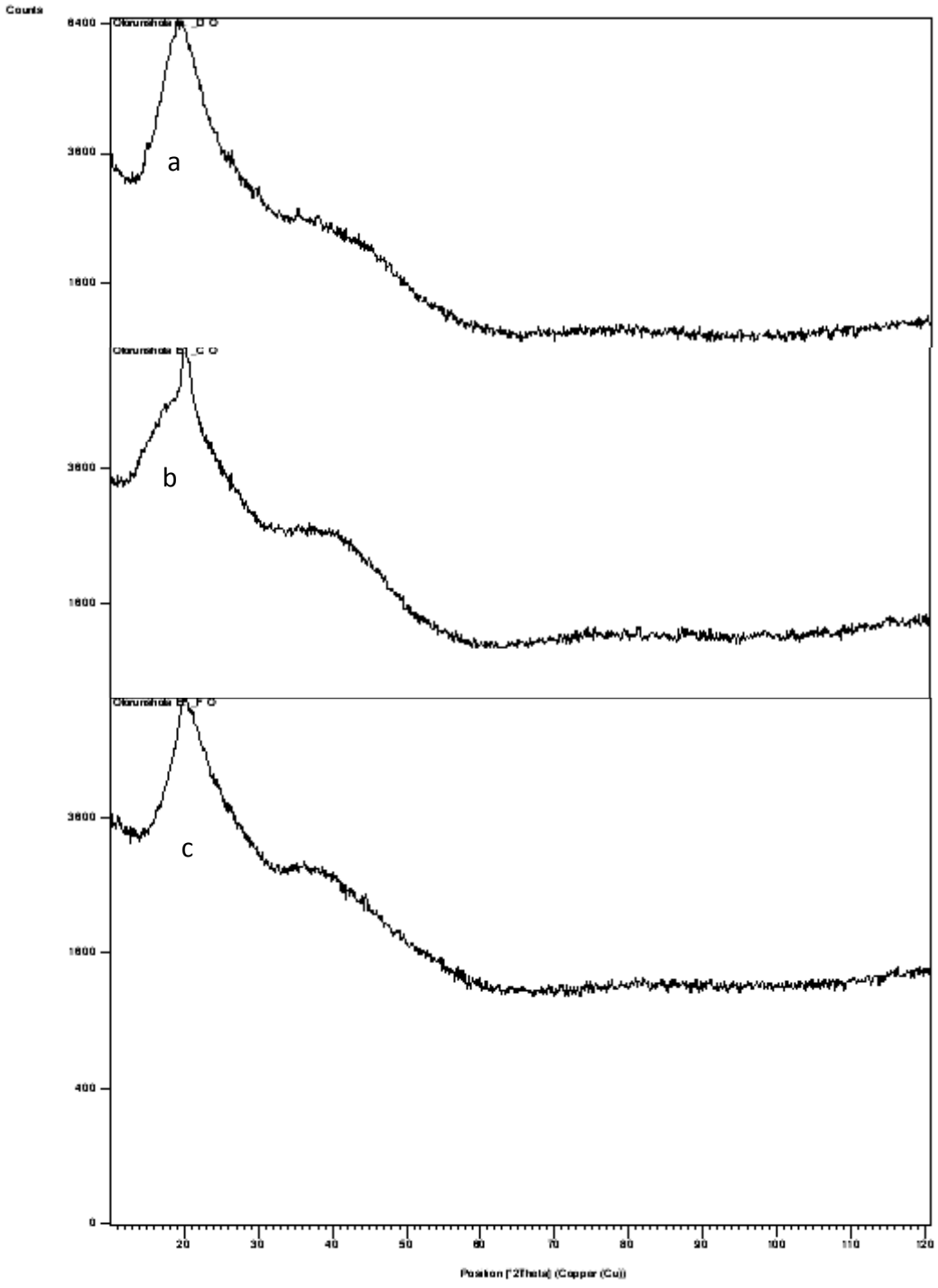


Figure 4.4 (ii) X-ray Diffraction Patterns of (a) Afzelia Gum (b) Prosopis Gum (c) Sodium Carboxymethylcellulose

4.3 BACTERIAL LOAD

The total viable count per unit gram of the different gums is shown in Table 4.3. Among the natural gums examined, CSG had the highest load while KYG had the lowest.

4.4 SURFACE ACTIVITY

The plot of surface tension versus gum concentration is illustrated in Figure 4.5. At the low concentrations, increase in gum concentration for all the gums led to decrease in surface tension of water. At a point (which is unique for each gum), further increase in gum concentration did not result in decrease in surface tension of water. This is equivalent to the critical micelle concentration (CMC) of the gum.

The critical micelle concentration of the gums and the surface tension at CMC are shown in Table 4.4. The critical micelle concentration was in the order SCMC < PRG = AFG = ACG < CSG < KYG. The extent to which the gums could reduce the surface tension irrespective of the concentration was in the order ACG > SCMC > CSG = KYG = PRG > AFG.

Table 4.3 Total Bacterial Load of the Gums

Gum	Viable Bacterial Load (count/g)
CSG	$0.95 \pm 0.008 \times 10^4$
KYG	$0.91 \pm 0.003 \times 10^4$
ACG	$0.92 \pm 0.007 \times 10^4$
AFG	$0.93 \pm 0.010 \times 10^4$
PRG	$0.94 \pm 0.001 \times 10^4$
SCMC	$0.90 \pm 0.010 \times 10^4$

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

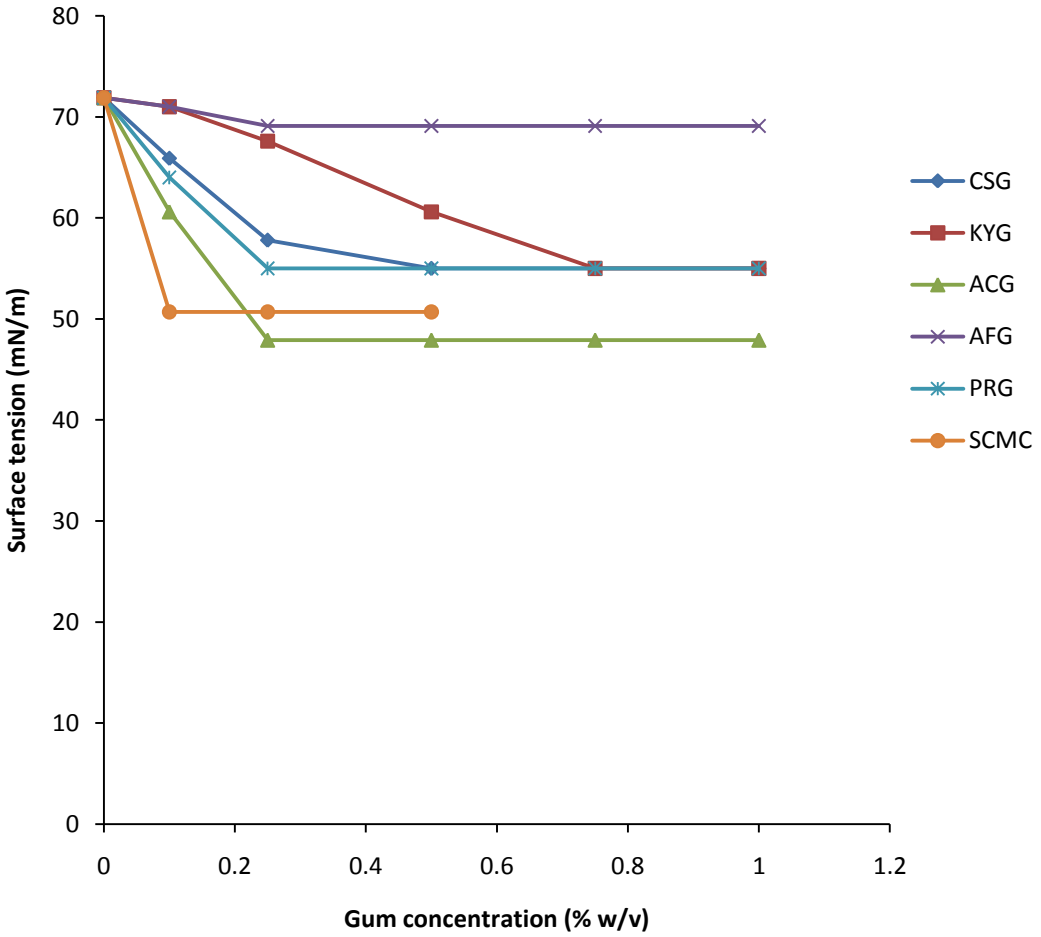


Figure 4.5 Plot of Surface Tension (mN/m) Versus Gum Concentration (% w/v)

Table 4.4 Critical Micelle Concentration (CMC) and Surface Tension at CMC

Gum	CMC (% w/v)	Surface Tension at CMC (mN/m)
CSG	0.50	55.0±0.00
KYG	0.75	55.0±0.00
ACG	0.25	47.9±1.17
AFG	0.25	69.1±1.20
PRG	0.25	55.0±0.00
SCMC	0.10	50.7±0.00

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

4.5 HYDROPHILE-LIPOPHILE PROPERTIES

4.5.1 Hydrophilicity

The parameters relating to the hydrophilicity of the gums are shown in Table 4.5. The solubility of the gums in water was in the order CSG > ACG > KYG > SCMC > AFG > PRG. There was a significant difference ($P < 0.001$) between the solubility of the exudate gums (CSG, ACG and KYG) and those of the seed gums (AFG and PRG). The solubility of each of AFG, PRG and SCMC increased significantly ($P < 0.001$) in 1 % w/v aqueous solution of sodium hydroxide.

The hydration capacity and swelling capacity followed the same trend of SCMC > PRG > AFG > KYG > CSG > ACG. The hydration capacity was higher than swelling capacity for all the gums except for prosopis gum. ACG and CSG had the lowest mean swelling time while PRG and SCMC had the highest value. The plot of $Log\frac{W_t}{W_d}$ vs Log time of hydration is shown in Figure 4.6. The values of 'n' and 'K' respectively derived from the slope and the y-intercept as well as the calculated mean swelling time are shown in Table 4.5.

Table 4.5 Parameters relating to the Hydrophilicity of the Gums

	G U M S					
Parameter	**CSG**	**KYG**	**ACG**	**AFG**	**PRG**	**SCMC**
Moisture sorption capacity (%)	55.90±0.18	73.35±2.42	74.55±0.78	55.00±0.00	76.95±0.40	122.45±0.02
Solubility in water (% w/v)	9.50±0.07	5.85±0.40	8.18±0.40	0.68±0.03	0.12±0.01	1.26±0.74
Solubility in 1% NaOH (% w/v)	8.30±1.49	7.10±2.20	9.50±0.49	7.60±0.00	7.00±2.13	6.80±2.27
Hydration capacity	1.70±0.02	2.31±0.32	1.50±0.40	2.35±0.18	3.00±0.40	5.27±0.00
Swelling capacity	1.12±0.00	1.45±0.07	1.06±0.01	2.08±0.00	3.56±0.02	4.13±0.01
Kinetic constant ‘K’	1.44	1.38	1.17	1.05	1.07	1.07
Swelling constant ‘n’	0.07	0.13	0.08	0.30	0.29	0.42
Swelling time (min)	20.00	30.00	20.00	30.00	70.00	70.00

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

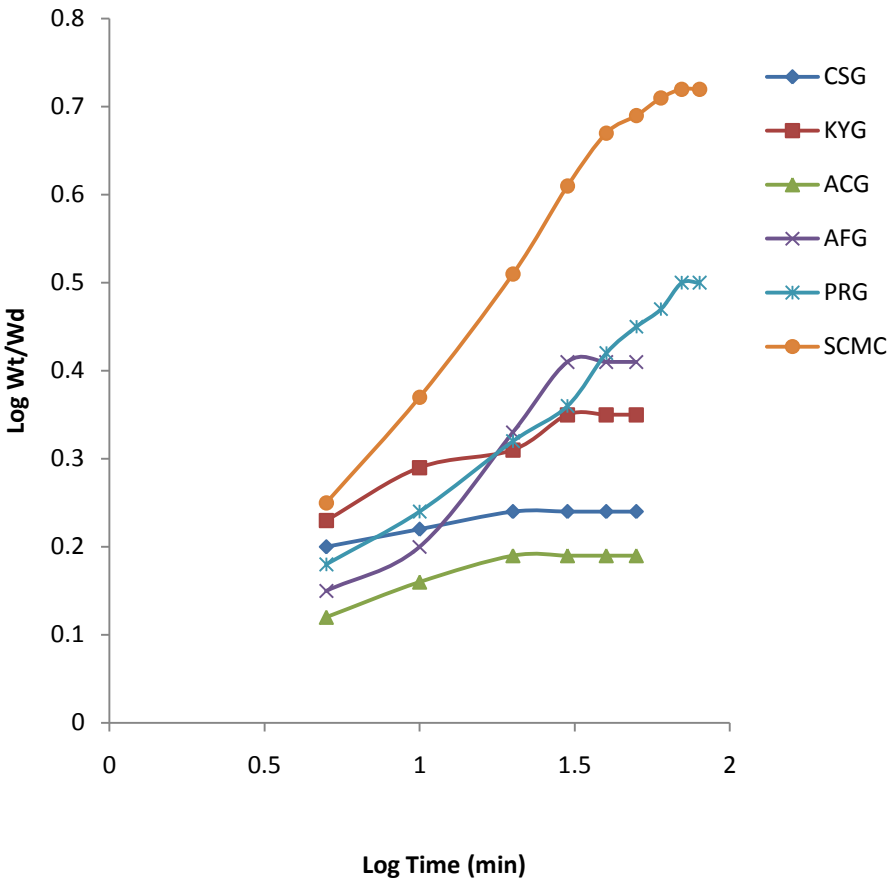


Figure 4.6 Graph of Log of Hydration Ratio Versus Log of Hydration Time

4.5.2 Hydrophile-Lipophile Balance (HLB)

The parameters relating to the HLB values of the gums are shown in Table 4.6. AFG, PRG and SCMC had significantly higher partition coefficient ($P < 0.05$) compared to CSG, KYG and ACG. There was no significant difference in the partition coefficient of CSG, KYG and ACG.

Phenol index and HLB values followed the same trend of CSG > KYG > ACG > SCMC > PRG > AFG. There was no significant difference between the phenol index and HLB values of CSG and KYG.

Table 4.6 Parameters relating to Hydrophile - Lipophile Balance

Gum	Partition coefficient	Volume of phenol (ml)	HLB value
CSG	0.48±0.11	16.83±0.07	16.09±0.08
KYG	0.47±0.11	16.63±0.22	15.91±0.25
ACG	0.48±0.06	14.60±0.25	14.10±0.27
AFG	0.89±0.35	9.70±0.33	9.74±0.36
PRG	0.95±0.05	11.40±0.49	11.26±0.53
SCMC	1.00±0.00	14.53±0.05	14.04±0.06

CSG= Cashew gum KYG= Khaya gum ACG= Acacia gum

AFG= Afzelia gum PRG= Prosopis gum SCMC= Sodium carboxymethylcellulose

4.6 COMPATIBILITY STUDIES

4.6.1 Artemether with Cashew Gum

The DSC thermograms of the pure drug, pure gum and 1:1 mixture of the drug and the gum are shown in Figure 4.7. The thermogram of pure artemether showed an endotherm with a sharp peak at 125 ^{O}C. This was immediately followed by an exotherm having a very sharp peak at 165 ^{O}C and then a very diffuse endotherm between 225 and 250 ^{O}C. The thermogram of pure cashew gum showed two endotherms with peaks at 70 ^{O}C and 305 ^{O}C respectively.

In the artemether - cashew gum mixture, the peak of the first endotherm was observed at 95 ^{O}C while that of the exotherm was observed at 175 ^{O}C. The second endotherm was a diffuse one over a wide temperature range of 200 – 300 ^{O}C.

The FTIR spectra of pure artemether, pure cashew gum and 1:1 mixture of artemether and cashew gum are shown in Figure 4.8. All the major peaks observed in the FTIR spectrum of artemether were seen in the artemether/cashew gum spectrum though with slight differences in position and/or intensity in some instances.

The XRD spectra of the pure drug, pure gum and 1: 9 mixture of the drug and the gum are shown in Figure 4.9. The peaks in artemether / cashew gum spectrum were of lower intensity compared to those of the pure drug. No new peak was formed.

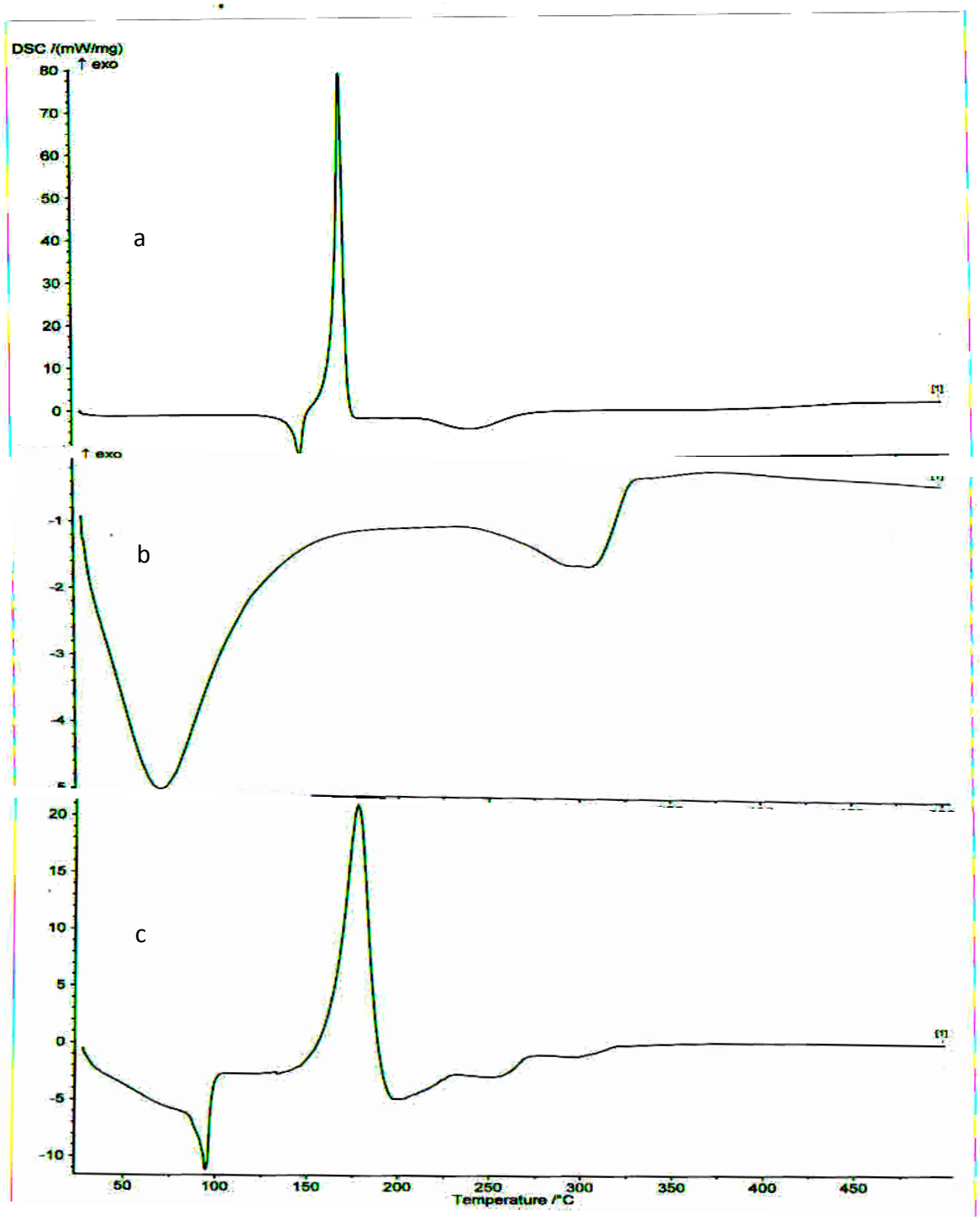


Figure 4.7 Differential Scanning Thermograms of (a) Artemether (b) Cashew Gum (c) Artemether + Cashew Gum

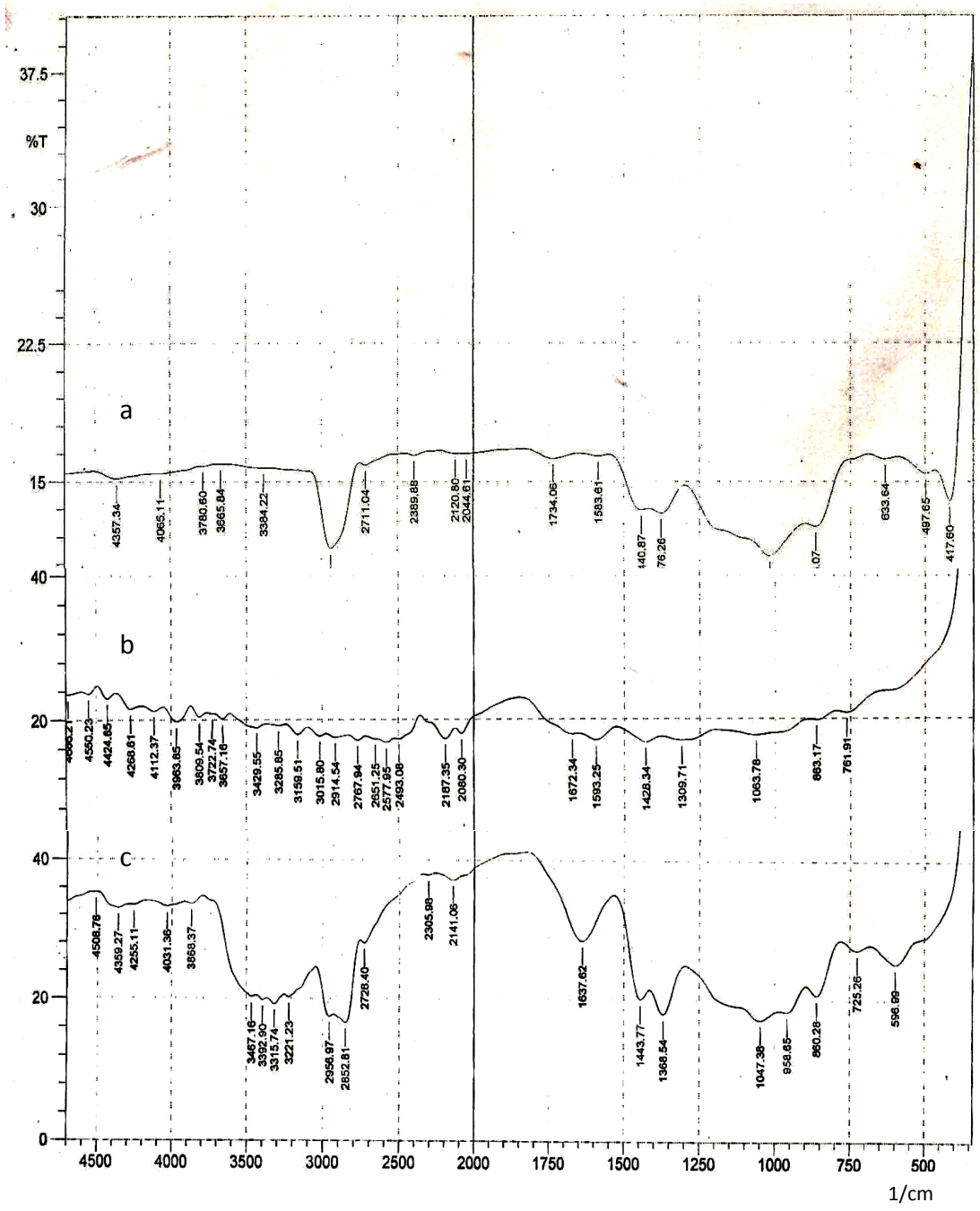


Figure 4.8 Fourier Transform Infrared Spectra of (a) Artemether (b) Cashew Gum (c) Artemether + Cashew Gum

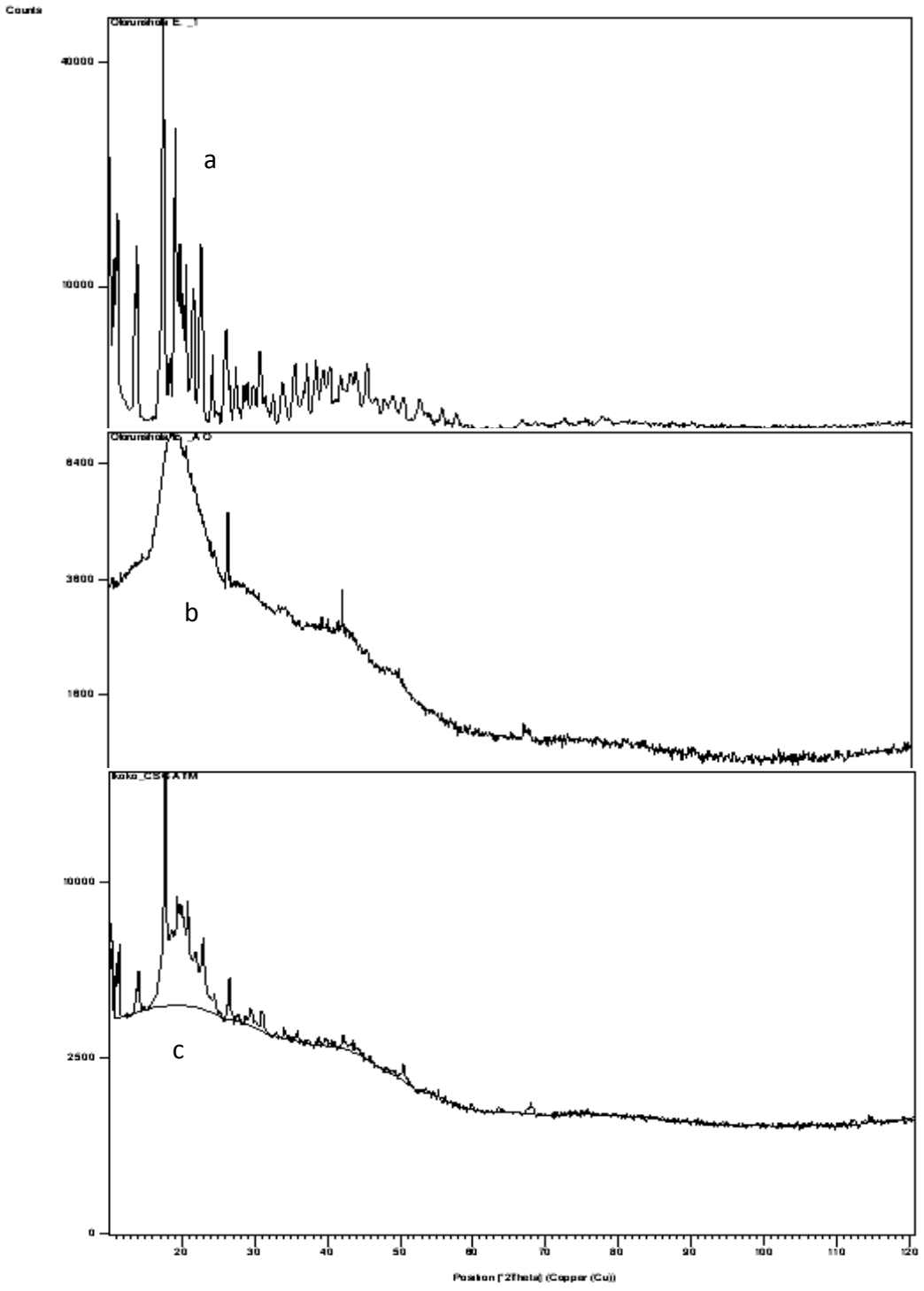


Figure 4.9 X-ray Diffraction Patterns of (a) Artemether (b) Cashew Gum (c) Artemether + Cashew Gum

4.6.2 Artemether with Prosopis Gum

The DSC thermograms of the pure drug, pure gum and 1:1 mixture of the drug and the gum are shown in Figure 4.10. An endotherm with a sharp peak at 125 ^{O}C followed by an exotherm with a very sharp peak at 165 ^{O}C and then a diffuse endotherm extending from 225 to 250 ^{O}C were observed in the thermogram of pure artemether. The thermogram of pure PRG showed two endotherms. The first one peaked at 62 ^{O}C while the second peaked at about 300 ^{O}C.

The thermogram of artemether – prosopis gum mixture showed an endotherm which peaked at 85 ^{O}C followed by an exotherm over the temperature range of 150 – 200 ^{O}C having a sharp peak at 175 ^{O}C. This was immediately followed by another endotherm which peaked at 210 ^{O}C and then a diffuse endotherm at about 300 ^{O}C.

The FTIR spectra of pure artemether, pure prosopis gum and 1:1 mixture of artemether and prosopis gum are shown in Figure 4.11. There were slight changes in the location of some peaks of the drug when it was mixed with the gum.

The XRD patterns of the pure drug, pure gum and 1: 9 mixture of the drug and the gum are shown in Figure 4.12. There was elevation of the base line of the peaks of artemether when it was combined with the gum.

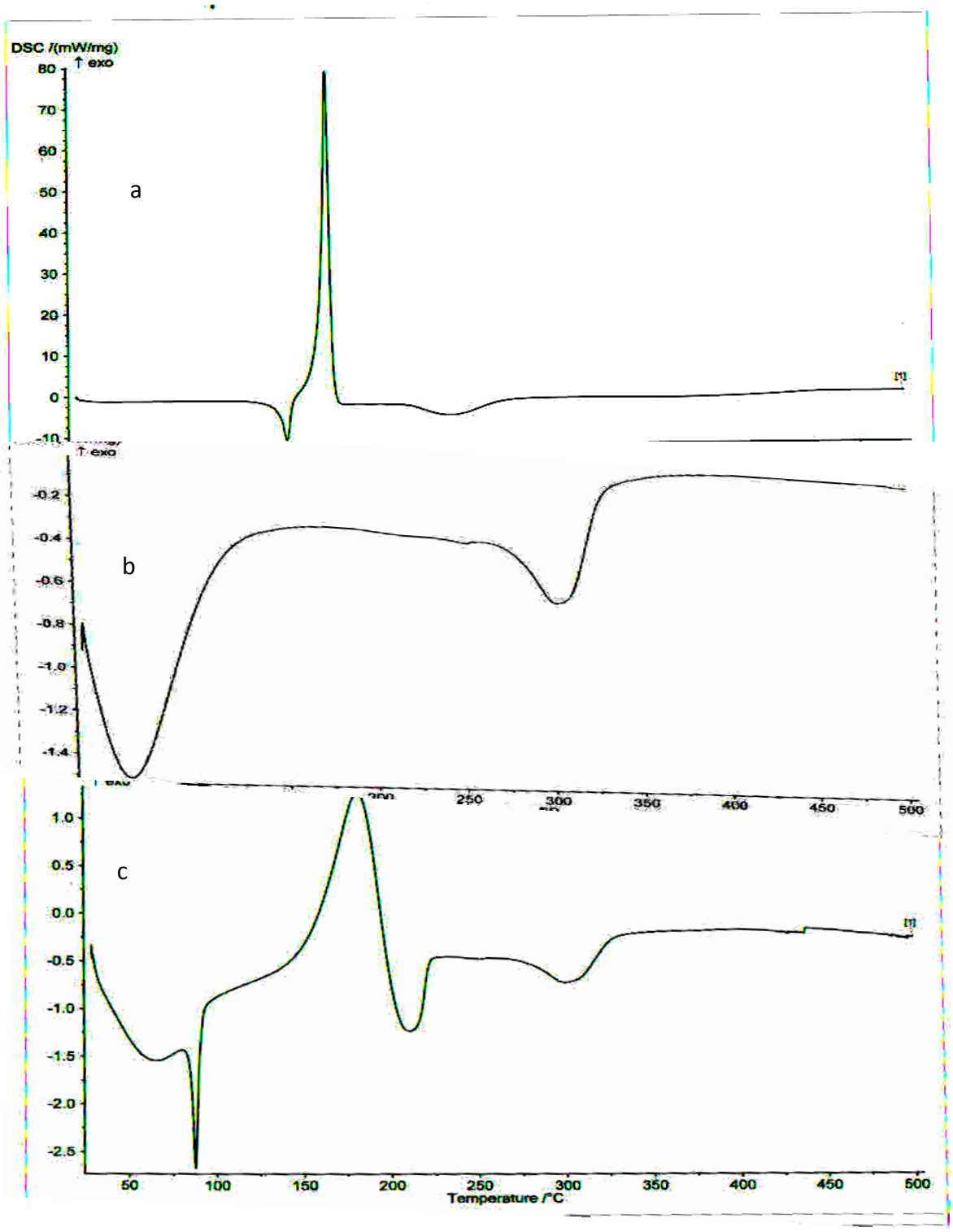


Figure 4.10 Differential Scanning Thermograms of (a) Artemether (b) Prosopis Gum (c) Artemether + Prosopis Gum.

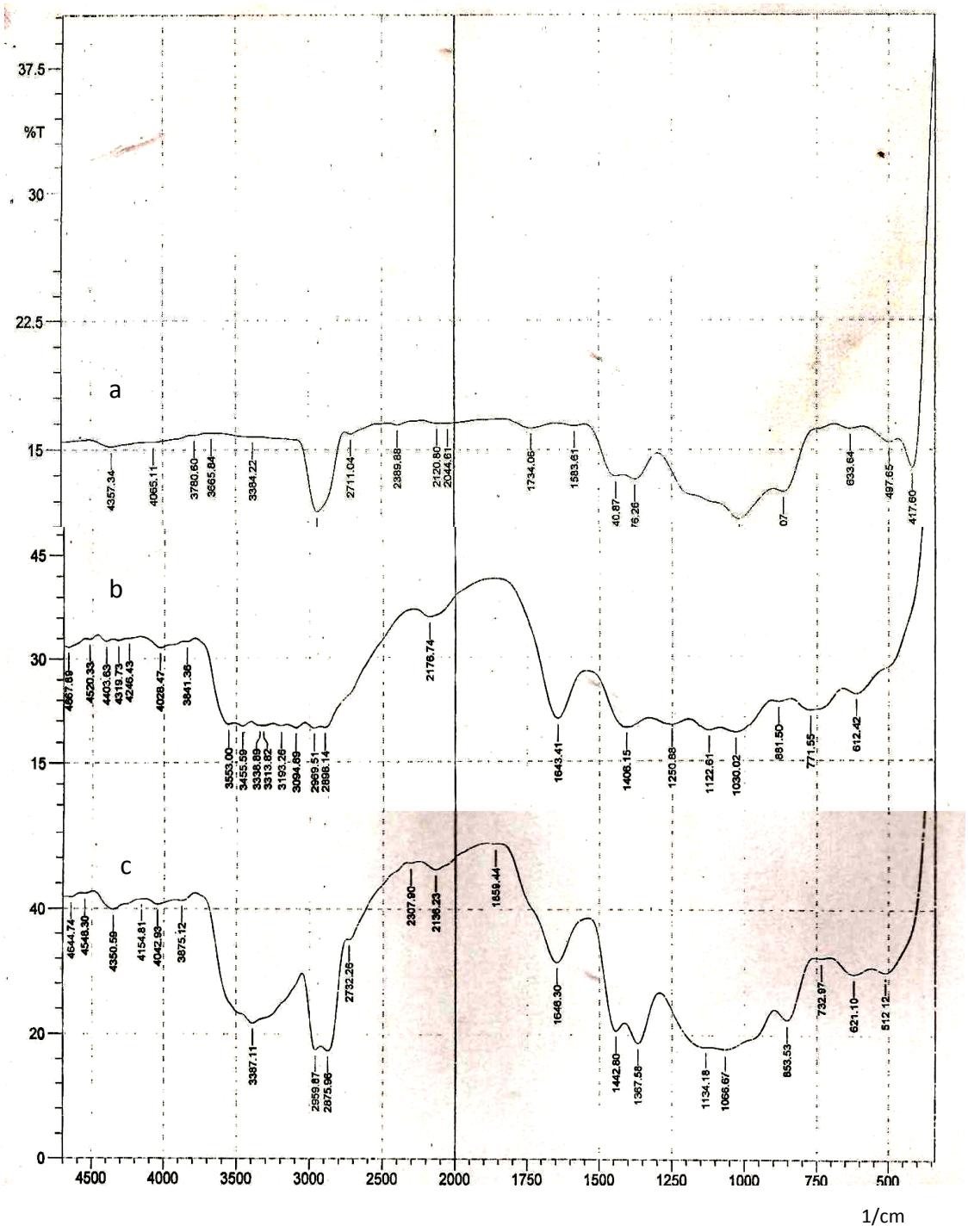


Figure 4.11 Fourier Transform Infrared Spectra of (a) Artemether (b) Prosopis Gum (c) Artemether + Prosopis Gum

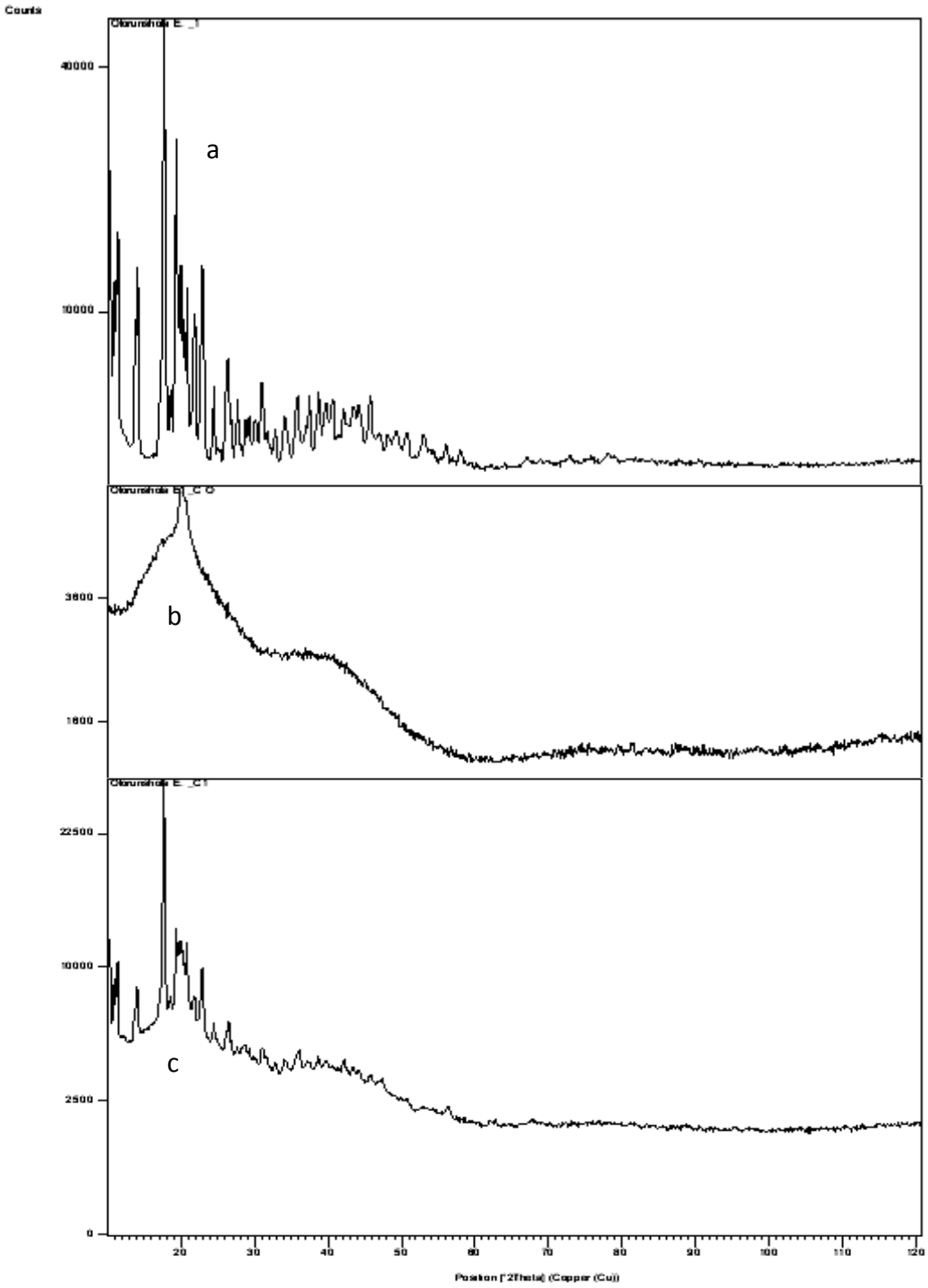


Figure 4.12 X-ray Diffraction Patterns of (a) Artemether (b) Prosopis Gum (c) Artemether + Prosopis Gum.

4.6.3 Artesunate Sodium with Cashew Gum

The DCS thermograms of the pure drug, pure gum and 1:1 mixture of the drug and gum are shown in Figure 4.13. The thermogram of pure ATS showed an endotherm which extended from 35 to 110 ^{O}C and peaked at 70 ^{O}C, an exotherm with a sharp peak at 120 ^{O}C, an endotherm which peaked at 135 ^{O}C and finally another endotherm which peaked at about 300 ^{O}C. Two endotherms with peaks at 70 ^{O}C and 305 ^{O}C were observed in the thermogram of pure cashew gum.

The thermogram of artesunate sodium – cashew gum mixture showed a diffuse endotherm which extended from 30 to 125 ^{O}C and peaked at 70 ^{O}C. This was followed by another endotherm having a sharp peak at 140 ^{O}C, and immediately by an exotherm with a sharp peak at 175 ^{O}C and then a very diffuse endotherm extending from 200 to 310 ^{O}C without a distinct peak.

The FTIR spectra of pure artesunate sodium, pure cashew gum and 1:1 mixture of artesunate sodium and cashew gum are shown in Figure 4.14. There was a positive shift of peaks of artesunate sodium appearing after 1250 cm^{-1} when it was combined with the gum.

The XRD patterns of the pure drug, pure gum and 1:9 mixture of the drug and the gum are shown in Figure 4.15. There was slight elevation in the base level and reduction in the intensity of major peaks of artesunate when it was combined with the gum.

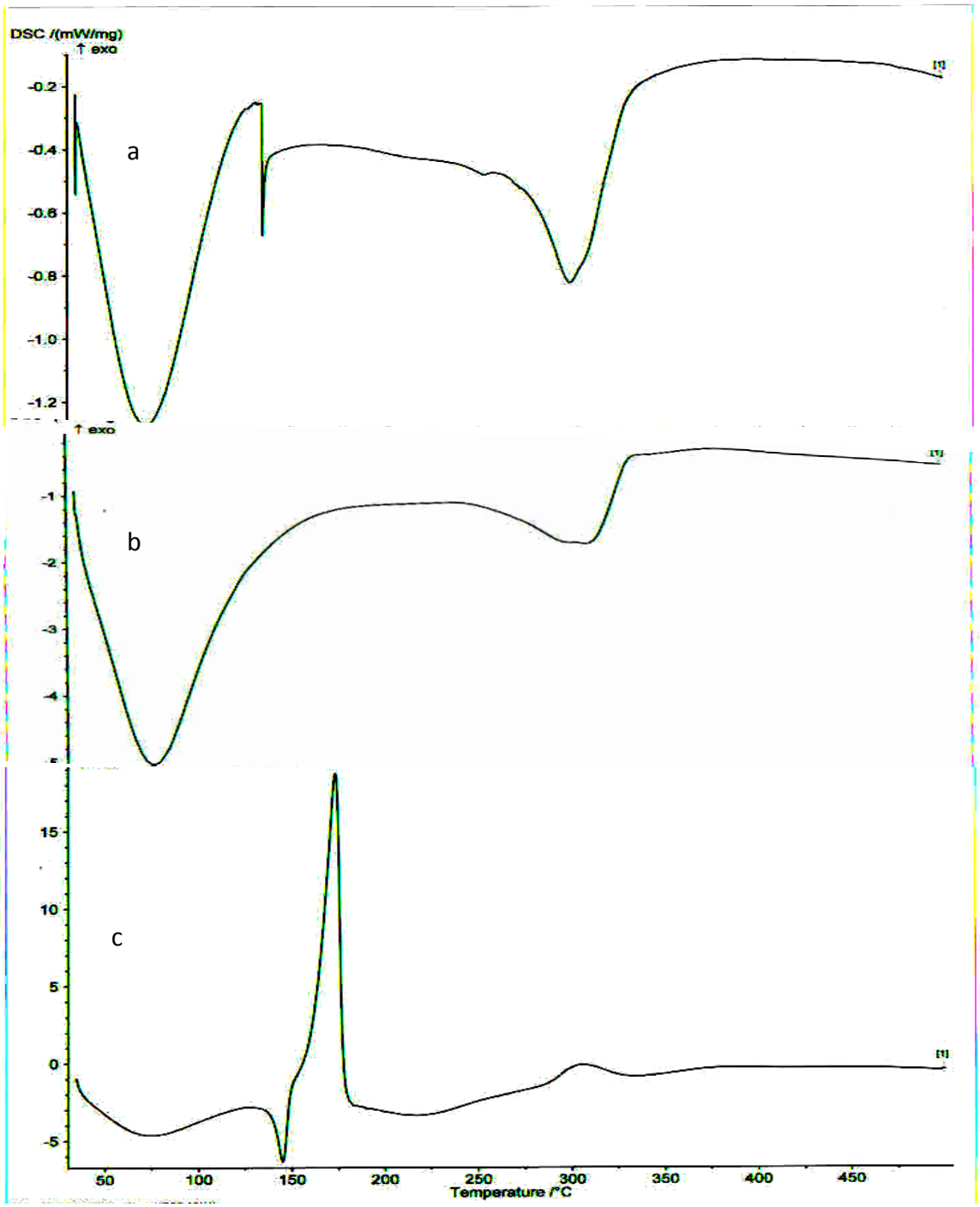


Figure 4.13 Differential Scanning Thermograms of (a) Artesunate Sodium (b) Cashew Gum (c) Artesunate Sodium + Cashew Gum

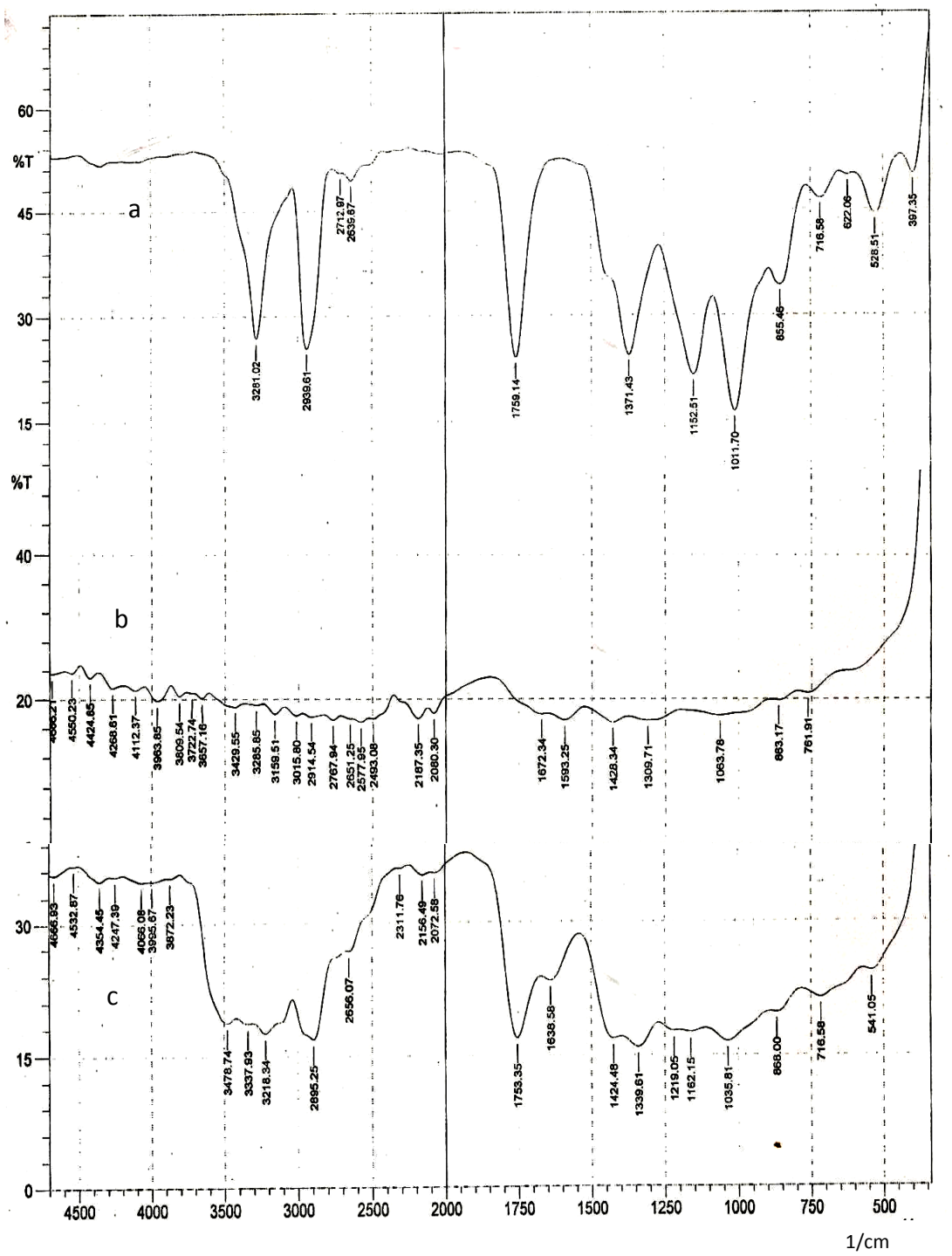


Figure 4.14 Fourier Transform Infrared Spectra of (a) Artesunate Sodium (b) Cashew Gum (c) Artesunate Sodium + Cashew Gum

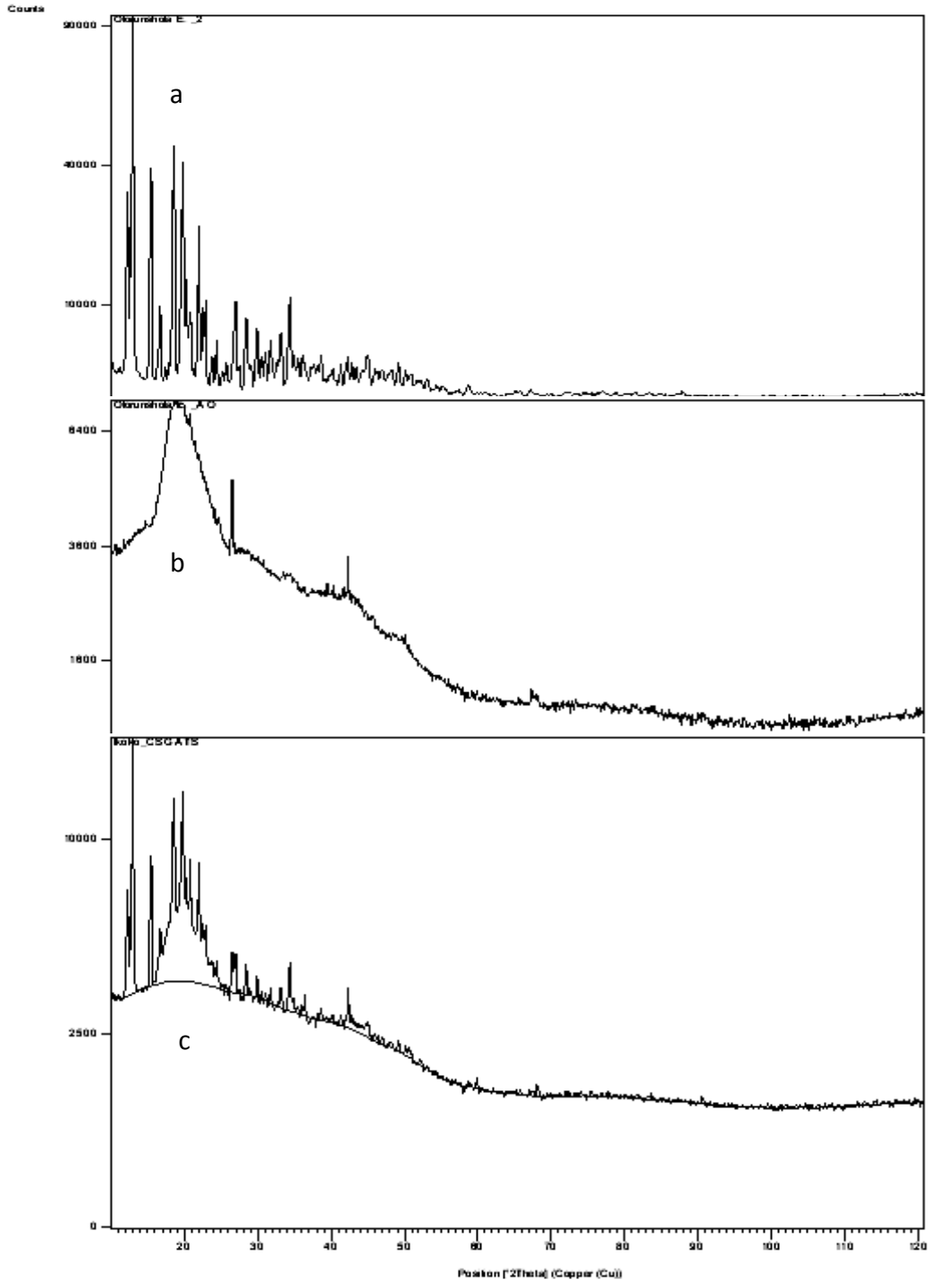


Figure 4.15 X-ray Diffraction patterns of (a) Artesunate Sodium (b) Cashew Gum (c) Artesunate Sodium + Cashew gum.

4.6.4 Artesunate Sodium with Prosopis Gum

The DCS thermograms of the pure drug, pure polymer and drug - polymer (1:1) mixture are shown in Figure 4.16. The thermogram of pure artesunate sodium showed an endotherm which peaked at 70 ^{O}C, an exotherm with a sharp peak at 120 ^{O}C, an endotherm which peaked at 135 ^{O}C and finally an endotherm with a peak at 300 ^{O}C. The thermogram of pure PRG showed two endotherms. The first thermogram peaked at 62 ^{O}C, while the second peaked at about 300 ^{O}C.

The first transition in the thermogram of artesunate sodium – prosopis gum mixture was a diffuse endotherm which peaked at 65 ^{O}C. The second transition was another endotherm having a sharp peak at 140 ^{O}C. This was immediately followed by an exotherm with a sharp peak at 168 ^{O}C and then a very diffuse endotherm which extended from 180 to 280 ^{O}C without a distinct peak.

The FTIR spectra of pure artesunate sodium, pure prosopis gum and 1:1 mixture of artesunate sodium and prosopis gum are shown in Figure 4.17. There was reduction in the intensity and sharpness of the peaks of the drug - polymer mixture.

The XRD patterns of the pure drug, pure polymer and drug-polymer (1:9) mixture are shown in Figure 4.18. There were slight changes in the position and d-spacing of the peaks of the drug - polymer mixture but no new peak was formed.

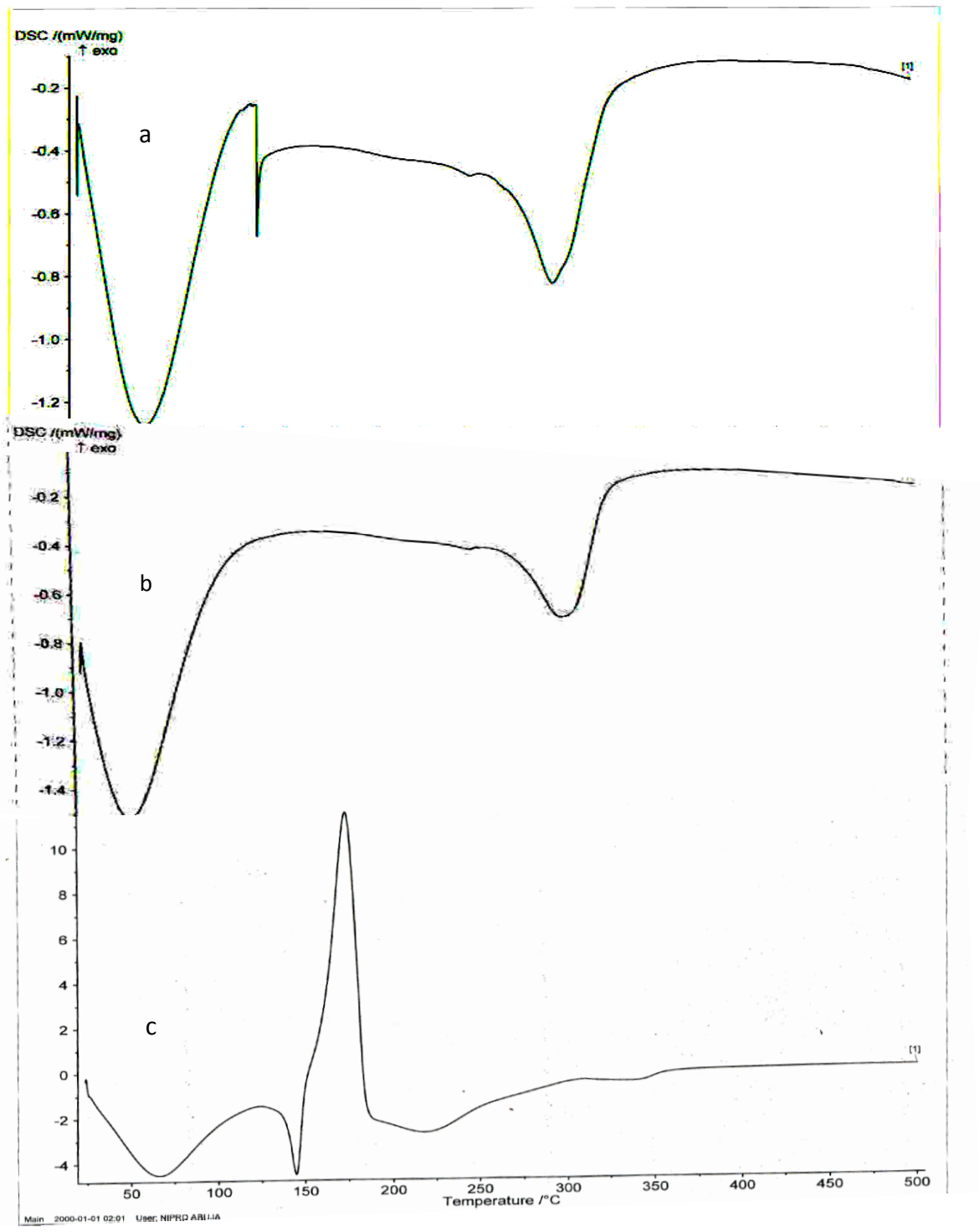


Figure 4.16 Differential Scanning Thermograms of (a) Artesunate Sodium (b) Prosopis Gum (c) Artesunate Sodium + Prosopis gum.

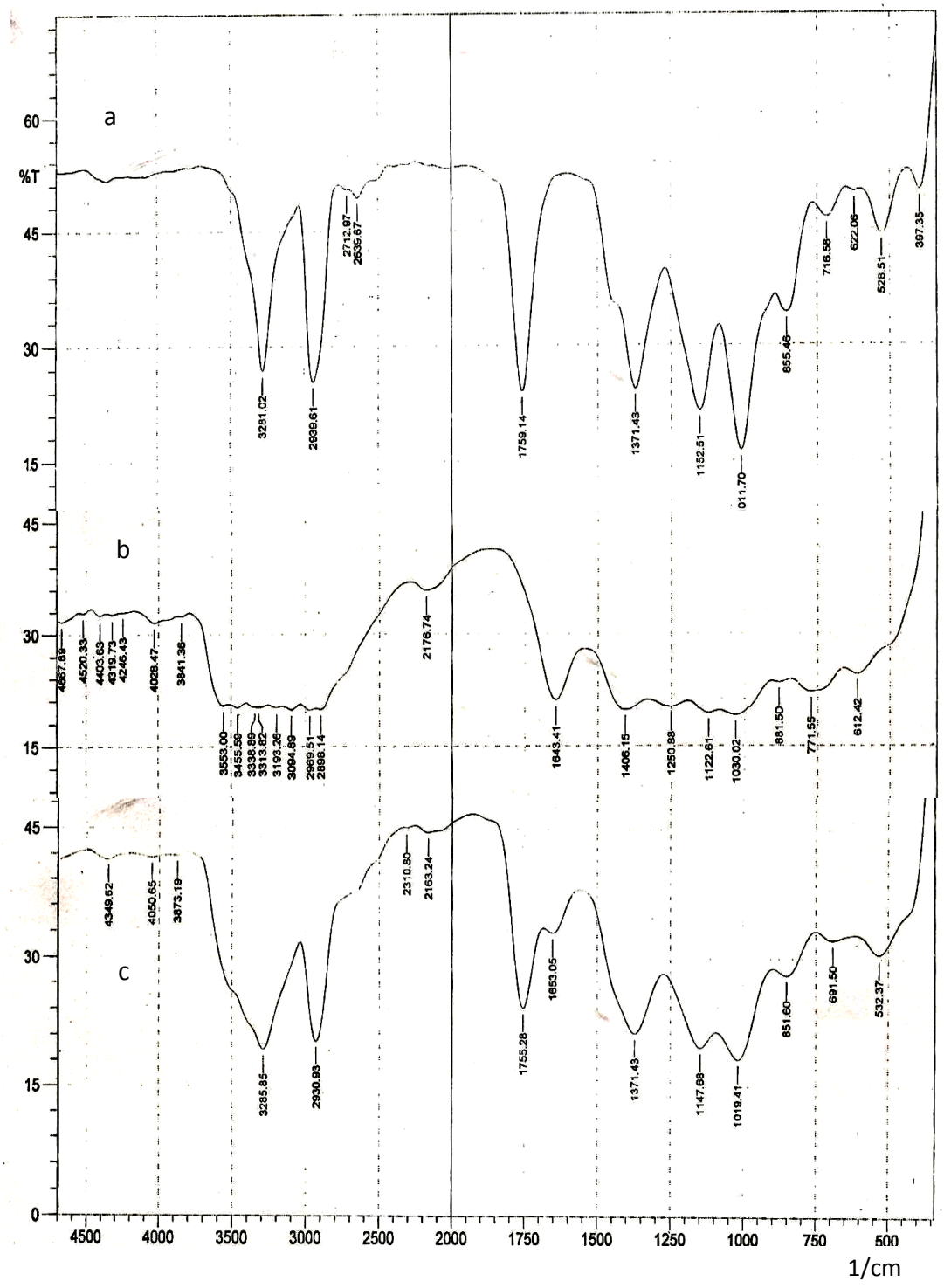


Figure 4.17 Fourier Transform Infrared Spectra of (a) Artesunate Sodium (b) Prosopis Gum (c) Artesunate Sodium + Prosopis Gum

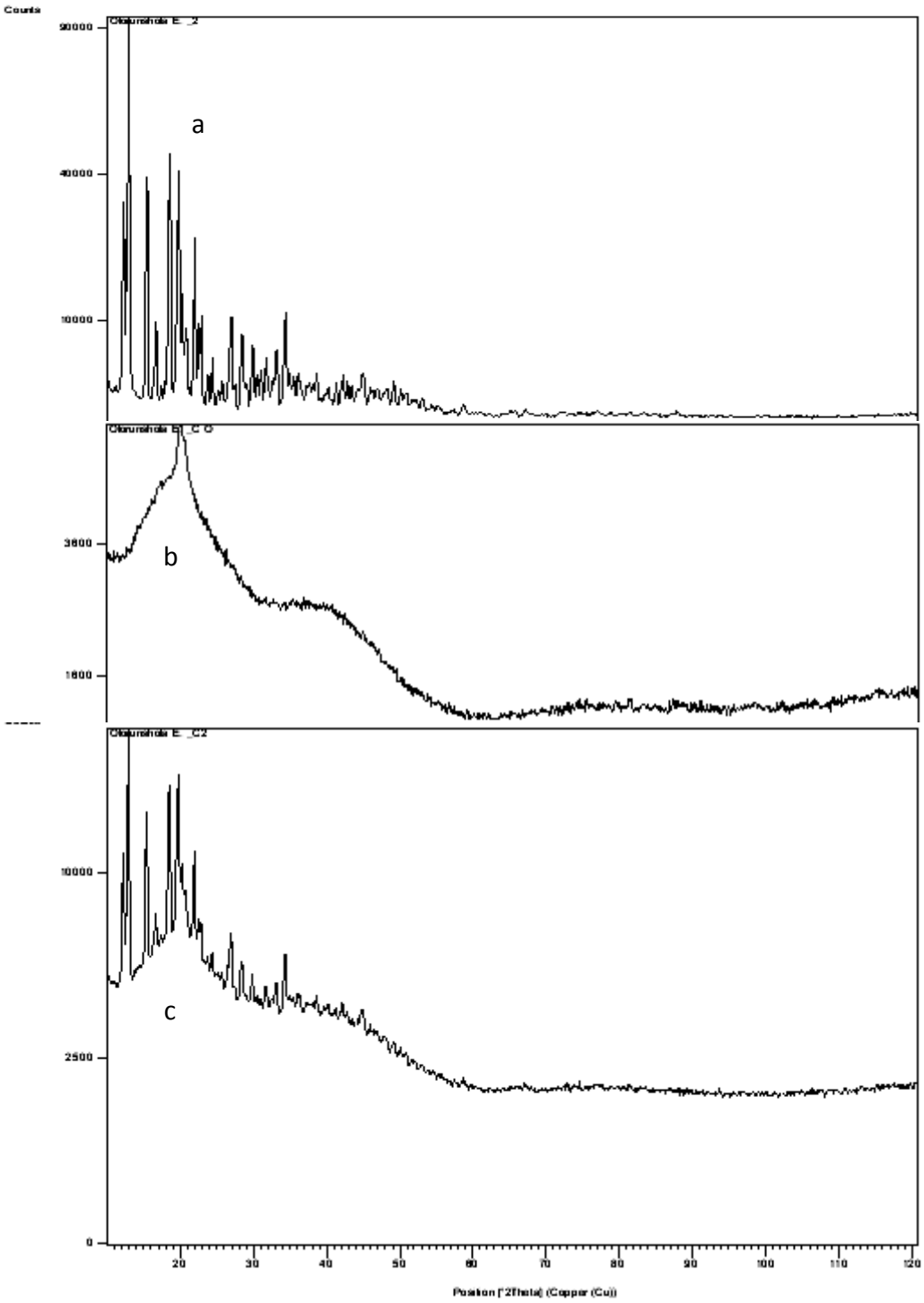


Figure 4.18 X-ray Diffraction patterns of (a) Artesunate Sodium (b) Prosopis Gum (c) Artesunate Sodium + Prosopis Gum.

4.7 EFFECT OF GUMS ON TABLET FORMULATION AND RELEASE OF ARTEMETHER

4.7.1 Effect of Gums on Artemether Granule Micromeritics

The properties of artemether granules containing different concentrations of gums with and without permeation enhancer are presented in Table 4.7. The angle of repose was in the range of 13.19 – 17.73 ^{O} while the flow rate was in the range of 6.56 – 9.63 g/s. There was no specific trend in the angle of repose and flow rate with respect to gum concentration. The angle of repose increased in the presence of chitosan.

The bulk density was within the range of 0.53 – 0.55 g/ml. There was no significant difference in the bulk density of the different granules. The tapped density was within the range of 0.59 – 0.66 g/ml and there was no significant difference in the values for the different granules.

The Hausner's ratio was in the range of 1.08 – 1.21 for granules containing cashew gum and 1.15 – 1.21 for granules containing prosopis gum. There was no significant difference in the Hausner's ratio of granules containing different binder concentrations with or without chitosan. The Carr's index was in the range of 7.99 – 17.17 % for granules containing cashew gum and 13.10 – 16.40 % for granules containing prosopis gum.

Table 4.7 Micromeritics of Artemether Granules

Batch	% in tablet Gum:Chitosan	Angle of repose (^{o})	Flow rate (g/s)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's ratio	Carr's Index (%)
ACG3	3 : 0	16.74 ± 0.35	7.02 ± 0.02	0.54 ± 0.01	0.61 ± 0.00	1.13 ± 0.01	11.48 ± 0.43
CSG1	1 : 0	15.53 ± 0.21	9.63 ± 0.00	0.55 ± 0.00	0.66 ± 0.00	1.21 ± 0.01	17.17 ± 0.50
CSG2	2 : 0	15.38 ± 0.59	8.50 ± 0.96	0.53 ± 0.01	0.60 ± 0.00	1.12 ± 0.02	10.60 ± 0.44
CSG3	3 : 0	17.73 ± 1.22	6.98 ± 0.32	0.53 ± 0.00	0.60 ± 0.00	1.14 ± 0.01	12.15 ± 0.48
CSG4	4 : 0	13.19 ± 0.23	8.86 ± 0.38	0.55 ± 0.01	0.62 ± 0.00	1.13 ± 0.01	11.29 ± 0.92
CSG2-C2	2 : 2	15.39 ± 0.07	7.76 ± 0.29	0.54 ± 0.02	0.59 ± 0.01	1.08 ± 0.02	7.99 ± 1.57
CSG2-C4	2 : 4	16.17 ± 0.13	8.21 ± 0.36	0.53 ± 0.00	0.64 ± 0.01	1.19 ± 0.00	16.22 ± 0.35
PRG1	1 : 0	16.09 ± 2.39	7.02 ± 0.55	0.53 ± 0.00	0.63 ± 0.00	1.21 ± 0.00	16.40 ± 0.53
PRG2	2 : 0	13.21 ± 0.35	6.56 ± 0.27	0.53 ± 0.00	0.62 ± 0.00	1.18 ± 0.02	15.48 ± 1.78
PRG3	3 : 0	14.26 ± 2.18	7.26 ± 0.60	0.54 ± 0.01	0.64 ± 0.01	1.18 ± 0.02	15.11 ± 1.05
PRG4	4 : 0	16.26 ± 0.59	6.84 ± 0.21	0.53 ± 0.00	0.61 ± 0.01	1.15 ± 0.01	13.10 ± 0.82
PRG2-C2	2 : 2	13.25 ± 0.17	6.68 ± 0.24	0.53 ± 0.00	0.63 ± 0.01	1.20 ± 0.01	16.30 ± 0.89
PRG2-C4	2 : 4	17.51 ± 1.27	7.89 ± 0.51	0.55 ± 0.00	0.64 ± 0.00	1.15 ± 0.01	13.54 ± 0.52

ACG3= 3 % w/w acacia gum CSG1= 1 % w/w cashew gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan
PRG1= 1 % w/w prosopis gum PRG2= 2 % w/w prosopis gum PRG3= 3 % w/w prosopis gum PRG4= 4 % w/w prosopis gum
PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

4.7.2 Effects of Gums on Physical and Release Properties of Artemether Tablets

The physical properties of artemether tablets containing different binder and permeation enhancer concentrations are shown in Table 4.8. The mean weight of tablets containing CSG as binder ranged from 271.50 to 279.15 mg, while those containing PRG as binder ranged from 271.80 to 286.15 mg. The diameter of tablets containing CSG as binder ranged from 8.01 to 8.05 mm, while their thickness ranged from 4.99 to 5.02 mm. The diameter of tablets containing PRG ranged from 8.02 to 8.05 mm, while their thickness ranged from 5.00 to 5.06 mm.

The crushing strength (CS) increased with increase in binder concentration for both gums with tablets containing PRG having higher crushing strength at all binder concentrations used. The presence of chitosan had no significant effect on crushing strength of tablets for both binders. There was no significant difference between the crushing strength of tablets containing 3 % w/w of CSG and that of tablets containing the same concentration of ACG. Tablets containing the same concentration of PRG had higher crushing strength.

The friability (FR) decreased with increase in binder concentration for CSG and PRG with tablets containing CSG having lower friability at all the binder concentrations used. While chitosan caused a significant reduction in friability of tablets containing PRG, it caused an insignificant reduction in those containing CSG. Tablets containing 3 % w/w CSG or 3 % w/w PRG had lower friability compared to tablets containing the same concentration of ACG.

Table 4.8 Physical Properties of Artemether Tablets

Batch	Mean weight (mg)	Diameter (mm)	Thickness (mm)	CS (kgf)	FR (%)	DT (min)	(CS/FR)/DT
ACG3	275.23 ± 1.98	8.04 ± 0.01	5.01 ± 0.01	4.60 ± 0.34	0.92 ± 0.03	3.23 ± 0.16	1.55 ± 0.29
CSG1	278.10 ± 2.03	8.05 ± 0.01	5.02 ± 0.02	4.10 ± 0.89	0.70 ± 0.01	2.50 ± 0.06	2.34 ± 0.31
CSG2	276.35 ± 1.60	8.01 ± 0.00	4.99 ± 0.01	4.50 ± 0.20	0.66 ± 0.14	2.16 ± 0.08	3.16 ± 0.14
CSG3	274.55 ± 1.46	8.05 ± 0.00	5.01 ± 0.01	4.60 ± 0.22	0.58 ± 0.10	2.24 ± 0.11	3.54 ± 0.15
CSG4	277.30 ± 2.02	8.04 ± 0.01	5.02 ± 0.01	5.20 ± 0.63	0.41 ± 0.04	2.99 ± 0.13	4.24 ± 0.26
CSG2-C2	271.50 ± 1.38	8.04 ± 0.01	5.00 ± 0.00	4.30 ± 0.11	0.55 ± 0.13	0.97 ± 0.04	8.06 ± 0.08
CSG2-C4	279.15 ± 1.32	8.04 ± 0.00	5.02 ± 0.02	5.00 ± 0.00	0.64 ± 0.32	1.25 ± 0.03	6.25 ± 0.12
PRG1	279.50 ± 1.63	8.05 ± 0.00	5.06 ± 0.01	4.50 ± 0.20	1.41 ± 0.38	28.98 ± 0.03	0.11 ± 0.00
PRG2	271.80 ± 2.66	8.04 ± 0.01	5.00 ± 0.01	4.60 ± 0.22	0.80 ± 0.18	37.89 ± 0.06	0.52 ± 0.04
PRG3	285.10 ± 1.39	8.03 ± 0.01	5.04 ± 0.01	5.20 ± 0.11	0.76 ± 0.06	59.77 ± 0.45	0.11 ± 0.02
PRG4	279.15 ± 2.23	8.02 ± 0.01	5.00 ± 0.01	5.50 ± 0.00	0.70 ± 0.00	69.71 ± 0.33	0.13 ± 0.01
PRG2-C2	286.15 ± 0.80	8.04 ± 0.00	5.04 ± 0.01	4.40 ± 0.09	0.51 ± 0.00	52.16 ± 0.01	0.17 ± 0.03
PRG2-C4	280.50 ± 1.22	8.02 ± 0.01	5.02 ± 0.01	4.50 ± 0.20	0.52 ± 0.00	67.44 ± 2.54	0.13 ± 0.01

ACG3= 3 % w/w acacia gum CSG1= 1 % w/w cashew gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan
PRG1= 1 % w/w prosopis gum PRG2= 2 % w/w prosopis gum PRG3= 3 % w/w prosopis gum PRG4= 4 % w/w prosopis gum
PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

There was no significant difference in the disintegration time (DT) of tablets containing different concentrations of CSG. The presence of chitosan caused a reduction in the disintegration time. The disintegration time of tablets containing PRG increased with increase in binder concentrations. The presence of chitosan also caused a significant decrease in the disintegration time of the tablets. Tablets containing 3 % w/w CSG had lower disintegration time, while those containing 3 % w/w PRG had higher disintegration time compared to tablets containing the same concentration of ACG.

For formulations without chitosan, 4 % w/w binder concentration gave the highest crushing strength-friability-disintegration time [(CS/FR)/DT] index for CSG while 2 % w/w binder concentration gave the highest index for PRG. For formulations containing chitosan, 2 % w/w chitosan gave higher (CS/FR)/DT index for both CSG and PRG.

The dissolution profile of tablets containing 3 % w/w of the different gums is illustrated in Figure 4.19. Batches containing CSG and ACG gave a drug release greater than 75 % while the batch containing PRG gave less than 75 % drug release in 1 h.

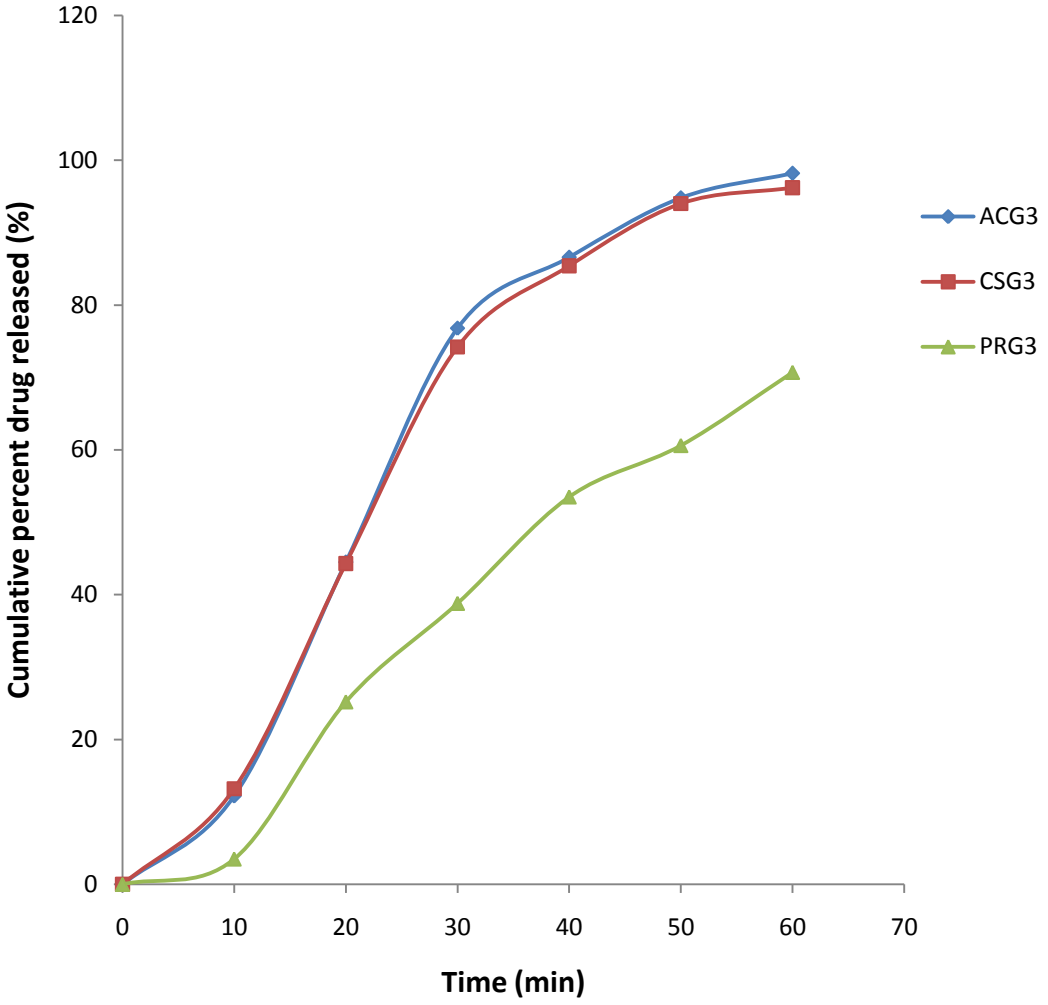


Figure 4.19 Dissolution Profile of Artemether Tablets Containing 3 % w/w of ACG, CSG and PRG.

4.7.3 Effect of Gums on Permeation of Artemether

(a) Simulated gastric fluid as donor medium

The plot of cumulative percent drug permeated under simulated gastric fluid condition versus time of permeation for tablets containing 3 % w/w binder concentration is shown in Figure 4.20. The permeability data of the different batches are shown in Table 4.9. While there was no significant difference in drug flux from tablets containing 3 % w/w ACG and 3 % w/w CSG, tablets containing the same concentration of PRG exhibited higher drug flux.

There was no significant difference in the flux of artemether from tablets containing different concentrations of CSG with or without chitosan; and the value ranged from 0.090 to 0.095 µg/cm^{2}s. Similarly, there was no significant difference in the permeation coefficient of drug from these tablets with or without the permeation enhancer; and the value ranged from 22.42 x 10^{-6} to 23.75 x 10^{-6} cm/s.

The amount of drug permeated in 30 min increased with increase in the concentration of CSG. The inclusion of chitosan led to decrease in the amount of drug permeated in 30 min from tablets containing 2 % w/w of CSG. The time for 95 % drug permeation increased with increase in concentration of CSG. It also increased with inclusion of chitosan.

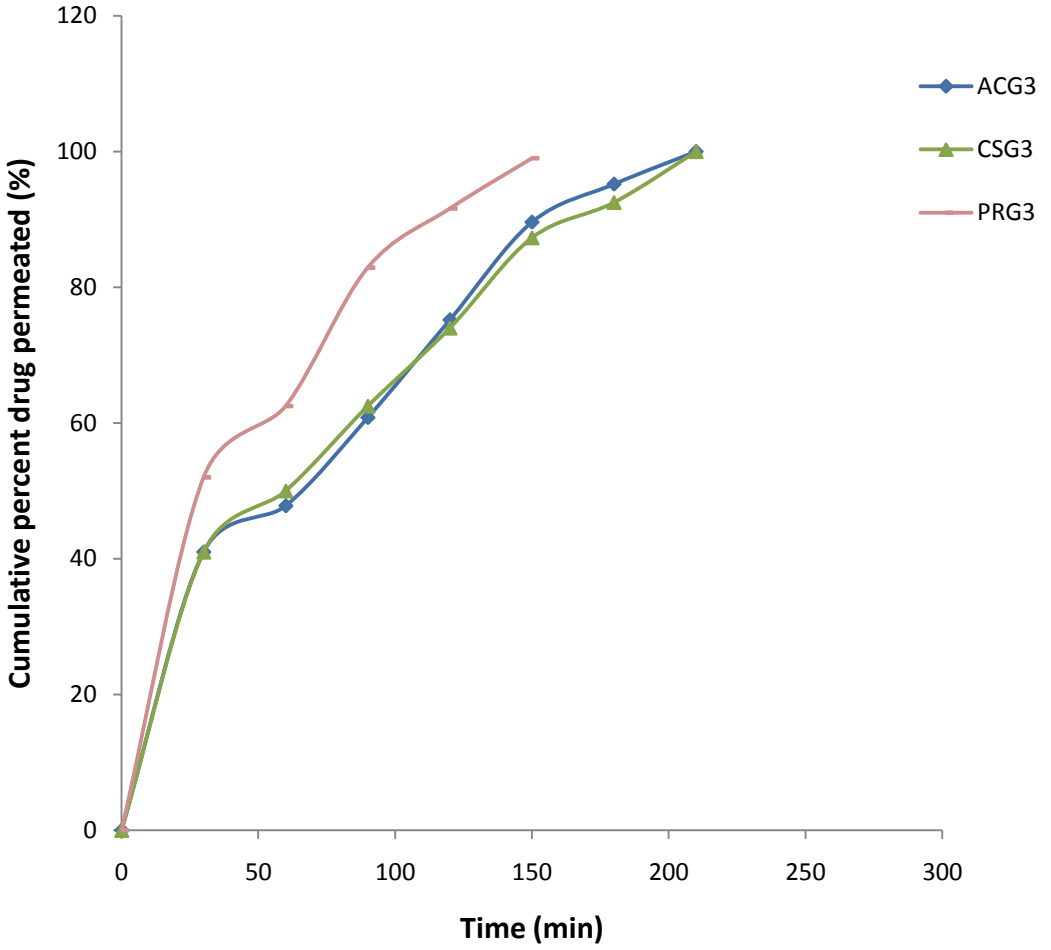


Figure 4.20 Permeation Profile of Artemether under Simulated Gastric Fluid Condition for Tablets containing 3 % w/w of ACG, CSG and PRG.

Table 4.9 Permeability Data of Artemether Tablet Formulations for Permeation under Simulated Gastric Fluid Condition

Batch	Drug Flux ($\mu g/cm^2.s$)	Permeation Coefficient x 10^{-6} (cm/s)	Drug Permeated in 30 min (%)	Time for 95 % Permeation (min)
ACG3	0.094 ± 0.02	23.50 ± 4.84	40.80 ± 0.04	179
CSG2	0.092 ± 0.03	23.00 ± 6.95	40.60 ± 0.00	162
CSG3	0.093 ± 0.02	23.18 ± 4.82	41.00 ± 0.05	188
CSG4	0.090 ± 0.01	22.42 ± 2.18	42.90 ± 0.10	200
CSG2-C2	0.092 ± 0.01	23.08 ± 2.72	34.30 ± 0.00	225
CSG2-C4	0.095 ± 0.00	23.75 ± 0.95	36.00 ± 0.08	225
PRG2	0.092 ± 0.01	23.08 ± 2.22	56.00 ± 0.00	133
PRG3	0.103 ± 0.02	25.68 ± 5.68	52.00 ± 1.70	135
PRG4	0.113 ± 0.01	28.25 ± 3.50	47.70 ± 3.41	136
PRG2-C2	0.124 ± 0.03	31.00 ± 7.40	41.80 ± 0.06	130
PRG2-C4	0.124 ± 0.02	31.00 ± 4.82	37.90 ± 0.00	130

ACG3= 3 % w/w acacia gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan
CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan PRG2= 2 % w/w prosopis gum
PRG3= 3 % w/w prosopis gum PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan
PRG4= 4 % w/w prosopis gum PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

The drug flux from tablets increased with increase in the concentration of PRG; and the presence of chitosan led to increase in the drug flux. However, there was no significant difference in the effect of 2 % w/w and 4 % w/w of chitosan. The value of permeation coefficient with or without chitosan followed the same trend as drug flux. The amount of drug permeated in 30 min decreased with both increase in the concentration of PRG and increase in the concentration of chitosan. There was no significant difference in time taken for 95 % drug permeation with increase in concentration of PRG. It decreased in the presence of chitosan.

(b) Simulated intestinal fluid as donor medium

The plot of cumulative percent drug permeated under simulated intestinal fluid condition versus time of permeation for tablets containing 3 % w/w binder concentration is shown in Figure 4.21. The permeability data of the different batches are shown in Table 4.10.

There was no significant difference in drug flux from tablets containing 3 % w/w ACG and 3 % w/w CSG while tablets containing the same concentration of PRG exhibited higher drug flux. The drug flux increased with increase in the concentration of CSG. It also increased with increase in the concentration of chitosan. The permeation coefficient of ATM from tablets containing CSG with or without chitosan followed the same trend as the drug flux. The amount of drug permeated in 30 min decreased with increase in the concentration of CSG. There was no significant difference in $t_{95\%}$ of drug from tablets containing different concentrations of CSG. Inclusion of chitosan (2 % and 4 % w/w) caused a decrease in $t_{95\%}$.

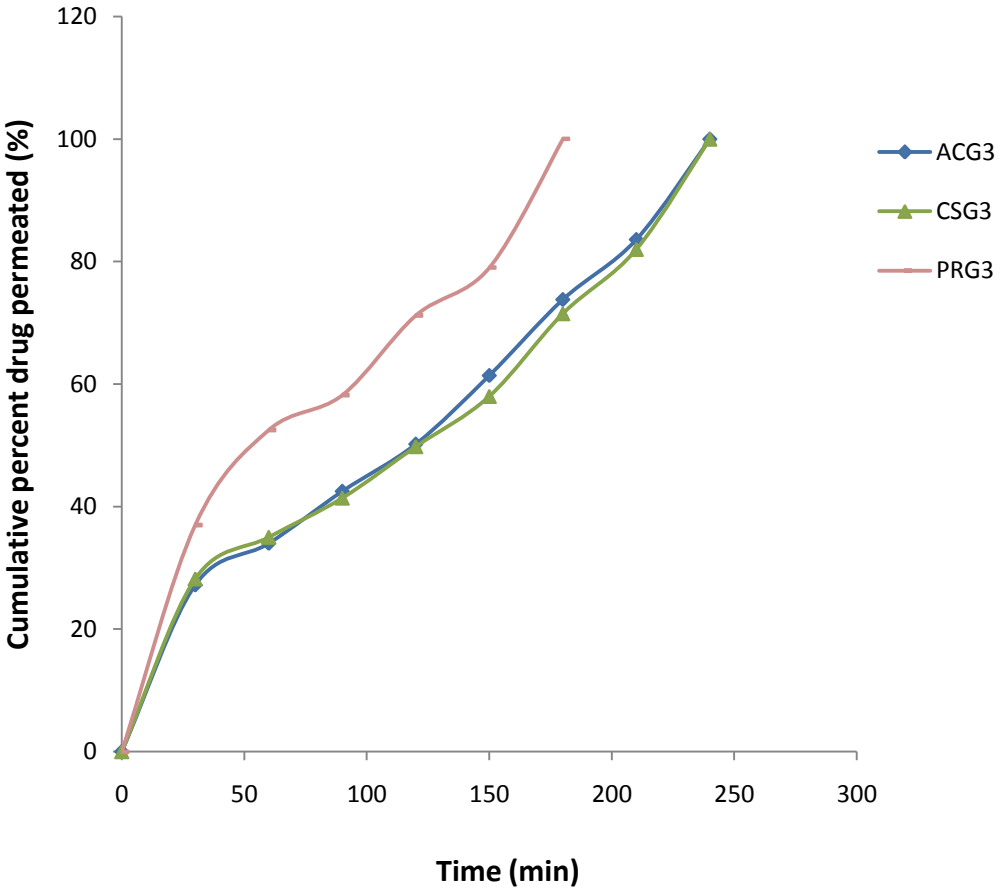


Figure 4.21 Permeation Profile of Artemether under Simulated Intestinal Fluid Condition for Tablets Containing 3 % w/w of ACG, CSG and PRG.

Table 4.10 Permeability Data of Artemether Tablet Formulations for Permeation under Simulated Intestinal Fluid Condition

Batch	Drug Flux ($\mu g/cm^2.s$)	Permeation Coefficient x 10^{-6} (cm/s)	Drug Permeated in 30 min (%)	Time for 95 % Permeation (min)
ACG3	0.102 ± 0.02	25.50 ± 4.00	27.20 ± 0.03	223
CSG2	0.097 ± 0.02	24.25 ± 4.50	29.94 ± 0.00	220
CSG3	0.103 ± 0.01	25.75 ± 1.75	28.10 ± 0.04	224
CSG4	0.110 ± 0.05	27.50 ± 1.25	26.40 ± 0.08	224
CSG2-C2	0.103 ± 0.01	25.75 ± 2.25	53.63 ±0.12	133
CSG2-C4	0.125 ± 0.01	31.25 ± 3.25	28.00 ± 0.41	139
PRG2	0.103 ± 0.02	25.75 ± 5.50	36.65 ± 0.02	169
PRG3	0.113 ± 0.02	28.25 ± 5.75	36.38 ± 0.05	170
PRG4	0.129 ± 0.03	32.25 ± 7.25	36.10 ± 0.07	170
PRG2-C2	0.116 ± 0.02	29.00 ± 5.75	27.79 ± 0.00	165
PRG2-C4	0.161 ± 0.02	40.25 ± 4.50	27.07 ± 0.00	145

ACG3= 3 % w/w acacia gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan
CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan PRG2= 2 % w/w prosopis gum
PRG3= 3 % w/w prosopis gum PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan
PRG4= 4 % w/w prosopis gum PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

The drug flux increased with increase in the concentration of PRG. It also increased with increase in the concentration of chitosan. The value of permeation coefficient of the drug with or without the permeation enhancer followed the same trend as drug flux. There was no significant difference in the amount of drug permeated in 30 min from tablets containing different concentrations of PRG. There was no significant difference in the time taken for 95 % drug permeation from tablets containing different concentrations of the gum. The value decreased with increase in the concentration of the permeation enhancer.

4.8 EFFECT OF GUMS ON TABLET FORMULATION AND RELEASE OF ARTESUNATE SODIUM

4.8.1 Effect of Gums on Artesunate Sodium Granule Micromeritics

The properties of artesunate sodium granules containing different concentrations of gums with and without permeation enhancer are presented in Table 4.11.

The angle of repose of granules containing CSG increased with increase in binder concentration and ranged from 15.94 to 22.84 ^{O}. It was not significantly affected by the presence of chitosan. The flow rate ranged from 7.94 to 12.08 g/s and there was no specific trend with respect to binder concentration. The angle of repose and flow rate of granules containing 3 % w/w CSG and those containing 3 % w/w ACG were not significantly different.

Table 4.11 Micromeritics of Artesunate Sodium Granules

Batch	% in tablet Gum:Chitosan	Angle of repose (^{o})	Flow rate (g/s)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's ratio	Carr's Index (%)
ACG3	3 : 0	17.85 ± 1.35	11.08± 0.52	0.53 ± 0.02	0.65 ± 0.02	1.22 ± 0.08	17.85 ± 5.21
CSG1	1 : 0	15.94 ± 2.37	12.08 ± 0.44	0.56 ± 0.01	0.69 ± 0.00	1.23 ± 0.01	18.84 ± 0.84
CSG2	2 : 0	16.80 ± 0.70	8.99 ± 0.94	0.51 ± 0.01	0.58 ± 0.01	1.13 ± 0.01	11.56 ± 0.53
CSG3	3 : 0	17.77 ± 0.93	11.15 ± 0.64	0.58 ± 0.01	0.68 ± 0.01	1.17 ± 0.00	14.64 ± 0.19
CSG4	4 : 0	22.84 ± 0.68	7.94 ± 0.05	0.56 ± 0.00	0.65 ± 0.01	1.17 ± 0.00	14.27 ± 1.24
CSG2-C2	2 : 2	16.22 ± 0.66	9.27 ± 0.91	0.58 ± 0.01	0.68 ± 0.01	1.18 ± 0.02	15.13 ± 0.64
CSG2-C4	2 : 4	15.49 ± 0.63	10.81 ± 0.07	0.56 ± 0.01	0.67 ± 0.01	1.20 ± 0.01	16.41 ± 0.75
PRG1	1 : 0	21.89 ± 0.45	11.69 ± 0.12	0.54 ± 0.00	0.64 ± 0.00	1.18 ± 0.01	15.11 ± 0.52
PRG2	2 : 0	17.96 ± 0.47	9.98 ± 0.27	0.58 ± 0.01	0.68 ± 0.01	1.17 ± 0.01	14.64 ± 0.85
PRG3	3 : 0	20.96 ± 0.57	10.66 ± 0.76	0.52 ± 0.01	0.63 ± 0.01	1.19 ± 0.00	15.58 ± 0.29
PRG4	4 : 0	17.20 ± 0.11	11.02 ± 0.65	0.57 ± 0.00	0.67 ± 0.00	1.17 ± 0.01	14.07 ± 0.43
PRG2-C2	2 : 2	18.59 ± 0.08	10.15 ± 0.52	0.53 ± 0.00	0.65 ± 0.01	1.23 ± 0.01	18.76 ± 1.00
PRG2-C4	2 :4	19.62 ± 1.63	8.96 ± 0.00	0.54 ± 0.01	0.63 ± 0.01	1.17 ± 0.04	14.28 ± 3.13

ACG3= 3 % w/w acacia gum CSG1= 1 % w/w cashew gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum

CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan

PRG1= 1 % w/w prosopis gum PRG2= 2 % w/w prosopis gum PRG3= 3 % w/w prosopis gum PRG4= 4 % w/w prosopis gum

PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

There was no specific trend in the angle of repose of granules containing PRG and the value ranged from 17.20 to 20.96 ^{o}. It was increased by the presence of chitosan. The flow rate ranged from 8.96 to 11.69 g/s.

The bulk density ranged from 0.51 to 0.58 g/ml for granules containing CSG and 0.52 to 0.58 g/ml for granules containing PRG. There was no significant difference in the bulk density of the granules. The tapped density ranged from 0.58 to 0.69 g/ml for granules containing CSG and 0.63 to 0.68 g/ml for granules containing PRG. There was no significant difference in the tapped density of the granules.

The Hausner's ratio was in the range of 1.13 to 1.23 for granules containing CSG and 1.17 to 1.23 for granules containing PRG. The Carr's compressibility index was in the range of 11.56 to 18.84 % for granules containing CSG and 14.07 to 18.76 % for granules containing PRG. There was no significant difference in the Carr's index of granules containing different concentrations of both gums.

4.8.2 Effect of Gums on Physical and Release Properties of Artesunate Sodium Tablets

The physical properties of artesunate sodium tablets containing different binder and permeation enhancer concentrations are shown in Table 4.12.

Table 4.12 Physical Properties of Artesunate Sodium Tablets

Batch	Mean weight (mg)	Diameter (mm)	Thickness (mm)	CS (kgf)	FR (%)	DT (min)	(CS/FR)/DT
ACG 3	282.40 ± 0.98	8.01 ± 0.01	5.02 ± 0.01	5.18 ± 0.76	0.95 ± 0.12	3.23 ± 0.55	1.69 ± 0.08
CSG1	282.00 ± 1.95	8.01 ± 0.01	5.03 ± 0.02	4.20 ± 0.03	1.04 ± 0.04	0.77 ± 0.07	5.24 ± 0.08
CSG2	269.00 ± 2.23	8.00 ± 0.01	4.96 ± 0.02	4.60 ± 0.04	0.72 ± 0.13	0.87 ± 0.03	7.34 ± 0.07
CSG3	287.70 ± 0.88	8.01 ± 0.01	5.04 ± 0.01	5.60 ± 0.26	0.34 ± 0.00	2.03 ± 0.00	8.11 ± 0.01
CSG4	277.30 ± 2.38	8.02 ± 0.02	5.00 ± 0.01	5.60 ± 0.09	0.34 ± 0.00	5.44 ± 1.00	3.02 ± 0.04
CSG2-C2	286.20 ± 2.30	8.02 ± 0.01	5.03 ± 0.02	6.20 ± 0.30	0.69 ± 0.11	1.19 ± 0.06	7.55 ± 0.14
CSG2-C4	284.65 ± 1.80	8.01 ± 0.01	5.04 ± 0.01	5.40 ± 0.61	0.57 ± 0.08	1.00 ± 0.00	9.47 ± 0.24
PRG1	275.60 ± 2.18	8.01 ± 0.01	5.02 ± 0.02	4.60 ± 0.26	1.21 ± 0.02	25.37 ± 1.70	0.15 ± 0.01
PRG2	290.55 ± 0.44	8.02 ± 0.00	5.02 ± 0.01	5.80 ± 0.18	0.78 ± 0.01	82.57 ± 0.80	0.09 ± 0.00
PRG3	273.65 ± 2.40	8.00 ± 0.01	4.96 ± 0.02	6.00 ± 0.28	0.56 ± 0.05	70.61 ± 0.12	0.15 ± 0.00
PRG4	284.70 ± 2.97	8.03 ± 0.01	5.00 ± 0.01	7.00 ± 0.58	0.29 ± 0.04	114.20 ± 1.58	0.21 ± 0.01
PRG2-C2	271.85 ± 1.74	8.02 ± 0.01	5.01 ± 0.02	5.00 ± 0.28	0.87 ± 0.00	32.89 ± 1.50	0.17 ± 0.01
PRG2-C4	279.70 ± 0.69	8.01 ± 0.00	5.00 ± 0.00	5.00 ± 0.14	0.79 ± 0.04	39.01 ± 0.35	1.62 ± 0.02

ACG3= 3 % w/w acacia gum CSG1= 1 % w/w cashew gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan
PRG1= 1 % w/w prosopis gum PRG2= 2 % w/w prosopis gum PRG3= 3 % w/w prosopis gum PRG4= 4 % w/w prosopis gum
PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

The average weight of tablets containing CSG as binder ranged from 269.00 to 281.70 mg while that of tablets containing PRG ranged from 271.85 to 290.55 mg. The diameter of tablets ranged from 8.00 to 8.02 mm for CSG and 8.00 to 8.03 mm for PRG while the thickness ranged from 4.96 to 5.04 mm for CSG and 4.96 to 5.02 mm for PRG.

The crushing strength increased with increase in concentration of binder for both gums. While the inclusion of chitosan led to increase in crushing strength for formulations containing CSG, it led to decrease in the parameter for formulations containing PRG. Tablets containing 3 % w/w CSG or 3 % w/w PRG had higher crushing strength compared to tablets containing the same concentration of ACG.

The friability of tablets decreased with increase in binder concentration for both gums. Inclusion of chitosan led to decrease in the friability of tablet containing CSG in a magnitude proportional to the quantity of chitosan added. Inclusion of chitosan led to insignificant increase in friability of tablets containing PRG. Tablets containing 3 % w/w CSG or 3 % w/w PRG had lower friability compared to tablets containing the same concentration of ACG.

The disintegration time of tablets increased with increase in concentration of binder for both gums. While chitosan caused an increase in the disintegration time of tablets containing CSG, it caused a decrease in that of tablets containing PRG. Tablets containing 3 % w/w CSG had lower disintegration time while those containing 3 % w/w PRG had higher disintegration time compared to tablets containing the same concentration of ACG as was obtained with artemether tablets.

In the absence of chitosan, formulation containing 3 % w/w had the highest (CS/FR)/DT index for CSG while formulation containing 4 % w/w had the highest index for PRG. Formulations containing 4 % w/w of chitosan had higher (CS/FR)/DT index compared to those containing 2 % w/w for both CSG and PRG.

The dissolution profile of tablets containing 3 % w/w binder concentration is shown in Figure 4.22. Tablets containing CSG and ACG gave drug release greater than 75 % in less than 40 min while tablets containing PRG gave less than 75 % drug release even after 1 h.

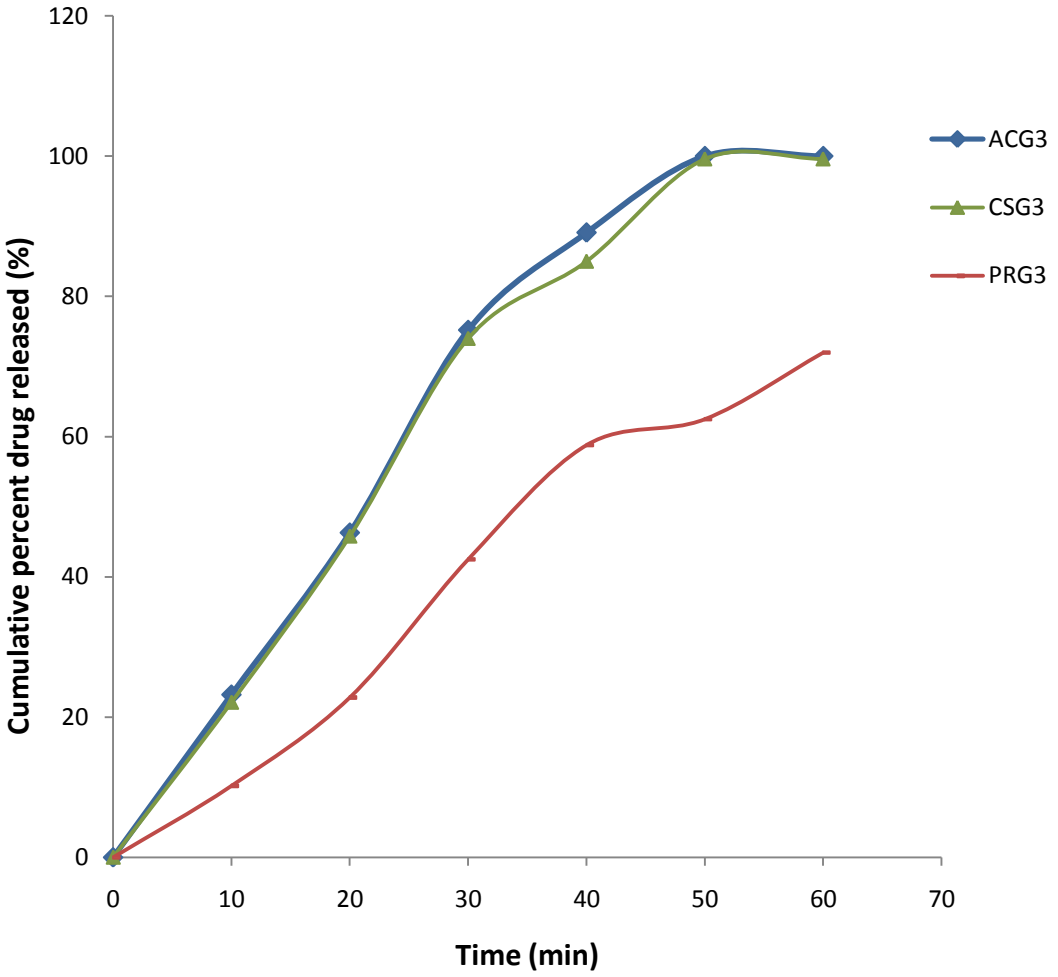


Figure 4.22 Dissolution Profile of Artesunate Sodium Tablets Containing 3 % w/w of ACG, CSG and PRG.

4.8.3 Effect of Gums on Permeation of Artesunate Sodium

(a) Simulated gastric fluid as donor medium

The plot of cumulative percent drug permeated under simulated gastric fluid condition versus time of permeation for tablets containing 3 % w/w binder concentration is shown in Figure 4.23. The permeability data of the different batches are shown in Table 4.13. There was no significant difference in drug flux from tablets containing 3 % w/w ACG and same concentration of CSG while tablets containing the same concentration of PRG exhibited significantly higher drug flux.

The drug flux from tablets containing different concentrations of CSG without chitosan ranged from 0.10 to 0.12 μg/cm^{3}s. There was increase in the drug flux with increase in the concentration of chitosan. The value of permeation coefficient followed the same trend as the drug flux for tablets containing different concentration of CSG with and without chitosan.

There was no significant difference in the amount of drug permeated in 30 min for the tablets containing 2 – 4 % of CSG without chitosan. While 2 % w/w of chitosan caused no significant change in the amount of drug permeated in 30 min, 4 % w/w of the enhancer caused a significant reduction. Increase in the concentration of CSG (without chitosan) did not result to a significant change in time for 95 % permeation of drug ($t_{95\%}$). The $t_{95\%}$ decreased in the presence of chitosan.

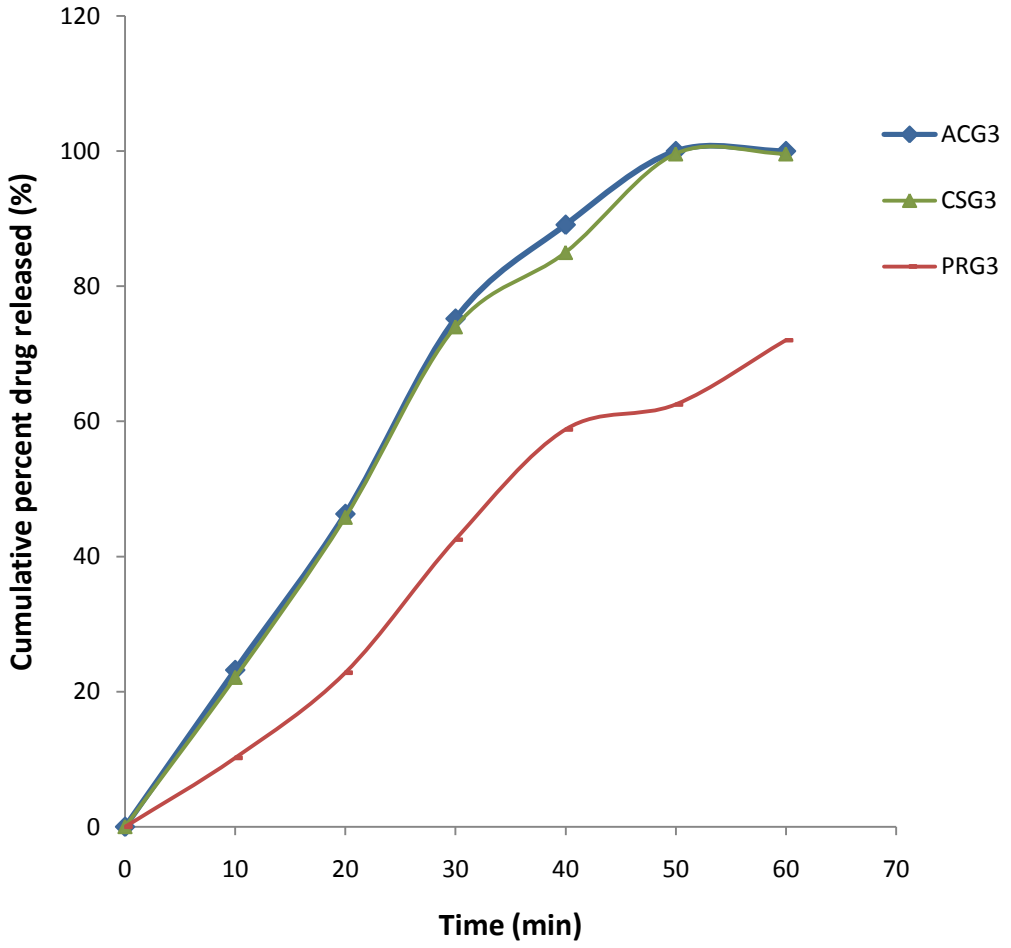


Figure 4.23 Permeation Profile of Artesunate Sodium under Simulated Gastric Fluid Condition for Tablets Containing 3 % w/w of ACG, CSG and PRG.

Table 4.13 Permeability Data of Artesunate Sodium tablet Formulations for Permeation under Simulated Gastric Fluid Condition

Batch	Drug Flux ($\mu g/cm^2.s$)	Permeation Coefficient x 10^{-6} (cm/s)	Drug Permeated in 30 min (%)	Time for 95 % Permeation (min)
ACG3	0.11 ± 0.01	11.42 ± 1.56	50.30 ± 0.40	188
CSG2	0.12 ± 0.02	12.33 ± 2.43	49.30 ± 0.00	195
CSG3	0.11 ± 0.02	11.36 ± 2.11	50.25 ± 0.00	190
CSG4	0.10 ± 0.02	10.35 ± 1.87	51.90 ± 0.00	178
CSG2-C2	0.21 ± 0.04	20.97 ± 3.50	57.60 ± 0.00	155
CSG2-C4	0.24 ± 0.03	24.20 ± 3.38	38.90 ± 0.00	155
PRG2	0.26 ± 0.01	26.55 ± 1.10	59.50 ± 2.06	110
PRG3	0.20 ± 0.02	20.23 ± 1.78	60.30 ± 1.71	120
PRG4	0.14 ± 0.03	13.77 ± 2.58	60.90 ± 1.42	150
PRG2-C2	0.24 ± 0.02	24.43 ± 1.78	63.30 ± 0.96	112
PRG2-C4	0.25 ± 0.02	24.78 ± 1.93	52.90 ± 0.67	110

ACG3= 3 % w/w acacia gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan
CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan PRG2= 2 % w/w prosopis gum
PRG3= 3 % w/w prosopis gum PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan
PRG4= 4 % w/w prosopis gum PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

Drug flux and permeation coefficient decreased with increase in concentration of PRG. The presence of chitosan had no significant effect on the values of drug flux and permeation coefficient for tablets containing 2 % w/w PRG. There was no significant difference in the amount of drug permeated in 30 min for tablets containing 2 – 4 % w/w of PRG. The presence of 4 % w/w chitosan caused a significant decrease in the amount permeated in 30 min. The time for 95 % permeation increased with increase in binder (PRG) concentration. There was no significant change in $t_{95\%}$ with increase in the concentration of chitosan for tablets containing 2 % w/w PRG.

(b) Simulated intestinal fluid as donor medium

The plot of cumulative percent drug permeated under simulated intestinal fluid condition versus time of permeation for tablets containing 3 % w/w binder concentration is shown in Figure 4.24. The permeability data of the different batches are shown in Table 4.14. At binder concentration of 3 % w/w, there was no significant difference in the drug flux from tablets containing ACG, CSG and PRG.

There was increase in the drug flux and permeation coefficient at the steady state with increase in the concentration of CSG. An increase in these parameters was also observed with increase in the concentration of chitosan. However, there was no significant difference in the time taken for 95 % drug permeation for tablets containing different concentrations of CSG with or without chitosan.

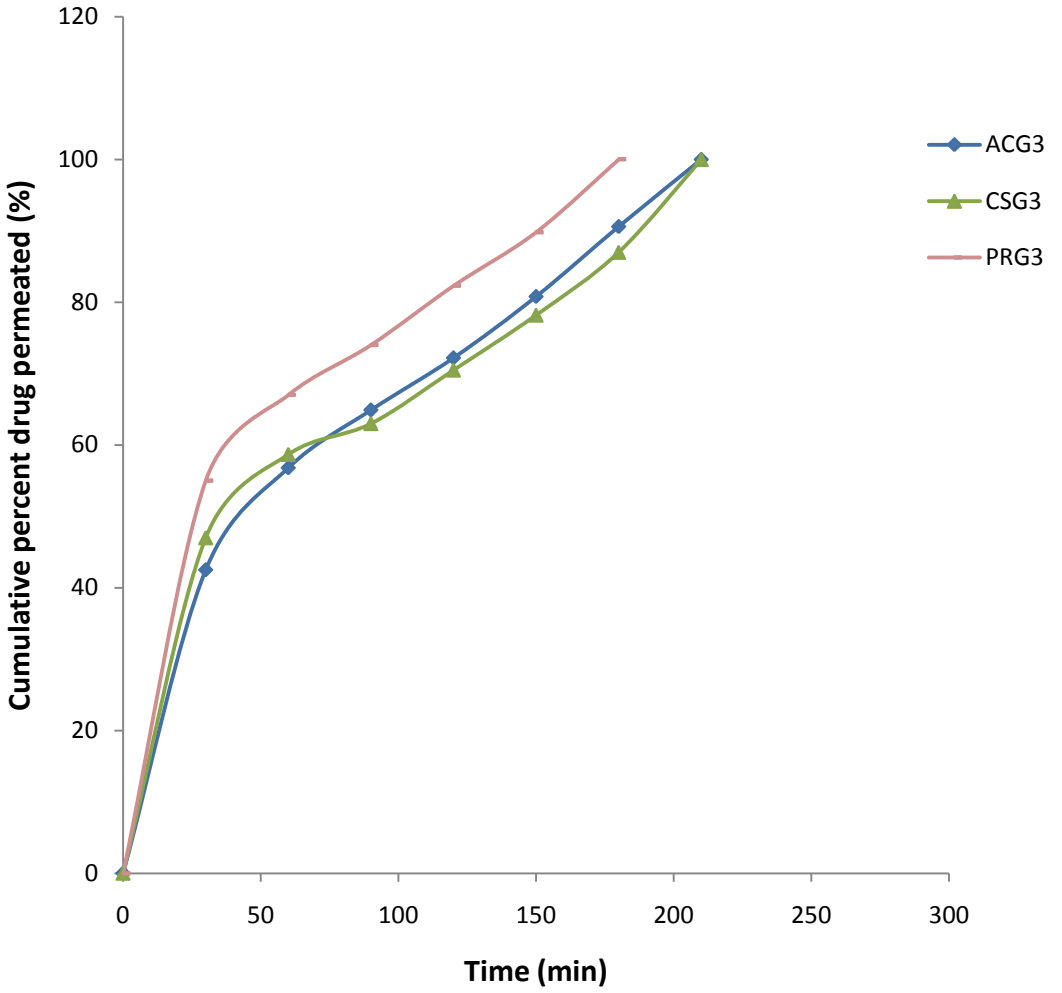


Figure 4.24 Permeation Profile of Artesunate Sodium under Simulated Intestinal Fluid Condition for Tablets containing 3% w/w of ACG, CSG and PRG

Table 4.14 Permeability Data of Artesunate Sodium Formulations for Permeation under Simulated Intestinal Fluid Condition

Batch	Drug Flux ($\mu g/cm^2.s$)	Permeation Coefficient x 10^{-6} (cm/s)	Drug Permeated in 30 min (%)	Time for 95 % Permeation (min)
ACG3	0.17 ± 0.03	16.65 ± 3.11	42.50 ± 0.53	195
CSG2	0.15 ± 0.04	14.70 ± 3.98	52.04 ± 0.23	190
CSG3	0.16 ± 0.01	15.68 ± 0.75	47.00 ± 0.81	200
CSG4	0.18 ± 0.01	17.71 ± 1.05	40.90 ± 1.16	204
CSG2-C2	0.17 ± 0.03	16.69 ± 3.31	45.29 ± 0.81	198
CSG2-C4	0.20 ± 0.05	20.13 ± 5.02	36.27 ± 1.17	190
PRG2	0.15 ± 0.03	15.19 ± 3.11	55.25 ± 0.00	160
PRG3	0.14 ± 0.01	14.72 ± 0.68	55. 52 ± 0.08	168
PRG4	0.12 ± 0.04	12.03 ± 4.23	55.88 ± 0.16	170
PRG2-C2	0.18 ± 0.03	18.28 ± 3.21	48.40 ± 0.01	175
PRG2-C4	0.18 ± 0.02	17.54 ± 1.95	52.88 ± 0.01	170

ACG3= 3 % w/w acacia gum CSG2= 2 % w/w cashew gum CSG3= 3 % w/w cashew gum
CSG4= 4 % w/w cashew gum CSG2-C2= 2 % w/w cashew gum + 2 % w/w chitosan
CSG2-C4= 2 % w/w cashew gum + 4 % w/w chitosan PRG2= 2 % w/w prosopis gum
PRG3= 3 % w/w prosopis gum PRG2-C2= 2 % w/w prosopis gum + 2 % w/w chitosan
PRG4= 4 % w/w prosopis gum PRG2-C4= 2 % w/w prosopis gum + 4 % w/w chitosan.

There was no significant difference in the amount of drug permeated in 30 min for tablets containing different concentrations of PRG. The amounts of drug permeated in 30 min from tablets containing PRG were higher than those containing corresponding concentrations of CSG.

The drug flux and permeation coefficient decreased with increase in the concentration of PRG. There was increase in drug flux and in permeation coefficient in the presence of chitosan. However, there was no significant difference in the effect of different concentrations of the permeation enhancer. The time taken for 95 % drug permeation from tablets containing PRG was lower than those containing corresponding concentration of CSG.

CHAPTER 5

DISCUSSION

5.1 PERCENTAGE YIELD

The two exudates (Cashew and Khaya) gave higher percentage yield of gum compared to the two seeds (Afzelia and Prosopis). The seeds are rich in protein and also contain substantial amount of fat (Adikwu *et al*., 2003; Builders *et al*., 2009). These materials were removed during the extraction and purification processes. The lower yields of gum from the seeds was thus expected. The yield of 48.0% w/w of cashew gum is lower than the value reported (78.5% w/w) by Ofori-Kwakye *et al*. (2010). It was suggested that the high yield obtained by them was due to the nature of the precipitating solvent (ethanol) used. Ethanol was used in this present work and the yield was not higher than that obtained by Kumar *et al*. (2009) who used acetone as precipitating solvent. Therefore, the difference in yield could not be due to solvent alone but also to other factors such as the source of exudates and the quality of the chemicals used for the extraction.

5.2 PHYSICAL, CHEMICAL AND THERMAL PROPERTIES

Physical Properties

In terms of the organoleptic properties, all the polymers are suitable for use as pharmaceutical excipients. The seed gums were fluffy in nature while the exudate gums were not. Therefore, the seed gums are less tightly packed than the exudate gums.

The angle of repose of KYG which fell between 20 and 30 ^{0} suggests good flow while those of CSG and ACG which fell between 30 and 40 ^{0} suggest fair flow. Those of AFG and PRG which fell between 40 and 50 ^{0} suggest poor flow while that of SCMC (> 50 ^{0}) suggests very poor flow (Wells and Aulton, 2007). Generally, the exudate gums have better flow compared to seed gums and SCMC.

From flow rate values, CSG, KYG and ACG had significantly higher flow rate. The particles of these three gums are spherical in shape. Besides, KYG had more of large particles and this could be responsible for its highest flow rate. Coarse particles are generally less cohesive than fine ones and thus possess better flow (Staniforth and Aulton, 2007). AFG, PRG and SCMC contained rod-shaped particles (Figure 4.1). For a given particle size, more spherical particles have better flow compared to irregular ones (Staniforth and Aulton, 2007). This is responsible for the poor flow of the rod-shaped particles of these polymers.

The bulk density of the exudate gums which is significantly higher than those of the seed gums correlates with the result of texture determination, which revealed that the seed gums were fluffy while the exudates gums were not (Table 4.1). The bulk density is dependent on particle packing; and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may therefore be more resistant to flow (Staniforth and Aulton, 2007). However, this was not the case with these experimental gums as the exudate gums with higher bulk density possess better flow. This can be explained by their spherical shape.

The Carr's index of ACG which fell below 15 % suggests excellent flow while those of CSG and KYG which fell between 16 and 21 % suggest fair flow. The value for AFG and PRG fell between 23 and 35 % corresponding to poor flow while that of SCMC which is > 33 % corresponds to very poor flow (Wells and Aulton, 2007). Therefore, there is a correlation between angle of repose and Carr's index as shown by Well and Aulton (2007).

A Hausner's ratio < 1.25 indicates good flow, 1.25 to 1.5 indicates fair flow, while values > 1.5 indicate poor flow (Wells and Aulton, 2007). The Hausner's ratio values of CSG, KYG and ACG indicate good flow; those of AFG and PRG indicate fair flow while that of SCMC indicates poor flow.

The relative density and viscosity of Afzelia gum are not significantly different from those reported by Ibezim *et al.* (2006). Relative density of 1.018 and viscosity of 143.4 cP were reported by these workers. Similarly, there is no significant difference between the relative density of 2 % dispersion of acacia gum and the 1.017 reported by these researchers. There is no significant difference between the percentage compressibility (Carr's index) of afzelia gum and the 27.16 % reported by Ibezim *et al*. (2006).

Chemical Properties

The moisture content was in the order ACG < CSG < KYG < AFG < PRG < SCMC. The moisture content of CSG is significantly lower than the 9.8 – 13.2 % reported by Gyedu-Akolo *et al*. (2008). This is possibly due to the difference in the extraction solvent and/or the extent of the initial drying. Water is known to catalyze many degradative processes including hydrolysis and microbial attack. The higher the

moisture content, the more liable is the polymer to hydrolytic degradation (Isah *et al.*, 2012). Therefore, acacia gum might be the most stable while sodium carboxymethylcellulose might be the least stable in the dry state.

The ash value of CSG (1.0 %) agrees with the value reported by Gyedu-Akolo (2008). An ash value of 0.5 – 1.2 % was reported by these researchers. The ash value of KYG is not significantly different from that of ACG and their values are significantly higher than that of CSG ($P < 0.001$). The value for the acacia gum (4.0 %) corresponds to 2.7 – 4.0 % reported by Mahmud (2009). Also, the ash value of AFG is significantly higher than that of PRG ($P < 0.001$). Ash value is a measure of the relative amount of inorganic substances in the gum (Mahmud, 2009). Therefore, the ranking of the total amount of inorganic substances in the gums is AFG > KYG > ACG = SCMC > PRG > CSG.

Khaya gum having the lowest pH and sodium carboxymethylcellulose having the highest pH (Table 4.1) might be reflective of the lowest amount of sodium in khaya gum and its highest amount in sodium carboxymethylcellulose (Table 4.2). KYG with the lowest pH is the most suitable for formulations having major absorption in the stomach while SCMC with the highest pH is the most suitable for formulations having major absorption in the intestine.

The pH of KYG is not significantly different from 4.20 reported by Mahmud (2009). Also, the value for afzelia gum is not significantly different from the 4.58 reported by Ibezim *et al*. (2006). All the polymers have pH in the acidic range showing their

commercial importance. According to Zhou (2009), basic polymers have limited commercial importance and acidic and neutral hydrocolloids are more widely used.

Calcium is the predominant ion in cashew gum. This is in agreement with the work of Ofori-Kwakye *et al.* (2010). Potassium and calcium content might be a good distinguishing factor between khaya and cashew gums. While potassium is the predominant ion (1600 mg/kg) in khaya gum, calcium is the predominant (2397 mg/kg) in cashew gum. The presence of metal ions affects the compatibility of the polymer with drugs (Zhou, 2009).

Afzelia gum and prosopis gum have abundant levels of magnesium ion and the difference in the concentration in both seeds is not significant. The two seed gums of all the polymers have the highest levels of potassium and magnesium ions. High level of these two ions might be associated with seed gums.

Afzelia gum and sodium carboxymethylcellulose had been described as cellulose-based polymers (Builders *et al.,* 2009). Prosopis gum with similar characteristics may be related to these two substances. The distributions of sodium and potassium ions in these polymers are inversely related. For instance, SCMC has the highest level of sodium ion and the lowest level of potassium ion while AFG has the lowest level of sodium ion and highest level of potassium ion. PRG has moderate level of both ions. Sodium is the predominant monovalent ion in SCMC while potassium is predominant in AFG and PRG. This feature distinguishes SCMC from the two seed gums.

The distribution of calcium ion in the three gums follows the same trend as that of potassium ion (AFG > PRG > SCMC). Afzelia gum and prosopis gum have significantly higher amount of calcium ion compared to SCMC. The two seed gums can be distinguished by the predominant divalent ion. Magnesium is the predominant divalent ion in PRG while calcium is predominant in AFG.

The United States Pharmacopoeia (2008) specifies the permitted daily exposure to copper as 2.5 mg. Afzelia gum has the highest copper concentration; and a 500 mg quantity of the gum will need to be consumed to reach this level of 2.5 mg copper. Obviously, no daily dose of medication will contain this amount of gum as excipient. Therefore, copper ion is within the acceptable limit in all the polymers. Afzelia gum contains the highest amount of copper ion and may be the most susceptible to auto-oxidation. This is the reason for the use of glass container during its extraction (Builders *et al*., 2009). Lead, a highly toxic metal is absent in all the gums.

Thermo-chemical Properties

The first endotherm in the thermogram of CSG can be ascribed to the enthalpy relaxation of the polymer (Chung *et al*., 2002). No exothermic transition was observed. Therefore, there was no clear crystallization of the polymer. The second endotherm can be ascribed to melting of the polymer and its peak (305 ^{O}C) represents the melting point. The thermogram of CSG is similar to that of hydroxypropylmethylcellulose reported by Builders *et al*. (2009). The latent heat of melting of the polymer was 386.36 J/g. This is the amount of energy required to melt a unit gram of the polymer (Builders *et al*., 2009).

The endotherm of the thermogram of KYG can be ascribed to the enthalpy relaxation of the polymer (Chung *et al*., 2002). Therefore, it could be said that the polymer experienced enthalpy relaxation over a wide range of temperature (20 to 250 ^{O}C). The diffuse exotherm represents degradation of the polymer (Iqbal *et al*., 2013). The latent heat of degradation was 454.50 J/g. Therefore, 454.50 J of heat was lost as 1 g of the polymer degraded. The thermogram returned to the base level at about 330 ^{O}C and no other obvious endotherm was observed as the polymer was heated to 500 ^{O}C.

The enthalpy relaxation of acacia gum was illustrated by the endothermic transition between 20 and 200 ^{O}C. The polymer has T_g of 85 ^{O}C as shown by the peak of the endotherm. It experienced degradation at 310 ^{O}C with latent heat of 363.63 J/g.

The endotherm in the thermogram of AFG can be attributed to enthalpy relaxation of the polymer. The exotherm which extended from 300 to 345 ^{O}C can be ascribed to crystallization of the polymer. From the peak of the exotherm, the polymer has crystallization temperature (T_c) of 325 ^{O}C which is close to 317.7 ^{O}C reported by Builders *et al*. (2009). According to these researchers, the polymer has two melting temperatures (273 and 335 ^{O}C) which were just before and just after the exotherm respectively. It was inferred by them that AFG exists in two forms. As one form was melting, the other form was crystallizing and vice versa. Therefore, the endotherms of melting might have been superimposed by the exotherm of crystallization. The 90.90 J/g observed as the latent heat of crystallization might thus be taken as the difference between the actual latent heat of crystallization and the latent heat of melting of the polymer.

The first endotherm in the thermogram of PRG can be ascribed to the enthalpy relaxation of the polymer (Chung *et al*., 2002). There was no exothermic transition in the thermogram. The second transition is another endotherm which can be ascribed to the melting of the polymer. The peak of the endotherm (300 ^{O}C) represents the melting temperature (T_m) of the polymer. The latent heat of melting was 106.07 J/g. There was no significant difference between the thermal transition of PRG and CSG. The two polymers exhibited similar behaviour as hydroxypropylmethylcellulose (Builders *et al*., 2009).

The enthalpy relaxation of sodium carboxymethylcellulose was illustrated by the endotherm which peaked at 70 ^{O}C. The diffuse exotherm which peaked at 295 ^{O}C revealed the crystallization of the polymer. The diffuse endotherm observed between 350 and 400 ^{O}C can be assumed to represent melting of the polymer as there was no other clear endotherm.

The enthalpy relaxation temperature of the polymers was in the order PRG < SCMC = CSG < AFG < ACG < KYG. Enthalpy relaxation is an endothermic process as it involves heat flow to the system. It is associated with increase in temperature and hence changes in heat capacity. It is a second order reaction just like glass transition (Horvat *et al*., 2005).

When polymers are heated beyond enthalpy relaxation, they attain an orderly arrangement forming crystals in a process called crystallization. Crystallization involves heat loss. Hence, it is an exothermic transition. Since, it takes place at a constant temperature; it is a first order reaction (Builders *et al*., 2009). As heating continues

beyond crystallization, a temperature (melting temperature) is reached when the crystals move out of the orderly arrangement. This is called melting. Heat gain is associated with melting. Hence, it is an endothermic transition. Just as in crystallization, melting takes place at a constant temperature. It is therefore, a first order transition (Horvat *et al*., 2005). Enthalpy relaxation could be directly accompanied by exotherm of polymer degradation as observed with KYG and ACG.

While glass transition and enthalpy relaxation are characteristic of amorphous domain of polymers (Turley and Kskkula, 1966), melting transition is characteristic of their crystalline domain (Builders *et al*., 2008). Polymers with low melting temperatures form crystallites having more chain flexibility and less laminar dipoles. Those with high melting temperatures form crystallites that are closely packed or they have high number of aromatic side chains (Builders *et al*., 2009).

The Fourier transform infrared spectra of cashew gum and khaya gum are very similar [Figure 4.2 (i)]. The diffuse peaks are indicative of the presence of impurities (Horvat *et al*., 2005). The first absorption peak of 761.91 cm^{-1} in cashew gum and 757.09 cm^{-1} in khaya gum correspond to the presence of cyclic nucei in the two polymers. The two spectra have similar peak pattern and may contain similar functional groups.

The prominent peak of cashew gum at 761.91 cm^{-1} could be assigned to C-H bending vibration of substituted cyclic hydrocarbon while at 2,914.54 – 3,265.65 cm^{-1} could be attributed to stretching vibration of the cyclic C-H. The peaks at 1,063.78 and 1,309.71 cm^{-1} could be assigned to O-H bending and C-O stretching of ether and alcohol. The peaks at 2,577.95 and 2,651.25 cm^{-1} could be assigned to stretching vibration of intra-

molecularly hydrogen bonded O-H group while 3,657.16 cm^{-1} peak could be assigned to stretching vibration of free O-H based on infrared spectroscopy bands of selected functional groups given by Coutts (2008).

In the FTIR spectrum of khaya gum, the peak at 757.09 cm^{-1} could be assigned to cyclic C-H bending vibration while those at 3,032.20 – 3,256.91 cm^{-1} could be attributed to stretching vibration of C-H in the substituted cyclic hydrocarbon. The peaks at 1,115.86 and 1,307.78 cm^{-1} could be assigned to O-H bending and C-O stretching of ether and alcohol. The peaks at 2,561.41 and 2,685.97 cm^{-1} could be assigned to stretching vibration of bonded hydroxyl group while the peak at 3,638.83 cm^{-1} could be assigned to stretching vibration of free O-H (Coutts, 2008).

The absorption of 597.95 cm^{-1} (< 600 cm^{-1}) found in acacia gum was not found in cashew nor khaya gum. However, peaks below 600 cm^{-1} are not used in characterization. In the FTIR spectrum of acacia gum, the peak at 783.13 cm^{-1} could be assigned to cyclic C-H bending vibration while those at 2,853.78 and 3,178.79 cm^{-1} could be assigned to C-H stretching vibration of the cyclic hydrocarbon. The peaks at 1,088.85 and 1,278.85 cm^{-1} could be assigned to O-H bending and C-O stretching of ether and alcohol. The peak at 3,484.52 cm^{-1} could be assigned to the stretching of bonded O-H group while that of 3,606.04 cm^{-1} could be assigned to stretching vibration of free O-H group (Figure 4.2) based on specifications of Coutts (2008).

The prominent peaks of Afzelia gum at 1,038.70 and 1,137.07 cm^{-1} could be assigned to 0-H bending vibration and C-O stretching vibration of ethers and alcohol. The peaks at 2,993.62 to 3,257.88 cm^{-1} could be assigned to C-H stretching vibration of the cyclic

hydrocarbon. The peak at 3,479.70 cm^{-1} could be assigned to O-H stretching of bonded hydroxyl group while that at 3,634.01 cm^{-1} could be assigned to stretching of free O-H [Figure 4.2 (ii)] based on specifications of Coutts (2008).

The FTIR spectra of PRG and SCMC were similar and slightly different from that of AFG. Both polymers have similar distinct absorptions. In the spectrum of prosopis gum, the peak at 771.55 cm^{-1} could be attributed to bending vibration of C-H in substituted cyclic hydrocarbon while those at 2,898.14 to 3,193.26 cm^{-1} could be assigned to C-H stretching of the cyclic hydrocarbon. The peaks at 1,122.81 and 1,250.88 cm^{-1} could be assigned to O-H bending and C-O stretching vibrations of ether and alcohol. The peaks at 3,455.59 and 3,553.00 cm^{-1} could be assigned to stretching vibrations of bonded O-H (Coutts, 2008).

In the FTIR spectrum of sodium carboxymethylcellulose, the peak at 766.75 cm^{-1} could be assigned to C-H bending of substituted cyclic hydrocarbon while those at 2,990.73 – 3,264.63 cm^{-1} could be attributed to C-H stretching of the cyclic hydrocarbon. The peaks at 1,058.98 – 1,297.17 cm^{-1} could be assigned to O-H bending and C-O stretching of ether and alcohol; 3,476.81 cm^{-1} could be assigned to O-H stretching of bonded O-H while the peak at 3,621.47 cm^{-1} could be assigned to O-H stretching of free hydroxyl group based on specifications of Coutts (2008).

The similarity in the peaks observed in the polymers shows that they are related. The dominance of carbon, hydrogen and oxygen atoms in these polymers with different bonds connecting them supports the fact that they are carbohydrate polymers.

From X-ray diffraction pattern, the major peaks of CSG, KYG and ACG lying at the same point is an indication that the three gums are the same type of polymer. The abundance of calcium in cashew gum was confirmed by the two additional peaks at 26.49 and 42.34 $^{0}2\Theta$. The shorter and more flattened peak of KYG indicates the presence of impurities (Nutan *et al*., 2005).

The presence of a single peak of the same height (6,400 ct) about the same point in the XRD pattern of AFG, PRG and SCMS is an indication that they are structurally related. SCMC is sodium salt of carboxymethylcellulose and afzelia gum had been described as a xyloglucan which is a hemicellulose (Builders *et al*., 2009). Prosopis gum, with a peak of the same height at the same position can thus be described as a xyloglucan. Therefore, afzelia gum, prosopis gum and sodium carboxymethylcellulose have the same backbone of cellulose.

Organic molecules are large; and their crystals have large unit cells. Their inter-planar spacings are therefore, large. The large spacing gives rise to diffraction peaks at small values of $^{0}2\Theta$. This is particularly true for amorphous materials (Shell, 2008). All the polymers have single major peak below 25 $^{0}2\Theta$ which is on the low side. They are therefore, amorphous organic materials.

5.3 BACTERIAL LOAD

The bacterial load of each of the gums was close to the 1.0 x 10^4 count/g limit. Natural gums are highly susceptible to microbial attack and this is the major limitation to their use as pharmaceutical excipients (Billany, 2007). Preservatives are normally incorporated when they are used in liquid and semi-solid formulations in order to

prevent microbial attack. The official limit of bacterial load for non-sterile products is 1 x 10^4 per g or ml (U.S.P., 2008)

5.4 SURFACE PROPERTIES

Increase in polymer concentration led to decrease in surface tension of water until a point where further increase in the polymer concentration did not lead to decrease in the surface tension (Figure 4.5). The concentration at which this occurred is termed the critical micelle concentration (CMC) of the surfactant. This phenomenon was observed with all the polymers. At concentrations above 0.5 % w/v, the dispersion of SCMC became sticky exhibiting high adhesive strength. Hence, the plot was terminated at this concentration for the dispersion of this polymer.

Gums, because of their ability to reduce surface tension of water at low concentration, can be said to be surface active. Surfactants are characterized by having two regions (hydrophilic and hydrophobic regions) and are termed amphiphiles. It is energetically favourable for them when dissolved to adsorb at interfaces (Attwood, 2007).

At low concentrations, the polymers were packed at the surface of water with the hydrophobic region orientated away from the aqueous phase causing a reduction in the surface tension of the liquid by an amount equal to the surface pressure. This led to the expansion of the surface layer (Fell, 2007). As the concentration of the polymer was increased, more of the molecules were packed at the surface layer causing further decrease in the surface tension until a point when the surface became saturated; that is, at critical micelle concentration (Florence and Attwood, 2007).

Above the critical micelle concentration, aggregates of colloidal dimensions were formed. These spherical aggregates are called micelles. The hydrophobic chains formed the core of the micelles and were shielded from the aqueous environment by the hydrophilic groups. Micelles are responsible for maintaining solubility in water and solubilization of water-insoluble compounds (Attwood, 2007).

The order of critical micelle concentrations of the polymers was SCMC < PRG = AFG = ACG < CSG < KYG. (Table 4.4). The modal critical micelle concentration was 0.25 % w/v which is not significantly different from the usual 0.20 % w/v for surfactants (Mahmud, 2009).

The lowest CMC (0.1 % w/v) observed with sodium carboxymethylcellulose may be attributed to the presence of $-CH_2COO^-Na^+$ in the molecule. Presence of ions generally decreases the critical micelle concentration of surfactant and increases micellar size. This is sequel to the increase in the force of repulsion between the similar charged groups in the micelle; promoting micelle growth and reducing the energy required for their formation (Attwood, 2007).

The two seed gums (prosopis and afzelia) have CMC of 0.25 % w/v which is significantly lower than those of exudate gums with the exception of acacia gum. The value of critical micelle concentration varies directly with the length of hydrophilic chain and inversely with the length of hydrophobic chain (Attwood, 2007). Therefore, polymers obtained from seed contain shorter hydrophilic chain or longer hydrophobic chain.

Acacia gum has the greatest surface tension lowering effect while afzelia gum has the lowest effect at critical micelle concentration (Table 4.4). At very low concentration of 0.1 % w/v, SCMC is the most effective in reducing surface tension of water. Prosopis gum at 0.25 % w/v is equivalent to 0.5 % w/v cashew gum and 0.75 % w/v khaya gum in lowering surface tension of water (Table 4.4).

Gums generally, are moderately active surfactants. However, because of their common use as pharmaceutical excipients (Mahmud, 2009), there is a need to consider their effect on drug solubilization and absorption.

A low concentration of surfactant increases absorption possibly due to enhanced contact of the drug with the absorbing membrane. Concentrations above CMC will either produce no additional effect or will cause decreased absorption depending on the nature of the drug including its water-solubility or whether non-absorbable micelles are formed (Attwood, 2007). Gums may have varying effect on absorption of artemether and artesunate whose major physical difference is solubility.

5.5 HYDROPHILE - LIPOPHILE BALANCE

All the polymers have moisture sorption capacity above 50 % with SCMC having the highest value. These values are significantly higher than those of starches (Olorunsola *et al*., 2011). Moisture sorption capacity is a measure of moisture sensitivity of a material and it reflects the relative physical stability of tablets formulated with the material when stored under humid conditions (Ohwoavworhua and Adelakun, 2005).

There was a significant difference in the water - solubility of the different polymers. The water - solubility of the three exudate gums are significantly higher than those of the seed gums. The solubility of cashew gum, khaya gum and acacia gum in dilute aqueous solution of sodium hydroxide was not significantly different from their solubility in distilled water. The solubility of afzelia gum, prosopis gum and sodium carboxymethylcellulose was significantly enhanced ($p < 0.001$) in the presence of dilute aqueous sodium hydroxide.

Afzelia gum had been described as a xyloglucan having a cellulose backbone. This was suggested by solubility enhancement in dilute aqueous sodium hydroxide (Builders *et al*., 2009). Prosopis gum can thus be equally described as a xyloglucan.

The difference in the hydration capacity of the polymers was significant, with AFG, PRG and SCMC having higher values. The hydration capacity of the polymers is directly related to the packing of the powdered gum. Afzelia gum, prosopis gum and sodium carboxymethylcellulose were found to be fluffy while CSG, KYG and AFG were not (Table 4.1). The hydration capacity was also found to be directly linked with the nature of the core of the polymer structure. Polymers with cellulose core had higher hydration capacity. The hydration capacity of a substance is a measure of the amount of water that can be taken-up by the substance (Isah *et al.*, 2012).

The kinetic constant 'K', swelling constant 'n' and mean swelling time 'MST' were obtained from the plot of Log W_t/W_d versus Log t. The kinetic constant 'K' is a parameter that is related to the macro-molecular network system of the polymer (Cao *et al.*, 2005). It is a measure of the rate of movement of water into the polymer. Cashew

gum, khaya gum and acacia gum had higher values of K compared to afzelia gum, prosopis gum and sodium carboxymethylcellulose. Relating the hydration capacity to the kinetic constant, it is clear that while the initial rate of water flow to CSG, KYG and ACG was higher, the eventual total water up-take by AFG, PRG and SCMC was higher.

The swelling constant 'n' is a measure of the rate of swelling of the polymer and the mean swelling time is the longest time swelling was observed in the polymer. Cashew gum, khaya gum and acacia gum have lower swelling rate and lower swelling time. They are not strong hydrogels and will not be suitable for use as swellable matrices. The continuous increase in swelling ratio and high mean swelling time observed with afzelia gum, prosopis gum and sodium carboxymethylcellulose are signs that they are true hydrogels (Builders *et al*., 2009).

A significant difference was observed in the swelling capacity of the polymers. It was in the order SCMC > PRG > AFG > KYG > CSG > ACG. SCMC had the highest hydration capacity, highest swelling capacity, highest swelling constant and highest mean swelling time while acacia had the lowest values of these parameters. Sodium carboxymethylcellulose is thus the strongest hydrogel while acacia gum is the weakest in the group.

There are several methods for determining hydrophile - lipophile balance of a surfactant. These include: oil/water partitioning method (Kruglioaokor, 2000), phenol titration method (Kruglioaokor, 2000), spontaneous emulsification method (Macedo *et al*., 2005), water-solubility method (Kruglioaokor, 2000), group numbers (Davies, 1957) and nuclear magnetic resonance analysis (Ben-Et and Tatarsky, 1972).

According to Kruglioaokor (2000), oil/water partition coefficient is inversely proportional to the HLB value of a surfactant. There was a significant difference in the partition coefficient of the polymers. The exudate gums had lower values of partition coefficient (Table 4.6) and would have higher HLB values. Conversely, the seed gums have higher values of partition coefficient and would have lower HLB values. Krugliaokor (2000) also stated that phenol index is directly proportional to HLB value. There was a significant difference in the phenol index of the polymers; with the exudate gums having higher values (Table 4.6). This is another indication that they are characterized by higher HLB values.

The HLB values were observed to be in the order CSG > KYG > ACG > SCMC > PRG > AFG. The exudate gums had significantly higher HLB values while the seed gums had significantly lower values. HLB is a measure of the relative hydrophilicity of surfactants (Davies, 1957). Therefore, exudate gums are more hydrophilic. The HLB values of the polymers ranged from 9.74 (AFG) to 16.09 (CSG). According to the classification by Davies (1957), surfactants having HLB values of 8 to 18 are oil-in-water emulsifiers. Therefore, all the polymers are oil-in-water emulsifying agents. Furthermore, the HLB values of KYG and CSG fell within 15 and 18 which is the range for solubilizing agents. Therefore, the two gums would likely possess solubilizing property.

5.6 COMPATIBILITY STUDIES

5.6.1 Artemether with Cashew Gum

Artemether is (+) – (3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR) - decahydro – 10 – methoxy – 3, 6, 9 – trimethyl - 3, 12 – epoxy – 12H - pyrano (4, 3 - j) – 1, 2 –

benzodioxepine. The Fourier transform infra-red spectrum showed major peaks at 417.6 cm^{-1}, 866.07 cm^{-1}, 1019.41 cm^{-1}, 1376.26 cm^{-1}, 1440.87 cm^{-1}, 1734.06 cm^{-1} and 2937.68 cm^{-1} (Figure 4.7).

The thermogram of artemether showed three transitions. The first endotherm can be ascribed to melting of the drug being that the drug is already in the crystalline form. The melting point of the drug was 125 ^{O}C based on the peak of the endotherm. According to International Pharmacopoeia (2006), artemether has melting point of 86 – 90 ^{O}C. The pure alpha epimer however, behaves differently having higher melting point. This sample perhaps was a pure alpha form. The exotherm can be ascribed to recrystallization of the drug while the diffuse endotherm (225 to 250 ^{O}C) can be ascribed to the second melting of the drug.

On physically mixing cashew gum with artemether, an endotherm which peaked at 95 ^{O}C was the first observed transition. This can be ascribed to melting of artemether and enthalpy relaxation of cashew gum. The presence of cashew gum reduced the melting point of artemether from 125 ^{O}C to 95 ^{O}C. The exotherm can be ascribed to recrystallization of ATM. The presence of cashew gum increased the recrystallization temperature of artemether from 165 ^{O}C to 175 ^{O}C.

The second endotherm (200 to 300 ^{O}C) is a diffuse one without a clearly defined peak. It can be ascribed to melting of cashew gum and melting of the crystallite of artemether. The melting of the polymer and the drug are superimposed in this endotherm.

The peak at 417.6 cm^{-1} in the FTIR of artemether could not be assigned to any functional group as there is no literature for characterizing using absorption below 600 cm^{-1}. The peak at 866.07 cm^{-1} could be assigned to C-H bending vibration of cyclic hydrocarbon while the peak at 2,937.68 cm^{-1} could be assigned to stretching vibration of the C-H in the cyclic hydrocarbon. The peak at 1,019.41 cm^{-1} could be assigned to stretching vibration of C-O in ether. The peaks at 1,376.26 cm^{-1} and 1,440.87cm^{-1} could be assigned to bending vibration of C-H in the attached – CH_3 groups while that of 1,734.06 cm^{-1} could be assigned to C=O stretching vibration of lactone ester (Coutts, 2008).

The FTIR spectrum of cashew gum showed major peaks at 761.91; 2,914.54 – 3,265.65; 2,577.95 – 2,651.25 and 3,657.16 cm^{-1} which could be assigned to C-H bending of cyclic hydrocarbon, C-H stretching of cyclic hydrocarbon, stretching vibration of hydrogen bonded O-H group and stretching vibrations of free O-H group respectively (Coutts, 2008).

All the major peaks observed in the FTIR spectrum of artemether were retained even in the presence of cashew gum. However, there were slight changes in the position and intensity of the peaks. There was a shift of the first peak observed at 417.6 cm^{-1} to position 596.99 cm^{-1}. The peak at 866.07 cm^{-1} shifted to 860.28 cm^{-1}, still in the region typical of bending vibration of C-H of cyclic hydrocarbon. A single major peak at 2,937.68 cm^{-1} typical of stretching vibration of C-H of cyclic hydrocarbon was observed in the spectrum of pure artemether while two peaks at 2,852.81 cm^{-1} and 2,956.97 cm^{-1} were observed in the artemether/cashew gum mixture. This does not imply formation of new compound as such stretching vibrations were observed with pure artemether and

pure cashew gum. The stretching vibration due to C-O of ether observed at 1,019.14 cm^{-1} shifted to 1,047.38 cm^{-1} while the bending vibration of C-H of the trimethyl groups of artemether observed at 1,376.26 cm^{-1} and 1,440.87 cm^{-1} shifted to 1,368.54 cm^{-1} and 1,443.77 cm^{-1} respectively in the artemether / cashew gum mixture. The stretching vibration of the lactone ring was observed at 1,637.62 cm^{-1}.

The X-ray diffraction pattern of artemether showed major peaks of intensity 15,684 ct at 11.31 $^{0}2\Theta$; 47,392 ct at 17.64 $^{0}2\Theta$; 26,796 ct at 19.27 $^{0}2\Theta$ and 12,243 ct at 19.91 $^{0}2\Theta$. Pronounced peaks were also observed at 21.79 $^{0}2\Theta$ and 22.80 $^{0}2\Theta$ (Figure 4.9). The XRD pattern of pure cashew gum showed a pronounced peak typical of amorphous organic substance at 20 $^{0}2\Theta$ (Shell, 2008). The peak had intensity above 6,400 ct. Two minor peaks were also observed at 26.49 $^{0}2\Theta$ and 42.34 $^{0}2\Theta$ corresponding to calcium ion (Figure 4.9).

There was no major difference in the XRD patterns of artemether / cashew gum mixture and that of pure artemether. The only difference observed was in the intensity of the peaks observed before 20.00 $^{0}2\Theta$. The peaks in artemether / cashew gum spectrum were of lower intensity compared to those of pure artemether. This was expected as there was no peak observed with pure cashew gum below 20.00 $^{0}2\Theta$. There was superimposition of the major peak of cashew gum when it was combined with artemether. No new compound was formed as observed from the XRD patterns.

5.6.2 Artemether with Prosopis Gum

The first endotherm in the thermogram of artemether – prosopis gum mixture can be ascribed to enthalpy relaxation of prosopis gum and melting of artemether. The

presence of prosopis gum reduced the melting point of artemether from 125 ^{O}C to 85 ^{O}C. The prosopis gum had greater effect compared to cashew gum in lowering the melting temperature of artemether.

The sharp exotherm which can be ascribed to recrystallization of artemether showed that the presence of prosopis gum increased the recrystallization temperature from 165 to 175 ^{O}C. The endotherm which peaked at 210 ^{O}C can be ascribed to melting of the crystallite of artemether while the endotherm which peaked at 300 ^{O}C can be ascribed to melting of prosopis gum.

Prosopis gum and cashew gum had similar effect on raising recrystallization temperature of artemether. However, unlike in the case of ATM – CSG mixture in which melting of the polymer and the drug were superimposed, the melting of the polymer and the drug were distinct in the ATM – PRG mixture.

The FTIR spectrum of prosopis gum showed major peaks at 771.55 cm^{-1} and 2,898.14 to 3,193.26 cm^{-1}. These could be respectively assigned to bending vibration of C-H and stretching vibration of the C-H of cyclic hydrocarbon (Section 5.2). It also showed two major peaks at 1,122.81 and 1,250.88 cm^{-1} which had been assigned to stretching vibration of C-O and two other peaks at 3,455.59 and 3,553.00 cm^{-1} which had been assigned to stretching vibration of bonded O-H (Coutts, 2008).

All the major peaks observed in the FTIR spectrum of pure artemether were retained in the presence of prosopis gum (Figure 4.10). However, there were slight changes in the location of the peaks. There was a shift of the first peak from 417.6 to 512.12 cm^{-1}.

There was also a shift of the peak showing bending vibration of the hydrocarbon C-H from position 866.07 cm^{-1} to 853.53 cm^{-1}. Two peaks signifying stretching vibration of C-H of cyclic hydrocarbon were observed at 2,875.96 and 2,959.87 cm^{-1} in the spectrum of artemether / prosopis gum mixture. The peaks at 621.1 cm^{-1} and 1,646.3 cm^{-1} could be the magnified peaks in prosopis gum spectrum. There was a shift from 1,019.41 cm^{-1} to 1,066.67 cm^{-1}, from 1,376.26 cm^{-1} to 1,367.5 cm^{-1} and from1,440.87 cm^{-1} to1,442.80 cm^{-1} (Figure 4.10).

There was no major difference in the XRD pattern of pure artemether and that of artemether / prosopis gum mixture. The only difference noticed was in the base line of the peaks. There was elevation of the base line of the peaks of artemether formed around 20 $^{0}2\Theta$ when it was combined with prosopis gum (Figure 4.12). This could be due to the presence of the single peak of prosopis gum at 20.09 $^{0}2\Theta$. There was no new peak observed in the artemether / prosopis gum mixture. Hence, artemether and prosopis gum are compatible.

5.6.3 Artesunate Sodium with Cashew Gum

Artesunate sodium is 3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR – decahydro – 3,6,9 – trimethyl – 3,12 – epoxy – 12H – pyrano (4,3-j) -1,2 –benzodioxepine – 10- ol hemisuccinate sodium. The Fourier transform infra-red spectrum showed major peaks at 528.51 cm^{-1}, 855.46 cm^{-1}, 1011.70 cm^{-1}, 1371.43 cm^{-1}, 1759.14 cm^{-1}, 2939.16 cm^{-1} and 3281.02 cm^{-1} (Figure 4.13).

The first endotherm (with peak at 70 ^{O}C) in the thermogram of artesunate sodium can be ascribed to the enthalpy relaxation of the drug while the exotherm can be ascribed to

its crystallization. Therefore, it has crystallization temperature of 120 ^{O}C. The next transition which is an endotherm can be attributed to melting of the drug. Hence, it has melting point of 135 ^{O}C which is in consonance with the value reported by Esimone *et al*. (2008). Melting point of 132 – 135 ^{O}C was reported by these researchers. The last endotherm cannot be attributed to any transition other than melting. Therefore, there could be two forms of artesunate sodium crystallites.

The two endotherms in the thermogram of cashew gum had been attributed to the enthalpy relaxation and melting of the polymer. The first endotherm in the thermogram of artesunate sodium – cashew gum mixture can be attributed to enthalpy relaxation of cashew gum and that of artesunate sodium. The second endotherm can be attributed to melting of the drug. The presence of cashew gum had no significant effect on the melting point of artesunate sodium. The exotherm can be attributed to recrystallization of artesunate sodium while the last endotherm can be ascribed to melting of cashew gum. The melting of cashew gum was not significantly affected by the presence of artesunate sodium.

The peak at 855.46 cm^{-1} in the FTIR spectrum of artesunate sodium can be attributed to bending vibration of C-H in an cyclic hydrocarbon while that at 2,939.61 cm^{-1} can be attributed to stretching vibration of the C-H in the cyclic hydrocarbon. The presence of C-O in ether was indicated by peaks at 1,011.70 cm^{-1} and 1,152 51 cm^{-1}. The bending vibration of C-H of the methyl groups was indicated by the peak at 1,371.43 cm^{-1}. The peak at 1,759.14 cm^{-1} could be assigned to stretching vibration of lactone ester while the peak at 3281.02 cm^{-1} could be assigned to O-H stretching vibration in H-bonded ether (Coutts, 2008).

The presence of cashew gum in the artesunate sodium / cashew gum mixture caused shifts in the FTIR peaks of artesunate sodium. There was a positive shift for those appearing after 1,250 cm^{-1} (Figure 4.13). There was no new peak in the spectrum of artesunate/cashew gum mixture implying no formation of new functional group.

The X-ray diffraction pattern of artesunate sodium showed major peaks at 12.22 $^0 2\Theta$ (intensity of 27,496.85 ct), 12.99 $^0 2\Theta$ (intensity of 92,266.16 ct), 15.44 $^0 2\Theta$ (intensity of 37,449.56 ct), 18.56 $^0 2\Theta$ (intensity of 44,345.87 ct), 19.79 $^0 2\Theta$ (intensity of 38,196.45 ct), 20.84 $^0 2\Theta$ (intensity of 6,528.94 ct), 21.97 $^0 2\Theta$ (intensity of 22,167.24 ct) and 22.92 $^0 2\Theta$ (intensity of 7,984.35 ct). There was no difference in the positions and d-spacing of XRD major peaks of pure artesunate and artesunate sodium / cashew gum mixture. However, there was elevation in the base level and hence reduction in the intensity of those major peaks. These could be due to superimposition of the peaks of cashew gum. No new peak was observed in the pattern of artesunate sodium/cashew gum mixture. Therefore, no new compound was formed.

5.6.4 Artesunate Sodium with Prosopis Gum

Just as with the thermogram of cashew gum, the two endotherms of prosopis gum had been attributed to the enthalpy relaxation and melting of the polymer. The first transition (which is an endotherm) in the thermogram of artesunate sodium – prosopis gum mixture can be ascribed to the enthalpy relaxation of prosopis gum and that of artesunate sodium. The second transition (another endotherm) can be ascribed to melting of the drug. Prosopis gum had no significant effect on the melting point of the drug. The exotherm can be attributed to recrystallization of artesunate sodium while the

last endotherm can be ascribed to melting of prosopis gum. The melting point of prosopis gum was significantly reduced by the presence of artesunate sodium.

All the major peaks observed in the FTIR spectrum of pure artesunate sodium were observed in the spectrum of artesunate sodium / prosopis gum mixture. There was no significant difference in the position of the peaks. However, there was reduction in their intensity and sharpness. For example, the peaks at 1,011.70 cm^{-1} and 1,152.51 cm^{-1} became blunter and much less intense in the presence of prosopis gum. Some peaks that were not in the spectrum of pure artesunate sodium were found in the spectrum of artesunate sodium / prosopis gum mixture. These include: those at 1653.05 cm^{-1}, 3873.19 cm^{-1}, 4050.65 cm^{-1} and 4349.62 cm^{-1}. The corresponding peaks were found in the spectrum of pure prosopis gum as 1643.41 cm^{-1}, 3841.36 cm^{-1}, 4028.47 cm^{-1} and 4319.73cm^{-1} (Figure 4.16).

The XRD pattern of prosopis gum had a single major peak at 20.09 $^{0}2\Theta$. All the major peaks in the XRD pattern of pure artesunate sodium were observed in the pattern of artesunate sodium / prosopis gum mixture. There were slight changes in the position and d-spacing of the peaks. The greatest extent of dislocation was observed in the peak at position 20.84 $^{0}2\Theta$ of artesunate sodium spectrum in the presence of prosopis gum. There was elevation of the base level and hence reduction in the intensity of the peaks in artesunate sodium / prosopis gum mixture. There was no new peak in the spectrum of artesunate sodium/ prosopis gum mixture. Therefore, no new compound was formed from the mixture.

Cashew gum is a galactan polymer (Lima *et al*., 2002) while prosopis gum is a xyloglucan polymer (Ren *et al.,* 2005). Therefore, artemether and artesunate sodium are compatible with the galactan and xyloglucan polymers. Cashew gum had significantly higher HLB value while prosopis gum had significantly lower HLB value. Hence, cashew gum and prosopis gum were used for the evaluation of effect of the tropical gums on the release of artemether (water-insoluble drug) and artesunate sodium (water-soluble drug) from tablets. Surface active agents may increase or decrease the extent and rate of drug delivery. Their effect on drug delivery depends on the nature of the drug especially, its water solubility (Ashford, 2007b).

5.7 EFFECT OF GUMS ON TABLET FORMULATION AND RELEASE OF ARTEMETHER

Artemether Granule Micromeritics

There was no significant difference in the angle of repose of granules containing different types and concentrations of binders. The increase in angle of repose in the presence of chitosan (permeation enhancer) is an indication that chitosan decreased the flowability of granules containing CSG and PRG. However, the increase in the angle of repose was not beyond the range of excellent flow. According to Wells and Aulton (2007), angle of repose below 20 ^{O} suggests excellent flow. The angle of repose of all the granules fell within this range and the granules were thus characterized as having excellent flow. All the granules possessed high flow rate above 5 g/s.

A Hausner's ratio of less than 1.25 indicates good flow (Wells and Aulton, 2007). Therefore, all the granules possess good flow. The Hausner's ratio was not significantly

affected by increase in binder concentration; neither was it significantly affected by the presence of chitosan.

Increase in binder concentration had significant effect on Carr's (compressibility) index. According to Wells and Aulton (2007), Carr's index below 15 % indicates excellent flow, 15-16 % indicates good flow, while 18-21 % indicates passable (fair) flow. Apart from granules containing 1 % CSG binder with fair flow, all the other granules exhibited good flow.

A passable flow is one that can be improved by the addition of a glidant (Wells and Aulton, 2007). To ensure excellent flow of all the granules, talc at a concentration of 1.5 % was added to all the batches before compression.

Physical Properties of Tablets

All the batches passed the test for uniformity of weight and dimensions. According to U.S.P. 31 – N.F. 26 (2008), not more than two of the individual weight should deviate from the average weight by more than 7.5 % and none should deviate by more than twice that percentage for tablets of mean weight of 130 - 324 mg. Also, no tablet should deviate by more than 5 % of the stated dimensions (diameter and thickness).

All the tablets passed the test for crushing strength. The crushing strength for tablets containing CSG ranged from 4.10 to 5.20 kgf while the value for those containing PRG ranged from 4.40 to 5.50 kgf. The increase in the crushing strength of tablet with increase in binder concentration for both polymers is in agreement with the work of Ibezim *et al*. (2006). Crushing strength is a measure of the structural strength of tablet

provided by the binder during compression process. Tablet strength is directly related to the magnitude of plastic deformation taking place during compression (Uhumwangho *et al*., 2006). Therefore, PRG experienced higher amount of plastic deformation compared to CSG as tablets containing PRG had higher crushing strength at all the binder concentrations.

A tablet is expected to have a friability of less than 1 % to pass quality assessment test (Rudnic and Schwartz, 2006). All the tablets containing different concentrations of CSG with or without chitosan passed the test for friability. For tablets containing the different concentrations of PRG, all but the batch containing 1 % w/w of the binder passed the test for friability. Hence, 2 % w/w is the minimum concentration of PRG needed for artemether tablet to pass friability test. The general decrease of friability with increase in binder concentration can be attributed to the formation of more solid bonds which conferred resistance to fracture and abrasion as the binder concentration was increased (Olorunsola *et al.*, 2012).

Tablets containing CSG had lower crushing strength and lower friability compared to those containing PRG at all the binder concentrations used. It can thus be inferred that CSG confers less resistance to crushing but confers more resistance to abrasion. Conversely, PRG confers more resistance to crushing but confers less resistance to abrasion. This anomalous behaviour implies that tablets containing PRG possesses higher tensile strength and higher brittle fracture index compared to those containing CSG. This observation is similar to that reported by Alebiowu and Itiola (2003) where tablets containing native plantain starch had higher tensile strength and higher brittle fracture index compared to native sorghum starch.

The disintegration time of tablets containing CSG with or without the chitosan ranged from 0.97 to 2.99 min while those containing PRG with or without chitosan ranged from 28.98 to 69.71 min. An uncoated tablet is expected to have disintegration time of less than 15 min to pass quality assessment test (U.S.P. 31 – N.F. 26, 2008). All the tablets containing CSG as binder passed test for disintegration while those containing PRG failed the test for uncoated tablets.

It is desired that a tablet should remain coherent during the handling period but still disintegrate when placed in the disintegration medium. The crushing strength-friability-disintegration time index provides a measure of these desired properties (Olorunsola *et al*., 2012). Batch CSG2-C2 (containing 2 % w/w CSG and 2 % w/w chitosan) had the highest (CS/FR)/DT index for tablets containing CSG as binder. Chitosan at concentration of 2 % w/w improved the tablet quality more than the enhancer at concentration of 4 % w/w. This is because chitosan at concentration of 4 % w/w led to increase in both friability and disintegration time. Batch PRG 2 (containing 2 % w/w PRG) had the highest (CS/FR)/DT index for tablets containing PRG as binder. This is because tablets containing higher concentrations of the polymer had very long disintegration time.

For a conventional tablet to pass dissolution test, at least 75 % of the drug must be released within 1 h (USP 31 – NF 26, 2008). Tablets containing 3 % w/w CSG passed the test for dissolution whereas those containing the same concentration of PRG failed the test. Therefore prosopis gum should not be used at concentration up to 3 % w/w for the formulation of conventional tablets.

The low disintegration time of artemether tablets containing CSG can be attributed to good water solubility of the gum (Table 4.5). Also, the fast dissolution rate of the tablets containing the gum can be linked to its surface activity. The gum has an HLB value of 16.09 ± 0.08 (Table 4.6) which falls within the range of surfactants having solubilizing property (Davies, 1957). All the concentrations of CSG used are suitable for tablet formulation of artemether while only low concentrations of PRG are suitable for formulation of the drug into conventional tablet to achieve an acceptable drug release.

The high disintegration time of tablets containing PRG can be attributed to its poor-water solubility (Table 4.5). The slow dissolution of tablets containing PRG can be linked to its high binding strength (Attama *et al*., 2000). The long dissolution time of tablets containing PRG and the ability of PRG to form hydrogel (Table 4.5) suggest the suitability of the gum for controlled release formulations.

Permeation under Simulated Gastric Fluid Condition

No significant difference in permeation coefficient was observed with tablets containing different concentrations of CSG with or without the permeation enhancer. Since all the tablets containing the gum as binder disintegrated within 3 min, the drug was made available for dissolution and absorption in relatively short time.

The increase in the amount of drug permeated in 30 min with increase in the concentration of CSG can be linked to the observed decrease in the disintegration time. Disintegration is the first step of drug release from tablets; and it plays an important role in the dissolution process (Olorunsola *et al*., 2012).

There was no significant difference in the time taken for 95 % drug permeation from tablets containing different concentrations of the polymer and the presence of chitosan did not lead to reduction in the time taken. Hence, desquamation of intestinal epithelial cells by chitosan (Kos *et al*., 2008) did not enhance permeation of the poorly water-soluble artemether under simulated gastric fluid condition.

According to Suputtamongkol *et al*. (2001), artemether attains peak plasma concentration in 2 h; and may undergo complete absorption within 4 h. Hence, cashew gum has a mild permeation enhancing effect on the drug and it reduced the $t_{95\%}$ to an average of 3 h.

The increase in drug flux and permeation coefficient with increase in the concentration of PRG shows that the polymer enhances the permeation of the poorly water-soluble artemether through biological membrane in the presence of simulated gastric condition. Presence of chitosan causes a further increase in permeation of artemether. It is obvious that while CSG has a better drug releasing property, PRG has a better permeation enhancing property when they are used as binders for the poorly water-soluble artemether.

Permeation under Simulated Intestinal Fluid Condition

There was increase in the permeation coefficient of artemether with increase in the concentration of CSG. However, there was little difference in the time taken for 95 % drug permeation from tablets containing different concentrations of the gum. This could

be due to decrease in the amount of drug permeated in the first 30 min with increase in the concentration of the gum.

The reduction in time taken for 95 % drug permeation in the presence of chitosan (2 % or 4 % w/w) is an indication of positive effect of chitosan on permeation of cashew gum – delivered artemether. The hydrophilic cashew gum gave an enabling environment for permeation enhancement of the poorly water-soluble artemether by chitosan. This is contrary to the report of Yin *et al*. (2009) who stated that chitosan is not effective as permeation enhancer at higher pH. Hence, permeation of a poorly water-soluble drug can be enhanced by delivering the drug using a cashew gum/chitosan system.

The increase in permeation coefficient of the drug with increase in the concentration of PRG can be attributed to decrease in interfacial tension with increase in the concentration of the surface active prosopis gum. The eventual time taken for 95 % drug permeation was however, not affected by increase in the concentration of the gum. This is sequel to the dual action of the gum.

The inclusion of chitosan caused a decrease in the amount of drug permeated in the first 30 min but subsequently caused an increase in permeation coefficient at steady state. According to Yin *et al*. (2009), chitosan has low solubility and hence poor permeation enhancing activity at neutral pH. Its solubility might have increased after 30 min when substantial amount of PRG had gone into solution.

It was earlier shown in this work that both CSG and PRG are capable of reducing the surface tension of water from 72 mN/m to 55 mN/m (Table 4.4). This surface activity

can be linked to the permeation enhancement. Surface active agents are capable of temporarily increasing membrane permeability (Ashford, 2007b). Prosopis gum has an additional quality of high bioadhesive strength (Attama *et al*., 2000) enabling the drug to have better contact with the biological membrane. This explains why PRG had a better permeation enhancing ability.

5.8 EFFECT OF GUMS ON TABLET FORMULATION AND RELEASE OF ARTESUNATE SODIUM

Granule Micromeritics

Angle of repose is an inverse measure of particle flowability and it relates to inter-granular cohesion (Wells and Aulton, 2007). The angle of repose of granules containing CSG increased with increase in binder concentration. Therefore, as the intra-granular binding strength increased with increase in binder concentration, the inter-granular cohesion also increased. The presence of chitosan did not cause a significant change in the angle of repose.

There was no significant difference in the angle of repose of granules containing different concentrations of PRG. At 2 % binder concentration, the presence of chitosan led to increase in angle of repose and the increase in the angle of repose was proportional to the concentration of chitosan used. Therefore, chitosan caused increase in inter-granular cohesion for granules containing PRG and artesunate sodium (Wells and Aulton, 2007). This phenomenon was also observed in the values of the flow rate.

The type and concentration of the binder had no significant effect on the bulk density of the granules neither had they any significant effect on the tapped density. An increase in the consolidated bulk density is advantageous in tableting (Adikwu *et al*., 2005).

The Hausner's ratio was below 1.25 for all the granules irrespective of the binder type or concentration. A Hausner's ratio below 1.25 is indicative of good flow (Wells and Aulton, 2007). All the granules possess good flow based on the Hausner's ratios.

According to Wells and Aulton (2007), Carr's index of 5-15 % indicates excellent flow, 15-16 % indicates good flow, 18 - 21 % indicates passable flow, while > 23 % indicates poor flow. Apart from granules containing 1 % binder, all the artesunate sodium granules containing CSG possessed good flow. All the granules containing different concentrations of PRG without chitosan possessed good flow. The flowability of granules containing 2 % PRG was reduced in the presence of 2 % chitosan. This can be attributed to increase in inter-granular cohesion (Wells and Aulton, 2007).

The suitability of CSG and PRG as binders for artemether and artesunate sodium are similar. While PRG is suitable at all the binder concentrations used (1-4 % w/w), CSG is only suitable at 2-4 % binder in terms of flow properties. The flowability of artemether and artesunate sodium granules containing 1 % of CSG (with 17-18 % Carr's index) was passable and can be improved by addition of a glidant (Wells and Aulton, 2007). The addition of 1.5 % talc to all the granules assured acceptable flowability for granules with passable flow.

Physical Properties of Tablets

All the batches passed the test for uniformity of weight and dimensions. The U.S.P. 31 – N.F. 26 (2008) states that not more than two of individual weight should deviate from mean weight by more than 7.5 % and none should deviate by more than 15 % for tablets of mean weight ranging from 130 to 324 mg. It also states that no tablet should deviate by more than 5 % of the stated dimensions (diameter and thickness).

The crushing strength of artesunate sodium tablets containing CSG with or without chitosan ranged from 4.20 to 6.20 kgf, while those of tablets containing PRG with or without chitosan ranged from 4.60 to 7.00 kgf. All the tablets passed the test for crushing strength. The increase in crushing strength with increase in binder concentration is in consonance with the result obtained with artemether tablets. Just as was obtained in artemether tablets, tablets containing PRG had higher crushing strength at all the binder concentrations used (1-4 % w/w). With chitosan increasing the crushing strength of CSG and decreasing that of PRG, it could be assumed that it enhanced the plastic deformation of CSG while decreasing that of PRG. Tablet strength is directly related to the amount of plastic deformation experienced by a plasto-elastic material during compression (Uhumwangho *et al*., 2006).

A friability of less than 1 % is expected for a tablet to pass friability test. Batches CSG1 and PRG1 failed the friability test while the other batches passed. Hence, a minimum of 2 % w/w binder concentration of CSG or PRG is required for artesunate tablet to pass friability test. Chitosan caused a decrease in friability of tablets containing CSG and an increase in the friability of those containing PRG. The same explanation of Uhumwangho *et al*., (2006) can be given for this phenomenon.

All the batches containing CSG as binder passed the test for disintegration time while those containing PRG as binder failed the test just as in the artemether tablet formulations. Chitosan caused an increase in disintegration time of formulation containing 2 % w/w of CSG and a decrease in the value for the formulation containing 2 % w/w of PRG. The increase in DT of tablets containing CSG (water-soluble gum) can be attributed to poor water-solubility of chitosan in a neutral environment (Yin *et al*., 2009). Chitosan might be more hydrophilic than the poorly water-soluble PRG for it to have decreased the DT of tablets containing PRG.

Tablets containing 2 % w/w binder with 4 % w/w chitosan had the highest (CS/FR)/DT index of all the batches for both CSG and PRG. Therefore, 4 % w/w chitosan, when compared to 2 % w/w chitosan imparted better physical properties to artesunate sodium tablets.

For a conventional tablet to pass dissolution test, at least 75 % of the drug must be released within 1 h (USP 31 – NF 26, 2008). The dissolution rate of tablets containing the same concentration (3 % w/w) of ACG and CSG were similar. Just like artemether tablets, artesunate sodium tablets containing CSG and ACG passed the test for dissolution whereas the batch containing the same concentration of PRG failed the dissolution test for uncoated tablet.

The low disintegration time of artesunate sodium tablets containing CSG can be attributed to the good water solubility of the gum and the high disintegration time of the tablet containing PRG can be linked to the poor water-solubility of the gum (Table 4.5)

as in the case of artemether tablets. Similarly, the fast dissolution rate of the tablets containing CSG can be attributed to the HLB value of 16.09 ± 0.08 which is in the range of surfactants possessing solubilizing property (Davies, 1957).

Permeation under Simulated Gastric Fluid Condition

There was no significant difference in the drug flux of artesunate sodium from tablets containing different concentrations of cashew gum (without chitosan) neither was there any significant difference in the permeation coefficient of the drug under the same condition. Similarly, there was no significant difference in the amount of drug permeated in 30 min neither was there any significant difference in the time taken for 95 % drug permeation from the tablets containing the different concentrations of the gum without chitosan.

The short disintegration time (less than 3 min) of all the tablets containing CSG without chitosan was responsible for the ready availability of the drug for dissolution and absorption. Disintegration is a vital step in the drug release process from tablets. The insignificant difference in the amount of drug permeated in 30 min for these batches is thus expected.

Despite the fact that cashew gum possesses moderate surface activity, no significant difference was observed in the permeation coefficient and in time for 95 % drug permeation by increasing the concentration of the gum. This observation can be attributed to the formation of non-absorbable complex by the incorporation of the water-soluble drug (artesunate sodium) in the micelles of the dispersion of CSG (Ashford, 2007b). This phenomenon could also be responsible for the delay in complete drug

permeation for all the tablets containing different concentrations of CSG without chitosan. According to Suputtamongkol *et al*. (2001), artesunate has t_{max} of 90 min achieving complete absorption within 180 min.

The presence of chitosan (2 % and 4 % w/w) caused a reduction in time for 95 % drug permeation to 155 min for tablets containing 2 % w/w of CSG. Even though the drug permeated in 30 min was higher for CSG2-C2, the drug flux was higher for CSG2-C4 resulting in the two formulations having the same $t_{95\%}$ of 155 min. The lower D_{30min} of the latter could be due to initial delay in drug release; and the eventual higher drug flux at steady state could be due to the higher concentration of the permeation enhancer in the formulation. The increase in the value of drug flux and permeation coefficient with increase in concentration of chitosan can be attributed to increase in the permeability of the intestine (Sonia and Sharma, 2011).

The lowest concentration of PRG (2 % w/w) gave the highest drug flux and the highest permeation coefficient. Evaluation of the surface activity of PRG in the earlier part of this work revealed that PRG at low concentration reduced the surface tension of water from 72 to 55 mN/m. Therefore, the high drug flux and high permeation coefficient of artesunate sodium at this binder concentration could be due to the effect of PRG on the permeability of intestine.

It has been reported that prosopis gum possesses high adhesive strength (Attama *et al*., 2000). Therefore, increase in the binder concentration would lead to increase in the binding strength of the polymer and slower release of the drug. High adhesive strength and/or formation of non-absorbable complex could be responsible for the low

permeation coefficient at high binder (PRG) concentration. The same explanation could be given for the observed increase in $t_{95\%}$ with increase in binder concentration. Incorporation of chitosan did not result to appreciable change in drug flux, permeation coefficient and $t_{95\%}$ for tablets containing 2 % w/w of PRG.

Permeation under Simulated Intestinal Fluid Condition

The decrease in the amount of artesunate sodium permeated in 30 min with increase in the concentration of CSG can be attributed to increase in the binding strength of the polymer with increase in concentration just as with other binders (Ibezim *et al*., 2006). The increase in the drug flux and the permeation coefficient with increase in the concentration of CSG is an indication that the polymer has a positive effect on permeation of artesunate sodium through biological membrane under SIF condition (Sharma *et al*., 2013). This can also be attributed to its ability to reduce surface tension.

Even though the presence of chitosan led to increase in permeation coefficient of drug from tablet containing CSG, there was no significant difference in the time taken for 95 % drug permeation from tablets with or without the permeation enhancer. This is in deviance with the result obtained for permeation under simulated gastric condition where the presence of the enhancer led to reduction in $t_{95\%}$ from 155 min. All these are in agreement with the report of Yin *et al*. (2009) where it was stated that chitosan is more soluble and more effective as permeation enhancer at acidic pH and possesses less activity at neutral pH.

The lowest concentration of PRG gave the highest permeation coefficient and the value decreased with increase in the concentration of the polymer. Prosopis gum is

characterized by high adhesive strength (Attama *et al*., 2000). Hence, the decrease in permeation coefficient with increase in polymer concentration can be attributed to increase in binding capacity of the polymer. It is thus advisable to use prosopis gum (a xyloglucan gum) at low concentration in order to achieve optimal binding as well as optimal drug release and permeation.

Even though the presence of chitosan led to increase in permeation coefficient at steady state, the delay and reduction in the permeation of the drug in the first 30 min resulted in insignificant difference in the time taken for 95 % drug permeation from tablets with or without the enhancer. This observation corresponds with that of permeation of the drug from the tablets containing CSG.

The permeation enhancer reduced the $t_{95\%}$ of ATS from tablets containing CSG and those containing PRG when placed in SGF. However, no significant difference was observed in the $t_{95\ \%}$ when the tablets were subjected to permeation studies under SIF. Therefore, chitosan is capable of enhancing permeation of water-soluble drugs delivered by both CSG and PRG and the effect is more pronounced on absorption at the gastric region. It also implies that epithelial cell desquamation by chitosan (Kos *et al*., 2008) as a complement of surface tension reduction by the tropical gums in enhancing drug permeation is more pronounced at lower pH.

Acacia gum and cashew gum at the same concentration of 3 % w/w exerted similar effect on the release and permeation of artemether and artesunate sodium. Cashew gum, a galactan polymer characterized as having high HLB value was found to be characterized by better release properties; while prosopis gum, a xyloglucan polymer

characterized as having lower HLB value was found to be characterized by better permeation enabling property when used at 2 % w/w concentration. Cashew gum has no significant effect on permeation of the slightly water-soluble artesunate sodium.

CHAPTER 6

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 SUMMARY

Cashew gum was extracted from exudates of *Anacardium occidentale L.*, khaya gum was extracted from exudates of *Khaya senegalensis*, afzelia gum was extracted from seeds of *Afzelia Africana*, while prosopis gum was extracted from seeds of *Prosopis africana*. Exudates from the tropical plants (cashew and khaya) contained higher percentage of gum compared to the seeds from the tropical plants (Afzelia and Prosopis).

The angle of repose, flow rate, Carr's compressibility index and Hausner's ratio revealed that the exudate gums possessed better flow than the seed gums. While dispersions of CSG, KYG and ACG had higher relative density; those of AFG and PRG had higher viscosity. The dispersion of SCMC had the highest value of relative density and viscosity.

The pH of 2 % w/v dispersions of the polymers was in the order KYG < CSG < AFG < ACG < PRG < SCMC. All the polymers have pH in the acidic region reflecting their economic and pharmaceutical importance. Afzelia and prosopis gums (seed gums) had the highest amount of potassium and magnesium ions. Calcium ion was observed to be the predominant ion in CSG while potassium was predominant in KYG. Copper ion was within the acceptable limit in all the polymers and lead was absent in all.

Cashew gum and prosopis gum have similar thermograms of two endotherms. Khaya gum, acacia gum, afzelia gum and sodium carboxymethylcellulose have similar thermograms consisting of an endotherm and an exotherm. The melting temperature T_m of the polymers was in the order AFG < PRG < CSG < KYG < ACG < SCMC. The Fourier transform infrared spectra of cashew and khaya gums were very similar and slightly different from that of acacia gum. The spectra of PRG and SCMC were similar and slightly different from that of AFG.

From X-ray diffraction, the single major peaks of CSG, KYG and ACG lying at the same point indicated that the three polymers are similar. The presence of a peak of the same height (6,400 ct), about the same point in the spectra of AFG, PRG and SCMC pointed to the fact that they are structurally-related. Afzelia gum had been described as a xyloglucan which is a hemicellulose and SCMC is a derivative of methylcellulose. Therefore, AFG, PRG and SCMC are cellulose-based. The dominance of carbon, hydrogen and oxygen atoms in all the polymers with different bonds connecting them supports the fact that the gums are carbohydrate polymers.

Increase in polymer concentration led to decrease in surface tension of water until a point (termed critical micelle concentration) where further increase in polymer concentration did not lead to decrease in the surface tension. The order of critical micelle concentration for the different polymers was SCMC < PRG = AFG = ACG < CSG < KYG. The modal CMC was 0.25 % w/v. The presence of partial charges on sodium carboxymethylcellulose might be responsible for the low CMC and high micellar size. The exudate gums had higher critical micelle concentration and might contain longer hydrophilic chain or shorter hydrophobic chain compared to the seed

gums. Acacia gum had the greatest surface tension lowering effect while afzelia gum had the lowest at the CMC. At very low concentration of 0.1 % w/v, SCMC was the most effective in reducing surface tension of water. The polymers generally possessed moderate surface activity.

All the polymers had moisture sorption capacity above 50 % with SCMC having the highest value of 122.45 %. Compared to starches, the polymers possess higher moisture sorption capacity. The water solubility of the three exudate gums was significantly higher than those of the seed gums and SCMC. The solubility of the exudate gums was not significantly enhanced in aqueous dilute alkali. In contrast, those of the two seed gums and SCMC were significantly enhanced ($p < 0.001$). There was no significant difference in the solubility of AFG, PRG and SCMC in dilute aqueous alkali.

The difference in the hydration capacity of the polymers was significant with AFG, PRG and SCMC having higher values. It was observed that the hydration capacity was directly related to the packing of the gum. AFG, PRG and SCMC which were fluffy had higher hydration capacity. While the rate of water flow to CSG, KYG and ACG was higher, the eventual total water up-take by AFG, PRG and SCMC was higher.

Cashew gum, khaya gum and acacia gum have lower swelling ratio and lower swelling time. There was a continuous increase in swelling ratio of PRG and SCMC over 1 h. The ranking order of the swelling capacity and mean swelling time was SCMC > PRG > AFG > KYG > CSG > ACG. SCMC had the highest hydration capacity, highest swelling capacity, highest swelling constant and highest mean swelling time, while ACG had the lowest value for these parameters.

There was a significant difference in the partition coefficient of the polymers. AFG, PRG and SCMC had higher values while CSG, KYG and ACG had lower values. There was no significant difference in the partition coefficient of CSG, KYG and ACG. The phenol index and hydrophile-lipophile balance of the polymers followed the same trend of CSG > KYG > ACG > SCMC > PRG > AFG. There was no significant difference in the phenol index and HLB values of CSG and KYG. Also, there was no significant difference in the values for ACG and SCMC.

Cashew gum, characterized as having higher HLB value, and prosopis gum, characterized as having lower HLB value, were selected for evaluation of the effect of gums on the release of water-insoluble drug (artemether) and slightly water-soluble drug (artesunate sodium). Compatibility studies using DSC, FTIR and XRD showed that artemether and artesunate sodium are compatible with the two polymers.

There was no significant difference in the angle of repose of artemether granules containing different types and concentrations of binders. All the granules possessed high flow rate above 5 g/s. The Hausner's ratio was not significantly affected by increase in gum concentration, neither was it significantly affected by the presence of chitosan. Apart from granules containing 1 % w/w CSG binder concentration with fair flow, all the granules exhibited good flow based on Carr's compressibility index.

All the artemether tablets had acceptable for crushing strength. Apart from the batch containing 1 % w/w PRG, all the tablets passed the test for friability. Artemether tablets containing CSG had lower crushing strength and lower friability compared to those containing PRG at all binder concentrations used. All the tablets containing CSG as

binder passed the test for dissolution rate while those containing greater than 2 % w/w PRG failed. Acacia and cashew gums at the same concentration of 3 % w/w exerted similar effect on the release and permeation of artemether.

There was no significant difference in the permeation coefficient of artemether from tablets containing different concentrations of CSG with or without chitosan under SGF condition. There was increase in the permeation coefficient of ATM with increase in concentration of CSG under SIF condition. The presence of chitosan caused a significant reduction in the time taken for 95 % permeation from tablets containing CSG. The permeation coefficient of ATM increased but the eventual time taken for 95 % drug permeation was not significantly affected by increase in the concentration of PRG under SIF condition.

The angle of repose of artesunate sodium granules containing CSG increased with increase in binder concentration. The value was not significantly affected by increase in the concentration of PRG. The Hausner's ratio was < 1.25 for all the granules irrespective of the binder type and concentration. Apart from the batch containing 1 % CSG, all the granules possessed good flow based on Carr's index.

All the tablets passed the test for crushing strength. As obtained with artemether tablets, tablets containing PRG had higher crushing strength at all the binder concentrations used. The minimum concentration of binder (CSG or PRG) for artesunate sodium tablets to pass friability test was 2 % w/w. Just like artemether tablets, all the batches containing CSG with or without chitosan passed the test for dissolution rate while those containing greater than 2 % w/w PRG failed. Acacia and cashew gums at the same

concentration of 3 % w/w exerted similar effect on the release and permeation of artesunate sodium.

There was no significant difference in the permeation coefficient of ATS from tablets containing different concentrations of CSG without chitosan under SGF condition. The presence of chitosan (2 % and 4 % w/w) caused reduction in the time taken for 95 % drug permeation. The permeation coefficient of the drug decreased with increase in the concentration of PRG; and incorporation of chitosan did not cause a significant change in the permeation coefficient for permeation under SGF condition. Hence, 2 % w/w PRG gave the best drug permeation of ATS. An increase in the permeation coefficient was observed at steady state with increase in the concentration of CSG for permeation under SIF condition. There was no significant difference in the time taken for 95 % drug permeation from tablets containing CSG with or without chitosan. Lower concentrations of PRG gave better permeation of artesunate sodium under SIF condition and the presence of chitosan did not cause a significant change in the permeation coefficient and time.

6.2 CONCLUSION

The exudates and seeds of the tropical plants used are rich sources of natural gums. The exudates contain higher amount of gum compared to the seeds. The gums from the exudates possess better flow properties compared to those from the seeds. Dispersion of sodium carboxymethylcellulose had the highest viscosity and relative density compared to the tropical gums and might form the most physically stable dispersions. The polymers can be distinguished by the relative abundance of the different metal ions and by the pH of their dispersions. They possess moderate surface activity. There is no

significant difference in their interfacial tension lowering effect but they possess different critical micelle concentrations. The exudate gums (CSG, KYG and ACG) are characterized by higher HLB values while the seed gums (AFG and PRG) are characterized by lower HLB values.

Artemether and artesunate sodium are compatible with both cashew gum and prosopis gum. Cashew gum is similar to acacia gum in terms of binding, release and permeation enabling properties. It confers more resistance to abrasion while prosopis gum confers more resistance to crushing. Cashew gum as a binder can be used over a relatively wide range of concentrations to achieve very good drug release though with minimal permeation enhancement. Prosopis gum has a good permeation enhancing effect on both water-soluble and poorly water-soluble drugs but must be used at low concentration. The release and permeation of the drugs are related to the surface properties of the gums used for their tablet formulations. The higher HLB value of cashew gum favours drug release, while the lower HLB value of prosopis gum favours drug permeation. This work has shown that tropical gums possess surface activity and exert effect on the release of artemether and artesunate sodium from their tablet formulations. Therefore, the null hypothesis is rejected and the alternate hypothesis is upheld.

This work has established the surface activity of some tropical gums (cashew, khaya, afzelia and prosopis gums). It has also established the HLB values of these polymers. The influence of surface activity and HLB values of the polymers on dissolution and permeation of drugs with different solubility has also been shown. These are the contributions of this work to knowledge.

6.3 RECOMMENDATIONS

The critical micelle concentration of these polymers should be taken into consideration while using them for formulation of dispersions. Therefore, the polymers should be used at concentrations below their CMC for formulating soluble drugs. For poorly soluble drugs whose absorption is dissolution-rate limited, incorporation of the polymers above the CMC will enhance dissolution and absorption.

Cashew gum and khaya gum were observed to have HLB values within the range of 15 and18. Hence, they could be investigated for use as solubilizing agents.

Dispersions containing 2 % w/v of afzelia gum or prosopis gum had viscosity of 144 - 171 and 306 – 375 mPa.s respectively. The two polymers could be used as gelling agents. They could also be investigated for use as swellable matrices for controlled release formulations based on their high hydration capacity, high swelling capacity, high swelling constants and high mean swelling times.

Cashew gum is hereby recommended for delivery of BCS class II drugs whose bioavailability challenge is low solubility while prosopis gum is recommended for delivery of BCS class III drugs whose bioavailability challenge is low permeability. Prosopis is also recommended for use at low concentrations for improving the delivery of BCS class IV drugs having low solubility and low permeability as bioavailability challenges.

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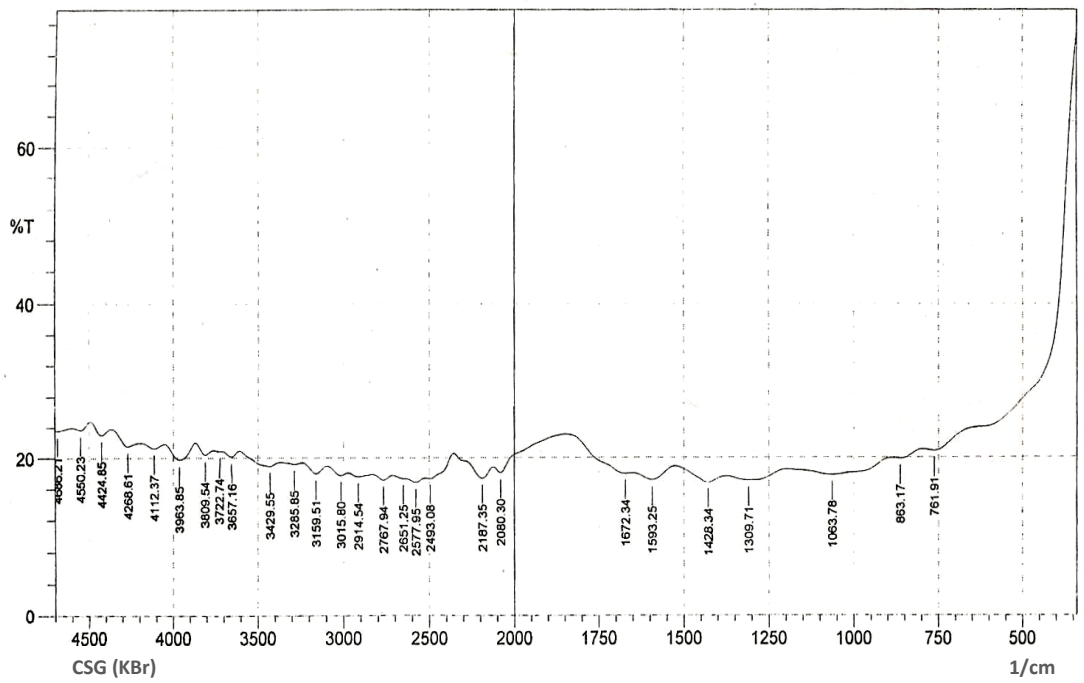
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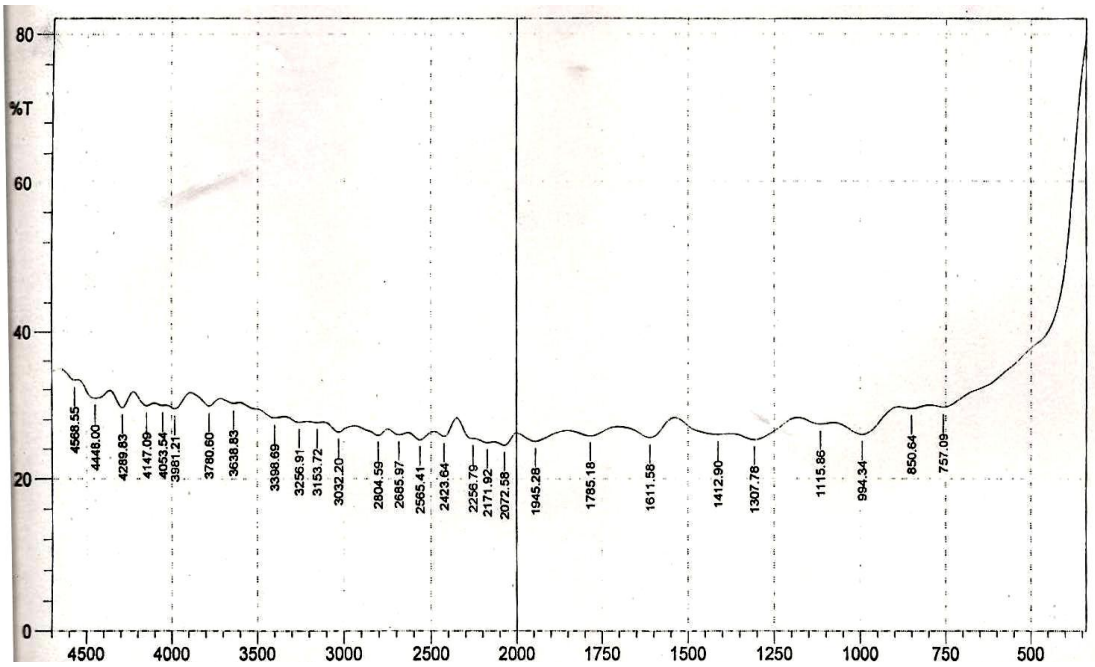
APPENDICES

A 1.1 FOURIER TRANSFORM INFRARED ANALYSIS OF CASHEW GUM



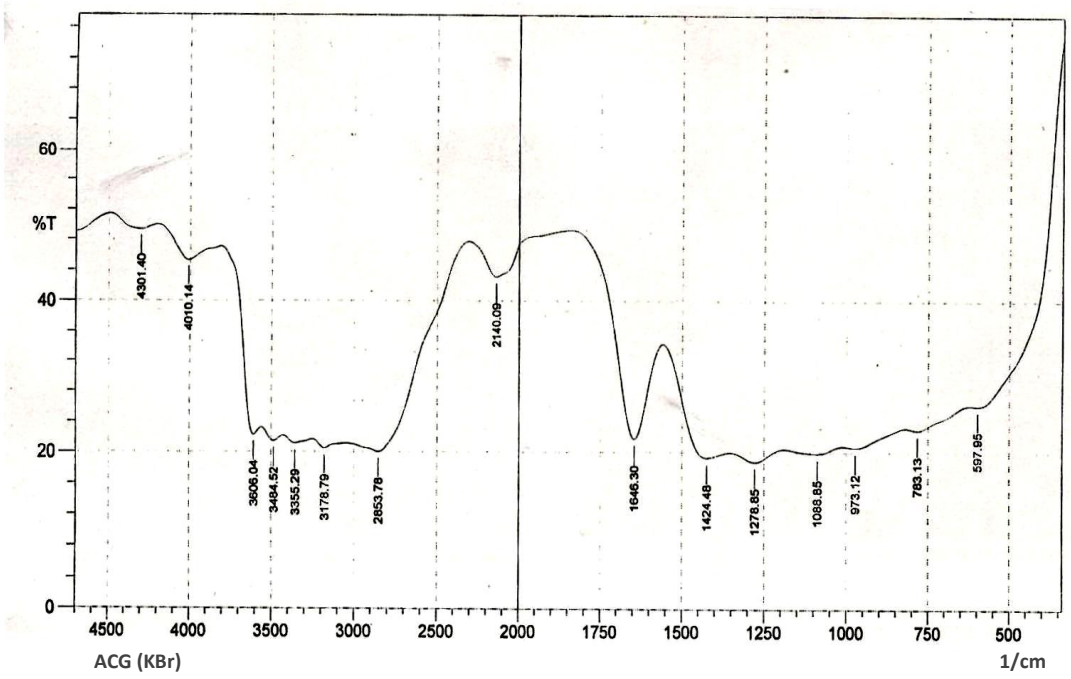
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	761.91	20.835	4.09	794.7	339.48	253.058	70.812
2	863.17	19.825	0.4	888.25	795.66	64.167	0.419
3	1063.78	17.739	1.373	1197.83	889.21	227.214	5.993
4	1309.71	17.057	0.87	1374.33	1198.8	132.923	2.381
5	1428.34	16.796	1.251	1525.74	1375.29	113.394	2.143
6	1593.25	17.085	1.332	1650.16	1526.71	92.553	1.936
7	1672.34	17.969	0.601	1846.9	1651.12	136.992	1.94
8	2080.3	18.116	1.319	2122.73	1847.87	188.819	1.878
9	2187.35	17.392	1.872	2354.2	2123.7	167.435	4.452
10	2493.08	17.361	0.592	2520.08	2355.16	121.477	2.297
11	2577.95	16.859	0.56	2639.67	2521.05	90.823	0.786
12	2651.25	17.381	0.065	2712.97	2640.64	54.688	0.097
13	2767.94	17.199	0.648	2831.6	2713.93	88.94	0.89
14	2914.54	17.617	0.385	2973.37	2832.56	105.581	0.677
15	3015.8	17.783	0.601	3094.89	2974.33	89.178	0.884
16	3159.51	17.989	1.19	3238.59	3095.85	104.211	1.911
17	3285.85	19.229	0.219	3364.93	3239.55	89.436	0.301
18	3429.55	18.978	0.895	3608.93	3365.9	172.042	3.238
19	3657.16	20.143	0.773	3711.17	3609.9	69.632	0.814
20	3722.74	20.87	0.038	3760.35	3712.13	32.762	0.024
21	3809.54	20.425	1.029	3868.37	3761.32	72.609	1.129
22	3963.85	19.783	2.12	4051.61	3869.33	124.672	4.469
23	4112.37	21.28	0.617	4194.35	4052.58	94.334	0.855
24	4268.61	21.537	1.238	4365.06	4195.31	110.649	1.921
25	4424.85	23.018	1.253	4490.43	4366.02	77.901	1.437
26	4550.23	23.661	0.677	4598.45	4491.4	66.302	0.682
27	4686.21	23.578	0.071	4700.68	4599.41	63.245	0.084

A 1.2 FOURIER TRANSFORM INFRARED ANALYSIS OF KHAYA GUM



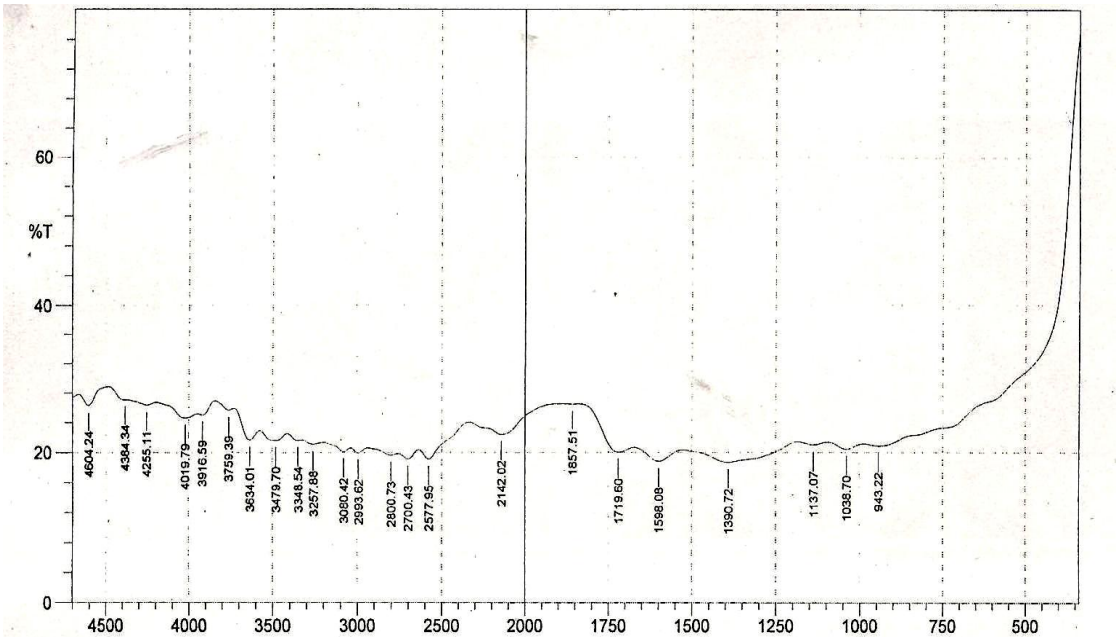
Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
757.09	29.582	4.56	796.63	339.48	195.199	52.482
850.64	29.382	0.331	887.28	797.59	47.464	0.222
994.34	25.896	2.529	1077.28	888.25	106.577	3.65
1115.86	27.314	0.44	1181.44	1078.24	57.69	0.391
1307.78	25.205	1.595	1376.26	1182.4	112.561	2.656
1412.9	25.926	0.587	1539.25	1377.22	93.28	1.394
1611.58	25.447	2.223	1704.17	1540.21	94.411	2.711
1785.18	25.75	0.956	1850.76	1705.13	84.539	1.093
1945.28	24.995	1.291	2002.18	1851.72	88.738	1.533
2072.58	24.468	1.02	2132.38	2003.14	77.799	1.176
2171.92	24.811	0.253	2253.9	2133.34	72.523	0.266
2256.79	25.403	0.056	2349.38	2254.86	54.571	0.458
2423.64	25.668	1.47	2480.54	2350.34	75.122	1.598
2565.41	25.212	1.043	2631.96	2481.5	88.58	1.223
2685.97	25.917	0.485	2748.65	2632.92	67.406	0.503
2804.59	25.823	0.976	2938.65	2749.62	109.198	1.397
3032.2	26.276	1.128	3118.03	2939.61	101.755	1.416
3153.72	27.59	0.087	3210.62	3119	51.167	0.064
3256.91	27.62	0.324	3341.78	3211.59	72.232	0.333
3398.69	28.199	0.564	3604.11	3342.75	140.305	0.91
3638.83	30.138	0.281	3715.99	3605.08	57.389	0.24
3780.6	29.803	1.304	3888.62	3716.95	88.247	1.414
3981.21	29.447	1.086	4034.25	3889.59	75.177	1.099
4053.54	29.898	0.095	4101.76	4035.22	34.801	0.053
4147.09	29.855	0.882	4224.25	4102.73	62.758	0.829
4289.83	29.609	2.172	4361.2	4225.21	69.715	2.022
4448	30.926	1.614	4549.26	4362.16	93.486	2.382
4568.55	33.296	0.319	4651.49	4550.23	47.52	0.226

A 1.3 FOURIER TRANSFORM INFRARED ANALYSIS OF ACACIA GUM



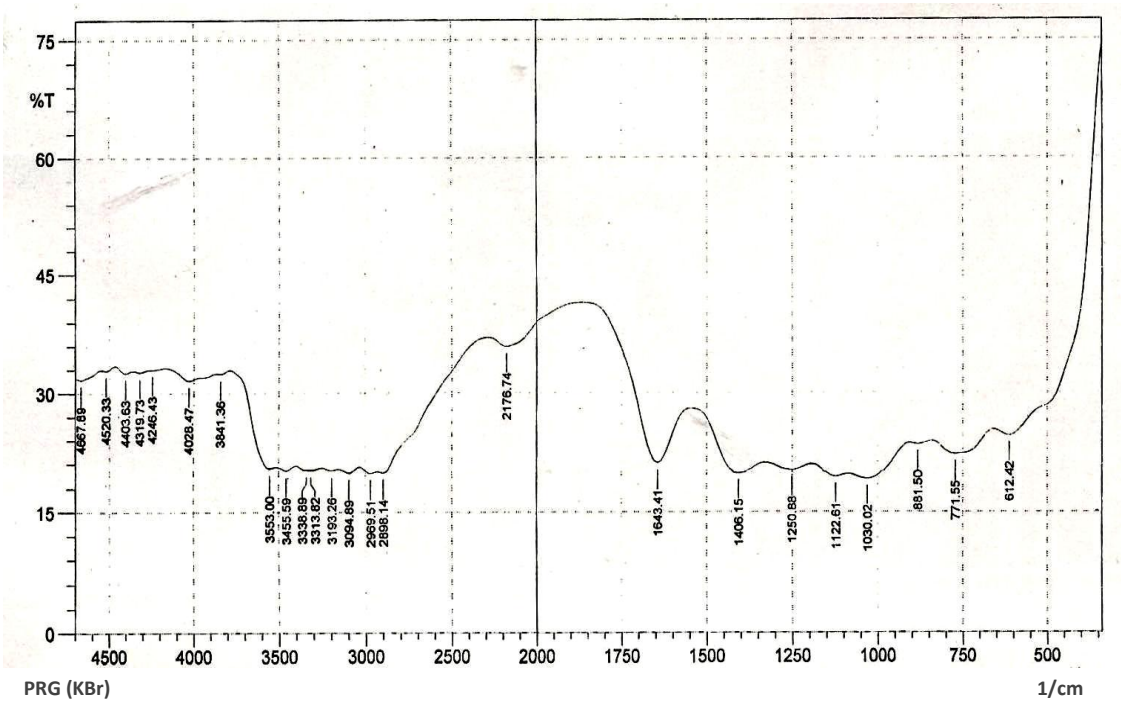
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	597.95	26.066	4.062	621.1	339.48	127.848	28.227
2	783.13	22.846	0.801	819.77	622.06	121.982	1.507
3	973.12	20.576	0.654	1011.7	820.74	127.216	1.289
4	1088.85	19.826	0.773	1189.15	1012.66	122.82	1.625
5	1278.85	18.729	1.407	1353.11	1190.12	115.821	2.446
6	1424.48	19.235	5.588	1559.5	1354.07	130.552	10.83
7	1646.3	21.678	17.148	1840.15	1560.46	128.203	21.06
8	2140.09	43.109	5.199	2308.87	1841.12	156.482	9.513
9	2853.78	19.98	8.168	3050.52	2309.83	401.411	34.14
10	3178.79	20.406	1.001	3250.16	3051.49	135.073	1.737
11	3355.29	21.046	0.839	3425.69	3251.13	116.92	1.57
12	3484.52	21.355	1.182	3558.78	3426.66	86.951	1.596
13	3606.04	22.188	5.368	3810.5	3559.75	118.835	5.17
14	4010.14	45.28	3.289	4195.31	3811.47	125.894	5.255
15	4301.4	49.34	1.151	4487.54	4196.28	87.753	1.803

A 1.4 FOURIER TRANSFORM INFRARED ANALYSIS OF AFZELIA GUM



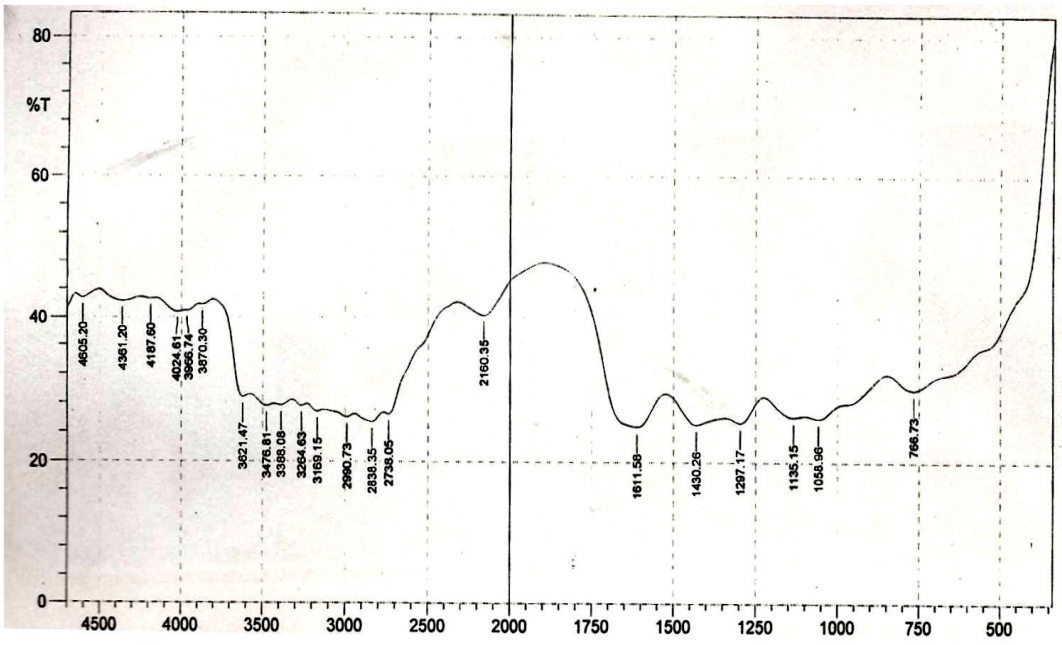
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	943.22	20.837	4.01	986.62	339.48	361.565	106.522
2	1038.7	20.421	0.788	1094.64	987.59	72.938	0.849
3	1137.07	20.954	0.416	1185.3	1095.6	60.499	0.39
4	1390.72	18.665	2.088	1526.71	1186.26	240.597	8.835
5	1598.08	18.789	1.684	1670.41	1527.67	100.813	2.493
6	1719.6	20.034	2.291	1838.22	1671.37	108.028	3.132
7	1857.51	26.472	0.024	1891.27	1839.19	30.048	0.01
8	2142.02	22.366	2.752	2332.98	1892.23	273.854	10.509
9	2577.95	19.072	2.028	2637.74	2333.94	203.719	4.929
10	2700.43	19.097	1.005	2761.19	2638.71	86.683	1.347
11	2800.73	19.641	0.361	2935.76	2762.16	121.007	0.48
12	2993.62	19.929	0.661	3037.99	2936.72	70.188	0.686
13	3080.42	20.085	0.696	3197.12	3038.95	108.176	0.842
14	3257.88	21.06	0.428	3323.46	3198.08	84.275	0.561
15	3348.54	21.569	0.307	3411.22	3324.42	57.301	0.326
16	3479.7	21.569	1.086	3573.25	3412.19	105.912	2.146
17	3634.01	21.661	2.411	3727.56	3574.21	97.536	3.479
18	3759.39	25.677	0.544	3841.36	3728.53	65.657	0.489
19	3916.59	25.039	0.708	3948.42	3842.33	62.527	0.65
20	4019.79	24.608	1.059	4196.28	3949.38	146.288	1.808
21	4255.11	26.335	0.564	4369.88	4197.24	99.011	0.709
22	4384.34	27.103	0.229	4482.72	4370.84	62.222	0.393
23	4604.24	26.3	1.868	4663.07	4483.68	100.016	1.846

A 1.5 FOURIER TRANSFORM INFRARED ANALYSIS OF PROSOPIS GUM



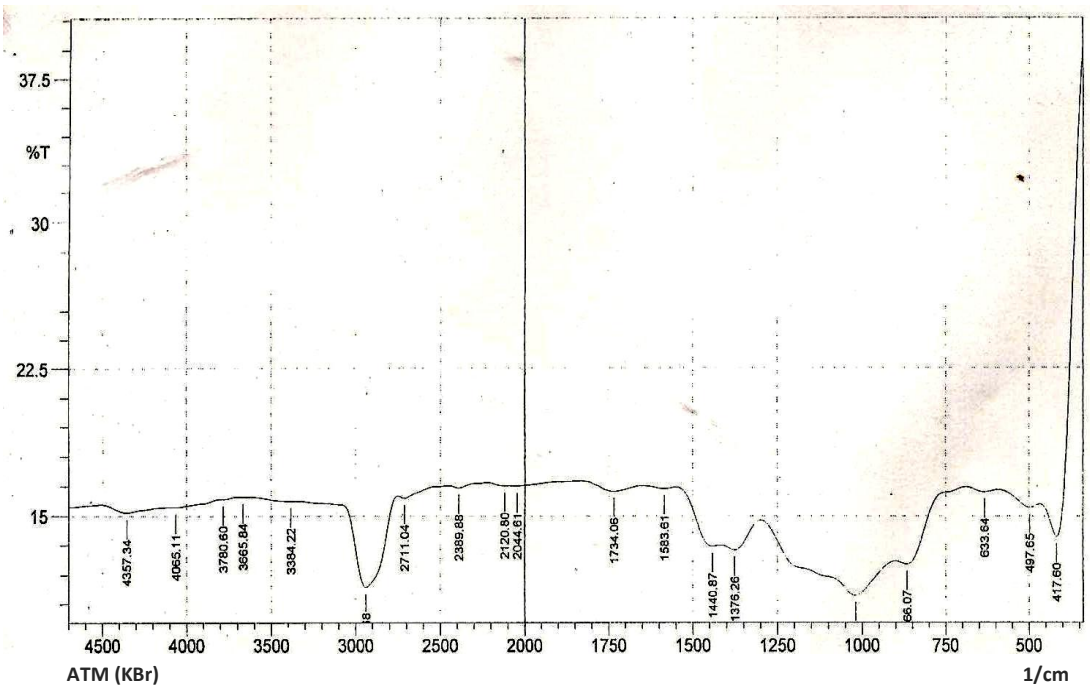
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	612.42	24.637	7.787	657.75	339.48	154.87	40.178
2	771.55	22.242	2.264	840.03	658.71	114.949	4.772
3	881.5	23.468	0.268	905.61	840.99	40.479	0.173
4	1030.02	19.188	1.756	1085.96	906.57	123.263	3.894
5	1122.61	19.472	0.685	1192.05	1086.92	73.527	0.829
6	1250.88	20.268	0.788	1328.03	1193.01	92.515	1.191
7	1406.15	19.919	3.668	1546	1329	139.79	6.969
8	1643.41	21.134	10.886	1867.16	1546.96	165.253	16.912
9	2176.74	35.865	2.296	2284.76	1868.12	175.377	5.831
10	2898.14	19.943	0.983	2930.93	2285.72	352.483	1.173
11	2969.51	19.844	0.43	3033.16	2931.9	70.531	0.499
12	3094.89	19.909	0.597	3154.68	3034.13	83.721	0.767
13	3193.26	20.259	0.182	3249.2	3155.65	64.688	0.213
14	3313.82	20.268	0.04	3324.42	3250.16	51.317	0.054
15	3338.89	20.266	0.103	3399.65	3325.39	51.184	0.13
16	3455.59	20.215	0.499	3515.38	3400.62	79.076	0.598
17	3553	20.468	1.818	3786.39	3516.35	158.637	3.791
18	3841.36	32.438	0.166	3863.55	3787.36	37.076	0.091
19	4028.47	31.596	1.271	4171.2	3864.51	150.679	2.362
20	4246.43	33.01	0.01	4250.29	4172.17	37.518	0.02
21	4319.73	32.67	0.236	4360.23	4251.25	52.731	0.155
22	4403.63	32.551	0.55	4463.43	4361.2	49.403	0.381
23	4520.33	32.915	0.229	4547.33	4464.39	39.824	0.139
24	4667.89	31.71	0.472	4700.68	4548.3	75.026	0.601

A 1.6 FOURIER TRANSFORM INFRARED ANALYSIS OF SODIUM CARBOXYMETHYLCELLULOSE



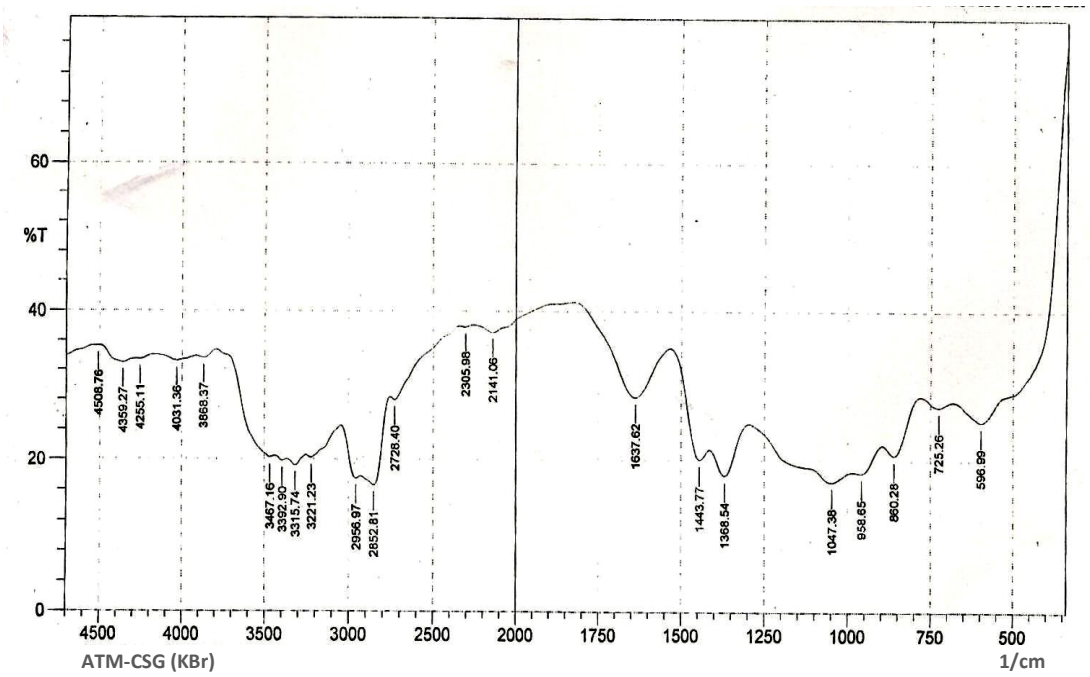
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	766.73	29.913	9.943	848.71	339.48	218.549	68.906
2	1058.96	25.955	1.304	1099.46	849.67	137.166	3.166
3	1135.15	26.153	0.889	1225.8	1100.43	71.224	1.098
4	1297.17	25.4	1.773	1341.54	1226.77	66.042	1.653
5	1430.26	25.155	2.524	1523.82	1342.5	104.698	3.549
6	1611.58	24.782	8.912	1894.16	1524.78	172.738	18.49
7	2160.35	40.313	3.99	2320.44	1895.12	156.011	8.144
8	2738.05	26.502	1.257	2767.94	2321.41	203.551	0.94
9	2838.35	25.431	1.201	2942.51	2768.91	101.716	1.905
10	2990.73	26.051	0.602	3128.64	2943.47	106.578	0.672
11	3169.15	26.863	0.525	3230.87	3129.61	57.277	0.444
12	3264.63	27.617	0.436	3319.6	3231.84	48.658	0.304
13	3388.08	27.695	0.368	3429.55	3320.57	60.368	0.341
14	3476.81	27.599	0.659	3577.11	3430.51	80.722	0.778
15	3621.47	28.81	2.898	3804.72	3578.07	102.701	2.707
16	3870.3	41.838	0.185	3888.62	3805.68	31.162	0.102
17	3966.74	40.95	0.115	3977.35	3889.59	33.668	0.083
18	4024.61	40.799	0.624	4153.84	3978.31	67.069	0.643
19	4187.6	42.663	0.112	4251.25	4154.81	35.603	0.056
20	4361.2	42.323	0.986	4503.93	4252.22	92.826	1.508
21	4605.2	42.776	0.693	4648.6	4504.9	52.286	0.464

A 1.7 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTEMETHER



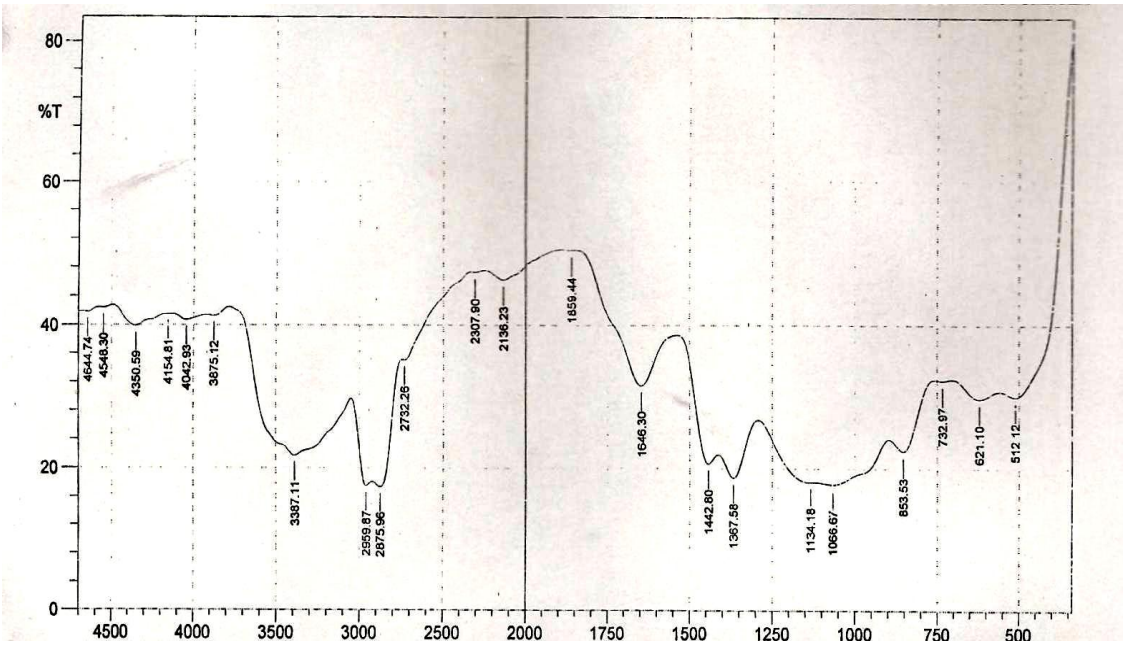
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	417.6	13.943	10.776	466.79	339.48	90.697	13.655
2	497.65	15.447	0.339	591.2	467.75	98.835	0.509
3	633.64	16.232	0.171	688.61	592.17	75.919	0.226
4	866.07	12.546	0.765	899.82	689.57	175.364	1.34
5	1019.41	10.941	2.384	1298.14	900.79	362.106	19.106
6	1376.26	13.265	0.683	1416.76	1299.1	101.234	1.279
7	1440.87	13.444	0.589	1547.93	1417.73	108.495	1.162
8	1583.61	16.393	0.086	1647.26	1548.89	77.121	0.109
9	1734.06	16.255	0.374	1835.33	1648.23	146.592	0.863
10	2044.61	16.51	0.058	2088.01	1836.29	196.129	0.137
11	2120.8	16.519	0.045	2220.14	2088.98	102.361	0.082
12	2389.88	16.427	0.14	2452.57	2221.11	180.731	0.251
13	2711.04	15.91	0.182	2750.58	2453.54	234.28	0.322
14	2937.68	11.376	4.564	3340.82	2751.55	497.213	26.47
15	3384.22	15.748	0.041	3622.44	3341.78	224.66	0.254
16	3665.84	15.959	0.009	3697.66	3623.4	59.177	0.009
17	3780.6	15.847	0.025	3799.89	3698.63	80.881	0.039
18	4065.11	15.442	0.049	4096.94	3800.86	238.92	0.423
19	4357.34	15.16	0.372	4511.65	4097.91	336.851	2.023

A 1.8 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTEMETHER + CASHEW GUM



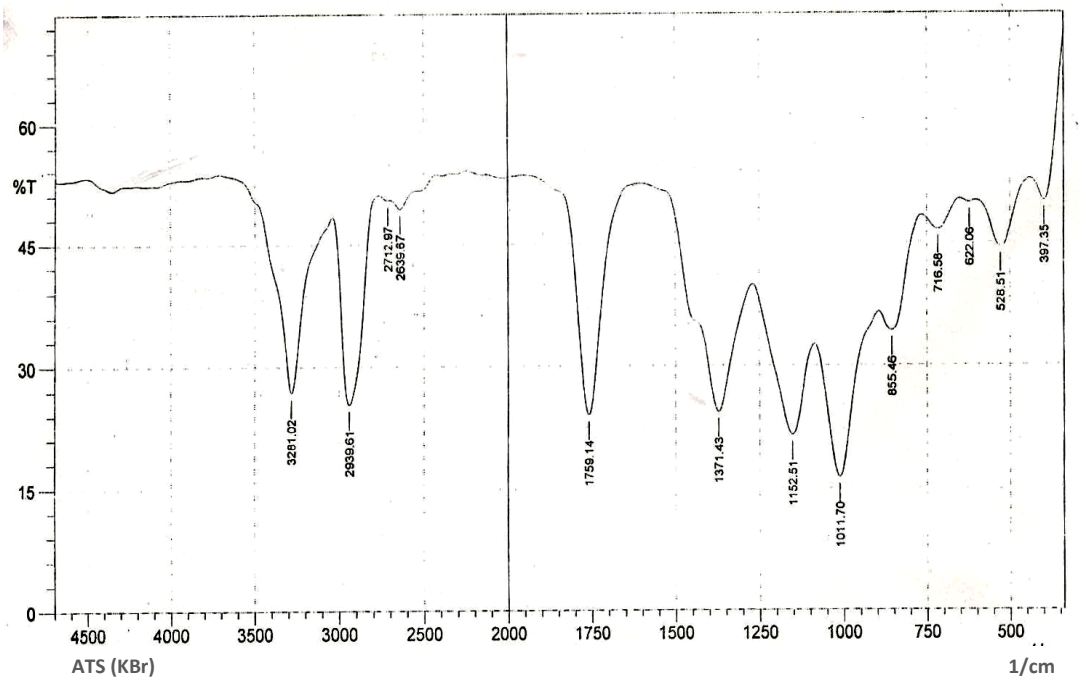
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	596.99	25.087	14.738	681.86	339.48	169.336	54.265
2	725.26	27.082	1.045	780.23	682.82	54.411	0.811
3	860.28	20.671	3.315	895	781.2	71.464	3.22
4	958.65	18.283	1.207	984.69	895.96	62.917	1.245
5	1047.38	17.154	2.554	1297.17	985.66	218.961	10.292
6	1368.54	17.952	4.768	1413.87	1298.14	79.033	5.265
7	1443.77	20.04	4.628	1533.46	1414.83	70.01	3.773
8	1637.62	28.298	8.832	1823.76	1534.42	135.893	14.013
9	2141.06	37.097	1.869	2254.86	1824.72	176.541	3.932
10	2305.98	37.868	0.192	2338.77	2255.83	34.867	0.087
11	2728.4	27.909	1.011	2755.41	2339.73	198.27	0.725
12	2852.81	16.622	5.778	2928.04	2756.37	121.115	9.976
13	2956.97	17.506	1.77	3045.7	2931.9	79.548	2.312
14	3221.23	20.2	0.882	3252.09	3046.67	135.725	2.266
15	3315.74	19.181	1.043	3366.86	3253.06	80.11	1.176
16	3392.9	19.79	0.36	3437.26	3367.82	48.482	0.246
17	3467.16	20.222	1.344	3792.18	3438.23	205.286	5.638
18	3868.37	33.521	0.651	3914.66	3793.14	57.036	0.533
19	4031.36	33.14	0.783	4171.2	3915.63	121.204	1.237
20	4255.11	33.338	0.187	4280.18	4172.17	51.134	0.125
21	4359.27	32.893	1.12	4503.93	4281.15	105.473	1.881
22	4508.76	35.195	0.006	4528.05	4504.9	10.494	0.001

A 1.9 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTEMETHER + PROSOPIS GUM



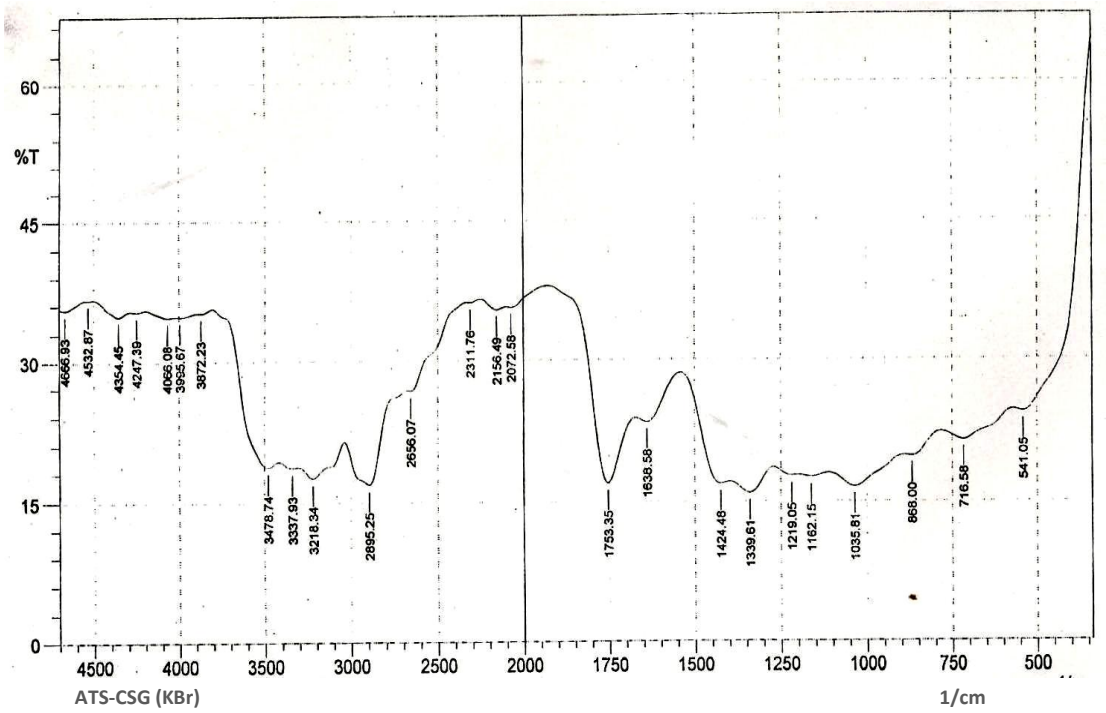
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	512.12	29.929	11.605	560.34	339.48	91.936	24.982
2	621.1	29.653	1.779	702.11	561.3	72.358	1.801
3	732.97	32.217	0.166	758.05	703.08	26.933	0.065
4	853.53	22.34	4.292	896.93	759.01	80.6	4.368
5	1066.67	17.746	1.827	1122.61	897.89	160.431	7.471
6	1134.18	18.1	0.546	1292.35	1123.57	114.364	3.396
7	1367.58	18.687	4.977	1411.94	1293.31	78.541	5.42
8	1442.8	20.646	5.243	1537.32	1412.9	69.773	3.988
9	1646.3	31.481	11.258	1845.94	1538.28	125.475	16.167
10	1859.44	50.297	0.027	1890.3	1846.9	12.944	0.006
11	2136.23	46.285	2.189	2251	1891.27	115.429	3.868
12	2307.9	47.267	0.137	2332.98	2251.97	26.278	0.054
13	2732.26	34.986	0.473	2746.73	2333.94	155.864	0.259
14	2875.96	17.328	5.294	2923.22	2747.69	112.632	8.459
15	2959.87	17.503	3.849	3049.56	2924.18	84.138	4.635
16	3387.11	21.704	13.845	3784.46	3050.52	415.312	85.527
17	3875.12	41.343	0.485	3918.52	3785.43	50.499	0.368
18	4042.93	40.746	0.791	4123.95	3919.48	78.832	0.802
19	4154.81	41.541	0.012	4171.2	4124.91	17.658	0.003
20	4350.59	39.876	2.39	4489.47	4172.17	122.931	3.976
21	4548.3	42.466	0.141	4573.37	4490.43	30.745	0.067
22	4644.74	41.842	0.268	4677.53	4574.34	38.785	0.144

A 1.10 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTESUNATE SODIUM



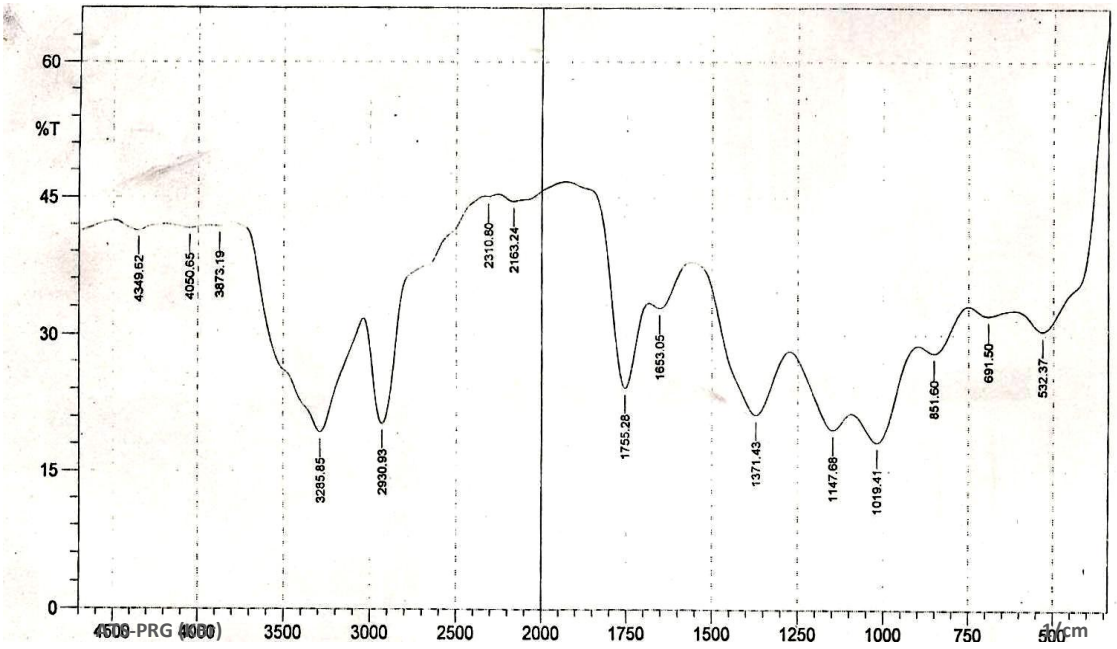
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	761.91	20.835	4.09	794.7	339.48	253.058	70.812
2	863.17	19.825	0.4	888.25	795.66	64.167	0.419
3	1063.78	17.739	1.373	1197.83	889.21	227.214	5.993
4	1309.71	17.057	0.87	1374.33	1198.8	132.923	2.381
5	1428.34	16.796	1.251	1525.74	1375.29	113.394	2.143
6	1593.25	17.085	1.332	1650.16	1526.71	92.553	1.936
7	1672.34	17.969	0.601	1846.9	1651.12	136.992	1.94
8	2080.3	18.116	1.319	2122.73	1847.87	188.819	1.878
9	2187.35	17.392	1.872	2354.2	2123.7	167.435	4.452
10	2493.08	17.361	0.592	2520.08	2355.16	121.477	2.297
11	2577.95	16.859	0.56	2639.67	2521.05	90.823	0.786
12	2651.25	17.381	0.065	2712.97	2640.64	54.688	0.097
13	2767.94	17.199	0.648	2831.6	2713.93	88.94	0.89
14	2914.54	17.617	0.385	2973.37	2832.56	105.581	0.677
15	3015.8	17.783	0.601	3094.89	2974.33	89.178	0.884
16	3159.51	17.989	1.19	3238.59	3095.85	104.211	1.911
17	3285.85	19.229	0.219	3364.93	3239.55	89.436	0.301
18	3429.55	18.978	0.895	3608.93	3365.9	172.042	3.238
19	3657.16	20.143	0.773	3711.17	3609.9	69.632	0.814
20	3722.74	20.87	0.038	3760.35	3712.13	32.762	0.024
21	3809.54	20.425	1.029	3868.37	3761.32	72.609	1.129
22	3963.85	19.783	2.12	4051.61	3869.33	124.672	4.469
23	4112.37	21.28	0.617	4194.35	4052.58	94.334	0.855
24	4268.61	21.537	1.238	4365.06	4195.31	110.649	1.921
25	4424.85	23.018	1.253	4490.43	4366.02	77.901	1.437
26	4550.23	23.661	0.677	4598.45	4491.4	66.302	0.682
27	4686.21	23.578	0.071	4700.68	4599.41	63.245	0.084

A 1.11 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTESUNATE SODIUM + CASHEW GUM



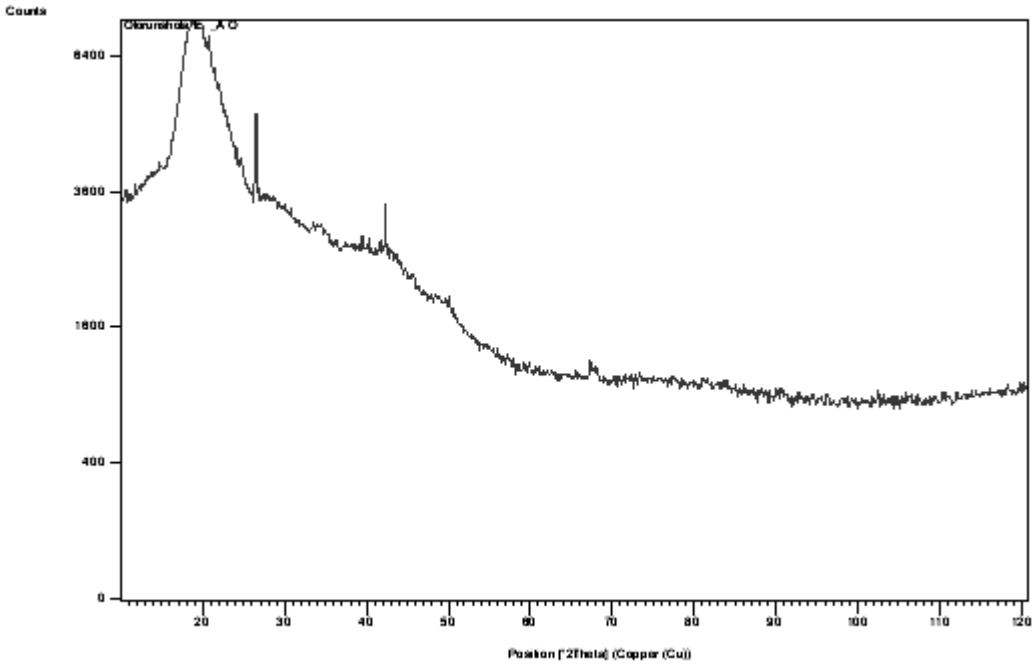
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	541.05	24.386	5.112	569.02	339.48	113.999	22.621
2	716.58	21.424	1.58	781.2	569.98	136.747	3.644
3	868	19.718	0.541	888.25	782.16	72.411	0.637
4	1035.81	16.538	2.023	1111.03	889.21	166.066	5.271
5	1162.15	17.52	0.283	1199.76	1112	66.061	0.319
6	1219.05	17.671	0.247	1271.13	1200.73	52.516	0.267
7	1339.61	15.878	1.857	1397.47	1272.1	96.97	2.939
8	1424.48	16.853	2.313	1540.21	1398.44	95.665	3.349
9	1638.58	23.388	1.611	1671.37	1541.18	77.586	1.717
10	1753.35	16.953	11.304	1928.88	1672.34	146.094	15.015
11	2072.58	35.632	0.431	2101.51	1929.84	75.114	0.59
12	2156.49	35.39	0.592	2251	2102.48	66.271	0.528
13	2311.76	36.136	0.115	2332.98	2251.97	35.687	0.065
14	2656.07	26.697	0.701	2679.21	2333.94	172.855	0.611
15	2895.25	16.864	6.686	3036.06	2680.18	240.242	20.027
16	3218.34	17.586	2.026	3307.06	3037.02	196.595	8.066
17	3337.93	18.633	0.247	3415.08	3308.03	77.553	0.362
18	3478.74	18.717	3.223	3805.68	3416.05	233.103	11.337
19	3872.23	35.202	0.129	3893.44	3806.64	39.183	0.093
20	3995.67	34.808	0.106	4023.64	3894.41	58.989	0.109
21	4066.08	34.74	0.273	4194.35	4024.61	77.298	0.327
22	4247.39	35.369	0.127	4284.04	4195.31	39.971	0.072
23	4354.45	34.882	0.955	4502.97	4285.01	97.832	1.279
24	4532.87	36.669	0.005	4541.55	4503.93	16.386	0.002
25	4666.93	35.589	0.311	4700.68	4542.51	70.131	0.32

A 1.12 FOURIER TRANSFORM INFRARED ANALYSIS OF ARTESUNATE SODIUM + PROSOPIS GUM



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	532.37	30.466	11.51	614.35	339.48	121.487	28.064
2	691.5	32.107	0.89	750.33	615.31	65.85	0.781
3	851.6	27.986	2.183	896.93	751.3	76.469	2.305
4	1019.41	18.18	6.011	1093.67	897.89	128.631	10.318
5	1147.68	19.552	3.841	1273.06	1094.64	114.93	6.086
6	1371.43	21.201	10.266	1560.46	1274.03	160.245	21.278
7	1653.05	32.907	1.673	1683.91	1561.43	55.985	1.174
8	1755.28	24.155	13.135	1927.92	1684.88	107.043	11.623
9	2163.24	44.563	1.12	2252.93	1928.88	111.707	2.355
10	2310.8	45.084	0.072	2331.05	2253.9	26.633	0.032
11	2930.93	20.204	13.52	3035.09	2332.02	322.407	27.124
12	3285.85	19.255	15.952	3797.96	3036.06	422.966	91.125
13	3873.19	41.822	0.27	3939.74	3798.93	53.112	0.213
14	4050.65	41.585	0.374	4191.46	3940.7	94.971	0.411
15	4349.62	41.306	0.941	4494.29	4192.42	114.328	1.336

A 2.1 X-RAY DIFFRACTION PATTERN OF CASHEW GUM



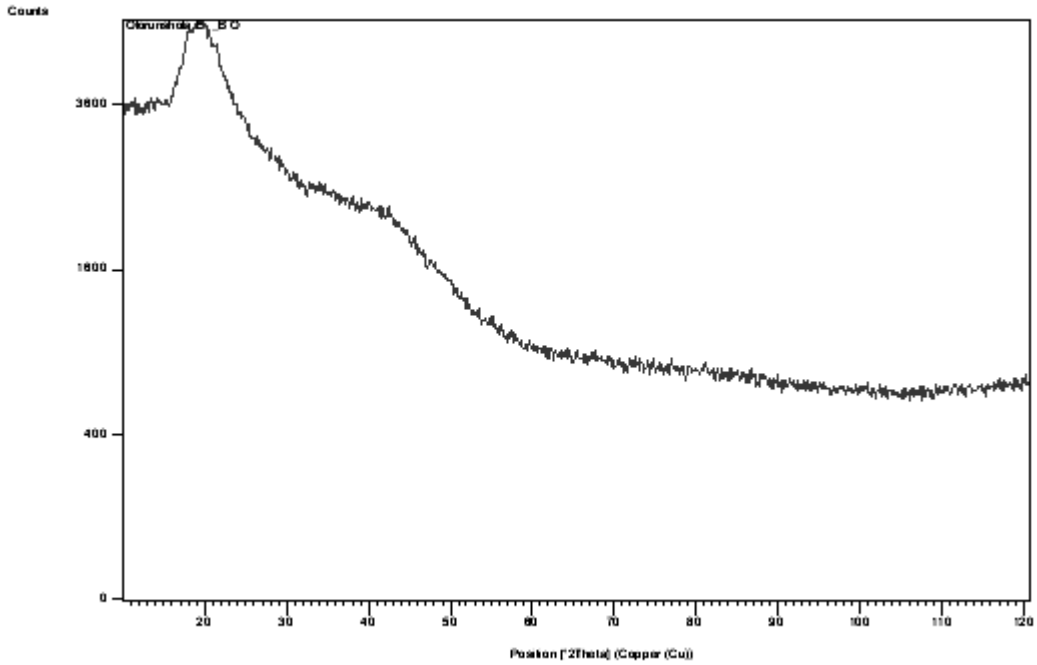
Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
26.4984	1623.53	0.2480	3.36379	100.00
42.3423	571.78	0.3024	2.13288	35.22

Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-058-0982	29	(5-Chloro-2-(2-(4-..	0.000	4.110	C22 H26 Cl F N2 O5..
	00-049-2096	19	Oxazepam-polyethyl..	0.000	0.511	C15 H11 Cl N2 O2 ·..
	00-037-1656	16	Calcium pantoate	0.000	13.953	C12 H20 Ca O8

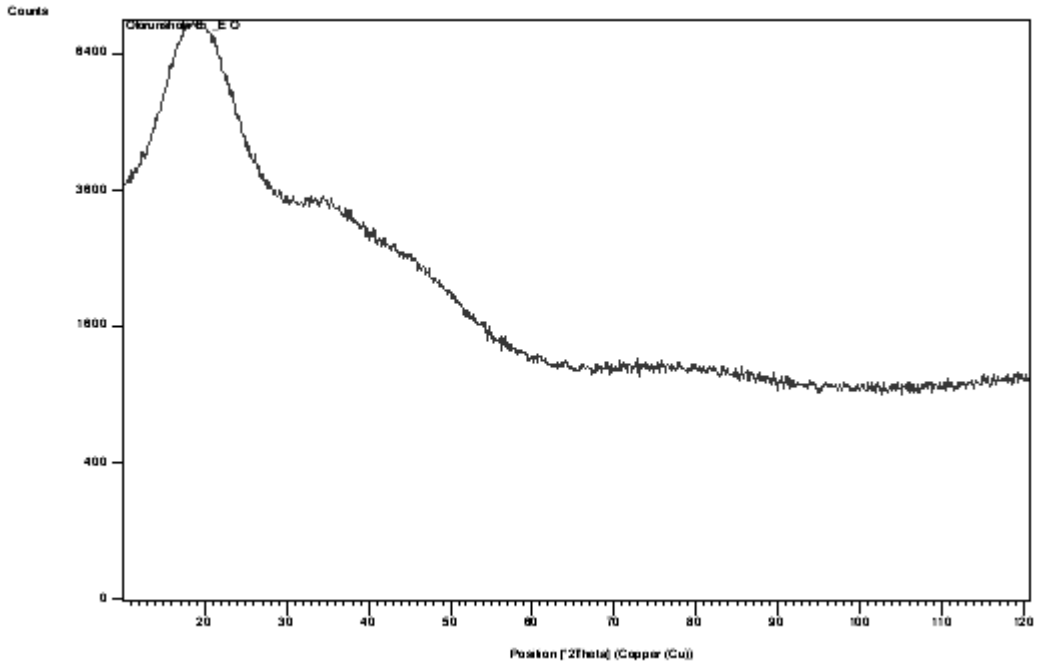
A 2.2 X-RAY DIFFRACTION PATTERN OF KHAYA GUM



Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-049-2297	82	7-chloro-1,3-dihyd..	0.000	3.975	C15 H11 Cl N2 O2
	00-043-1833	81	Oxyphenbutazone cy..	0.000	3.051	C76 H80 N8 O12 · C..
	00-058-0982	81	(5-Chloro-2-(2-(4-..	0.000	4.195	C22 H26 Cl F N2 O5..
	00-013-0954	65	Gramine	0.000	1.513	C11 H14 N2
	00-048-2077	81	1,3-Disteroyl-2-ol..	0.000	0.934	C112 H212 O12

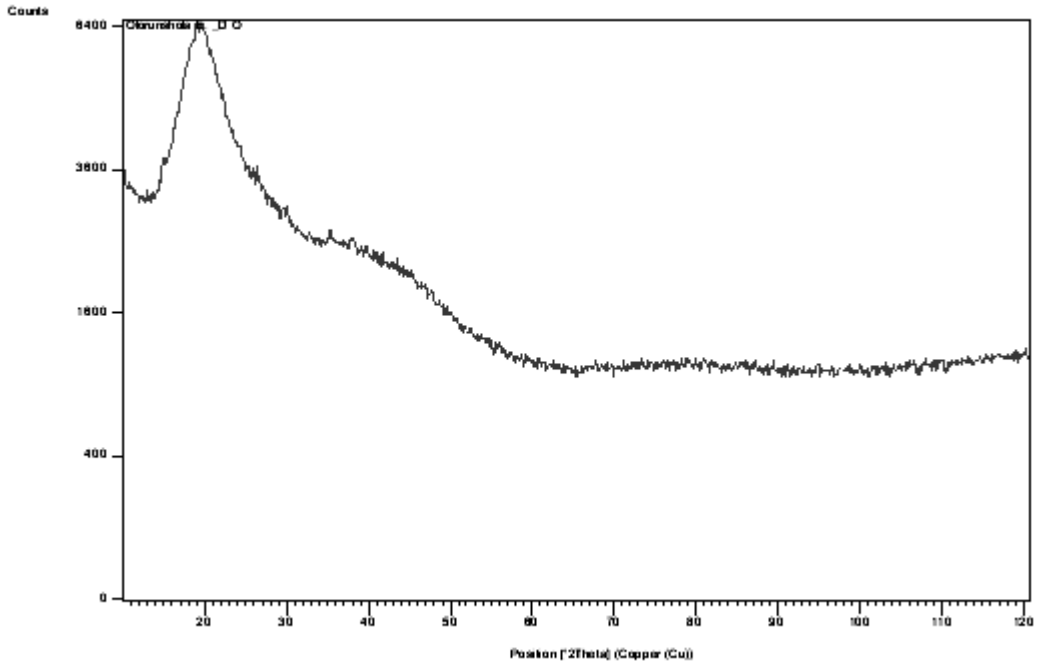
A 2.3 X-RAY DIFFRACTION PATTERN OF ACACIA GUM



Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-028-1941	94	Trimethyl amine si..	0.000	1.147	C3 H10 Cl3 N Si

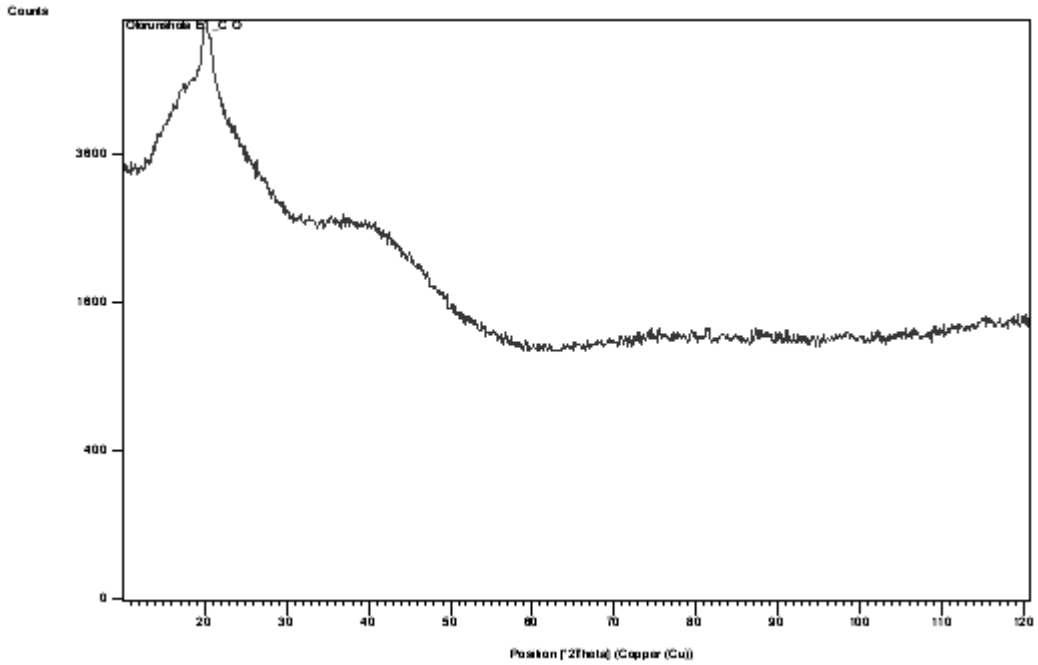
A 2.4 X-RAY DIFFRACTION PATTERN OF AFZELIA GUM



Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-058-0982	90	(5-Chloro-2-(2-(4-..	0.000	3.942	C22 H26 Cl F N2 O5..

A 2.5 X-RAY DIFFRACTION PATTERN OF PROSOPIS GUM



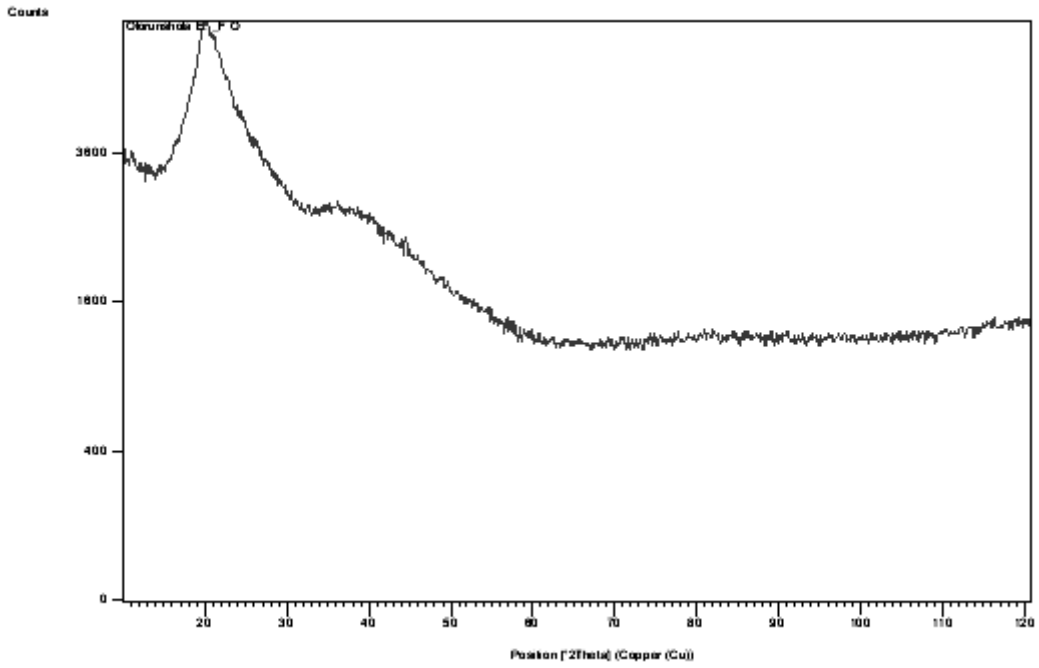
Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
20.0864	2708.90	0.7056	4.41710	100.00

Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-058-1385	65	Calcium undecanoat..	0.000	5.592	C22 H42 Ca O4 · H2 O

A 2.6 X-RAY DIFFRACTION PATTERN OF SODIUM CARBOXYMETHYLCELLULOSE



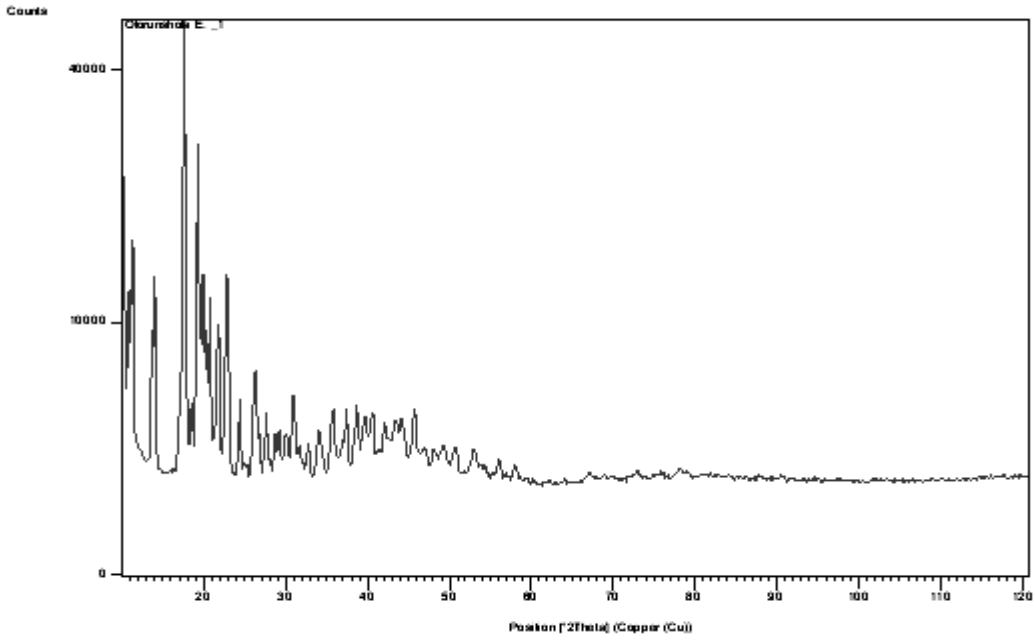
Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
19.8925	2630.42	0.8064	4.45971	100.00

Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-043-1832	70	Oxyphenbutazone be..	0.000	4.057	C38 H40 N4 O6 · C6..

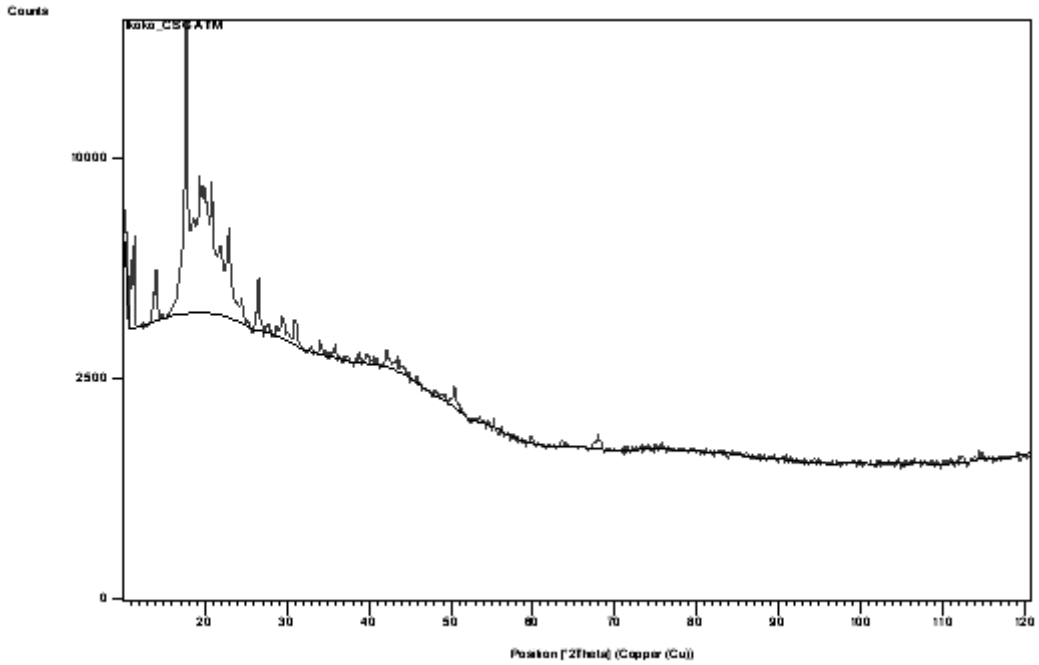
A 2.7 X-RAY DIFFRACTION PATTERN OF ARTEMETHER



Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
10.1810	13591.80	0.2480	8.68869	28.68
10.8051	9978.11	0.1653	8.18819	21.05
11.3102	15684.20	0.2480	7.82362	33.09
13.6628	5848.59	0.2480	6.48129	12.34
14.0589	12560.84	0.2480	6.29957	26.50
17.6390	47392.41	0.2480	5.02822	100.00
18.5163	2700.69	0.1653	4.79192	5.70
19.2677	26795.52	0.3306	4.60671	56.54
19.9064	12242.66	0.2480	4.46032	25.83
20.7814	10205.92	0.1653	4.27445	21.53
21.7903	7606.31	0.3306	4.07876	16.05
22.8003	12538.46	0.4133	3.90032	26.46
24.4227	3054.75	0.2480	3.64477	6.45
26.2825	4043.17	0.4133	3.39093	8.53
26.8306	1170.83	0.1653	3.32289	2.47
27.6493	2083.62	0.2480	3.22634	4.40
28.6799	1184.80	0.1653	3.11270	2.50
29.2186	1335.47	0.2480	3.05653	2.82
30.1735	1078.97	0.4133	2.96194	2.28
30.8979	3161.19	0.3306	2.89413	6.67
31.7442	763.55	0.2480	2.81888	1.61
32.8036	1089.30	0.3306	2.73022	2.30
34.0473	1655.08	0.4133	2.63329	3.49
35.7819	2439.27	0.4133	2.50951	5.15
37.4419	2353.45	0.1653	2.40198	4.97
38.7038	2401.85	0.3306	2.32652	5.07
39.7448	1782.88	0.4959	2.26795	3.76
40.6164	1763.47	0.3306	2.22127	3.72
42.0649	1137.64	0.2480	2.14807	2.40
43.3081	1409.43	0.4133	2.08925	2.97
44.2565	1497.14	0.4133	2.04666	3.16
45.7434	2093.73	0.3306	1.98353	4.42
48.1050	428.27	0.3306	1.89153	0.90
49.3541	729.07	0.2480	1.84654	1.54
50.8196	810.64	0.5786	1.79668	1.71
53.0308	714.40	0.4959	1.72686	1.51
56.0813	526.39	0.3306	1.63995	1.11
57.9990	381.43	0.4133	1.59021	0.80
67.2226	219.48	0.6612	1.39270	0.46
78.1713	243.79	0.6048	1.22176	0.51

A 2.8 X-RAY DIFFRACTION PATTERN OF ARTEMETHER + CASHEW GUM



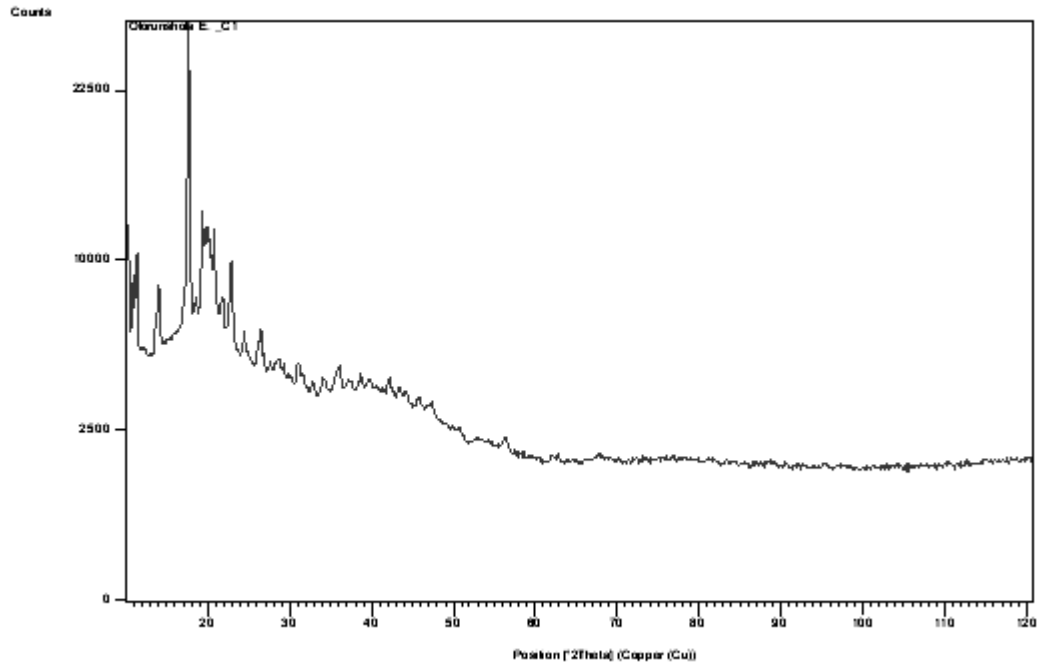
Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
10.2372	1975.51	0.3306	8.64104	14.86
10.8892	2021.92	0.1653	8.12514	15.21
11.3597	2946.20	0.1653	7.78960	22.16
14.1186	1678.02	0.2480	6.27306	12.62
17.7173	13292.97	0.2480	5.00617	100.00
19.3653	5040.94	0.2480	4.58370	37.92
20.8524	4844.52	0.2480	4.26005	36.44
21.8990	2229.53	0.3306	4.05877	16.77
22.9052	3042.81	0.2480	3.88269	22.89
26.5582	1634.25	0.2480	3.35636	12.29
27.7216	265.02	0.4959	3.21809	1.99
29.5091	525.35	0.3306	3.02710	3.95
31.0157	736.20	0.3306	2.88341	5.54
35.8111	257.10	0.4959	2.50753	1.93
42.2595	392.81	0.4959	2.13863	2.96
50.4942	467.12	0.2480	1.80749	3.51
68.1190	165.03	0.8064	1.37540	1.24

Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-051-1950	62	â-artemether	0.000	4.317	C16 H26 O5

A 2.9 X-RAY DIFFRACTIO NPATTERN OF ARTEMETHER + PROSOPIS GUM



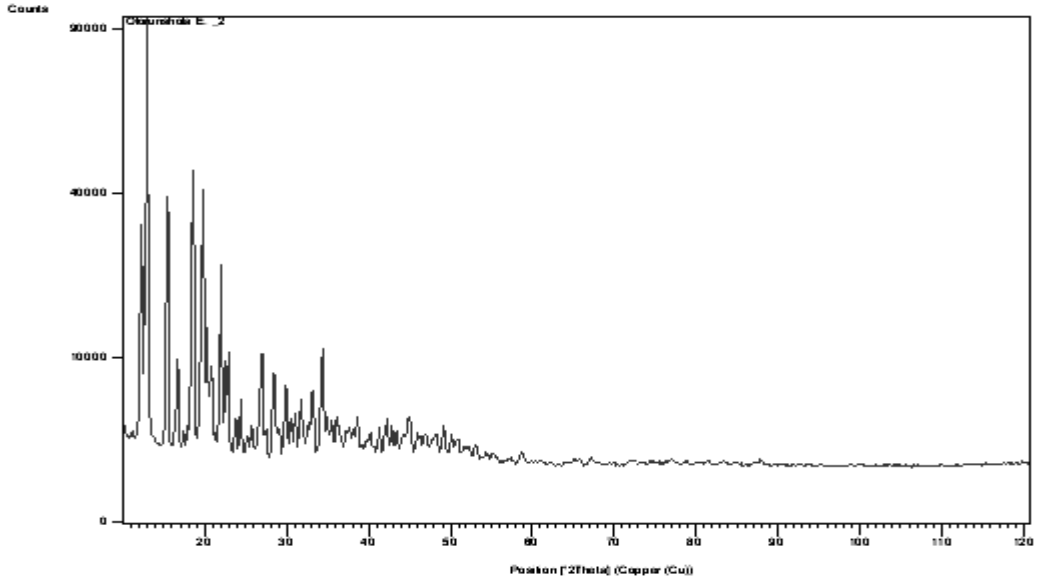
Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
10.2276	3759.10	0.3306	8.64921	16.12
10.8619	3719.97	0.1653	8.14550	15.95
11.3320	5271.79	0.2480	7.80862	22.60
14.0682	3244.55	0.2480	6.29543	13.91
17.6753	23326.45	0.3306	5.01797	100.00
18.5475	2233.52	0.2480	4.78391	9.58
19.3339	7128.26	0.2480	4.59108	30.56
19.9038	6321.71	0.2480	4.46090	27.10
20.8011	6225.20	0.2480	4.27045	26.69
21.8339	2409.37	0.3306	4.07072	10.33
22.8409	4605.37	0.3306	3.89348	19.74
24.4517	1106.11	0.2480	3.64051	4.74
26.4874	1543.06	0.2480	3.36517	6.62
28.7420	658.59	0.5786	3.10612	2.82
30.9769	791.76	0.4133	2.88693	3.39
32.8388	407.46	0.3306	2.72738	1.75
34.0256	614.77	0.4133	2.63491	2.64
36.1306	1043.86	0.2480	2.48609	4.47
37.3008	356.47	0.4959	2.41074	1.53
38.7680	536.68	0.3306	2.32282	2.30
42.1102	514.81	0.2480	2.14587	2.21
45.7528	357.19	0.4959	1.98315	1.53
47.4152	492.34	0.3306	1.91742	2.11
56.3753	280.72	0.7056	1.63074	1.20

Pattern List

Visible	Ref.Code	Score	Compound Name	Displ.[°2Th]	Scale Fac.	Chem. Formula
	00-051-1950	63	â-artemether	0.000	3.538	C16 H26 O5
	00-029-0391	38	Phurcalite	0.000	0.116	Ca2 (U O2)3 (P ..
	00-018-1865	39	3`-4"-2"`-Quinquep..	0.000	0.200	C30 H22
	00-051-1740	40	â-N H4 P F6	0.000	0.194	N H4 P F6
	00-048-2304	30	Oxolinic acid	0.000	0.127	C13 H11 N O5

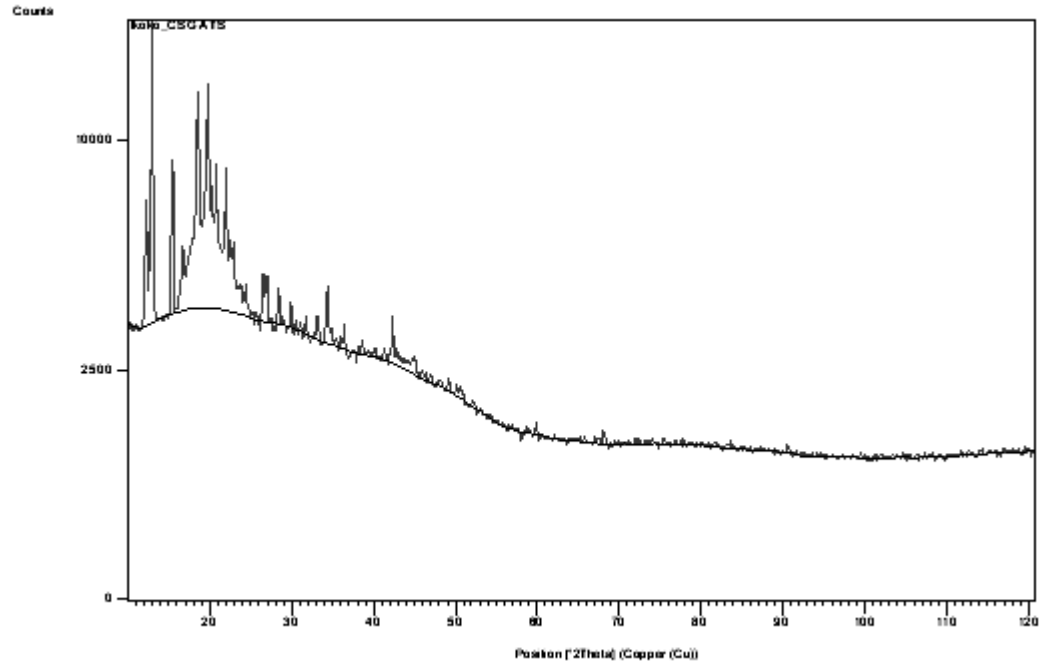
A 2.10 X-RAY DIFFRACTION PATTERN OF ARTESUNATE SODIUM



Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
12.2245	27496.85	0.1653	7.24045	29.80
12.9902	92266.16	0.3306	6.81533	100.00
15.4414	37449.56	0.2480	5.73852	40.59
16.7164	8144.28	0.2480	5.30360	8.83
17.4119	813.25	0.1653	5.09328	0.88
18.5592	44345.98	0.2480	4.78093	48.06
19.7877	38196.45	0.3306	4.48680	41.40
20.8400	6528.94	0.2480	4.26256	7.08
21.9698	22167.24	0.2480	4.04584	24.03
22.9198	7984.35	0.2480	3.88025	8.65
23.7684	1260.76	0.2480	3.74360	1.37
24.4062	3155.42	0.2480	3.64720	3.42
25.2306	194.96	0.2480	3.52987	0.21
25.7595	878.17	0.2480	3.45858	0.95
26.9618	8129.86	0.2480	3.30702	8.81
27.5183	347.66	0.1653	3.24139	0.38
28.4476	5409.64	0.3306	3.13759	5.86
29.9065	3984.45	0.2480	2.98777	4.32
30.5050	1034.23	0.1653	2.93051	1.12
31.0428	1459.69	0.1653	2.88095	1.58
31.7602	2910.44	0.3306	2.81750	3.15
33.1866	4075.20	0.2480	2.69958	4.42
34.3865	8468.32	0.2480	2.60808	9.18
34.9609	1406.93	0.1653	2.56653	1.52
35.5327	1192.82	0.2480	2.52653	1.29
36.1077	1294.94	0.3306	2.48761	1.40
37.2608	516.33	0.2480	2.41323	0.56
38.6453	1767.03	0.2480	2.32991	1.92
40.2460	893.84	0.2480	2.24086	0.97
41.3123	1142.37	0.2480	2.18545	1.24
42.2604	1906.88	0.3306	2.13859	2.07
42.8608	1369.84	0.1653	2.11001	1.48
43.4489	972.05	0.1653	2.08281	1.05
45.0438	2136.69	0.4959	2.01270	2.32
45.9290	903.13	0.2480	1.97595	0.98
46.9422	914.71	0.3306	1.93564	0.99
48.3022	933.51	0.3306	1.88427	1.01
49.1827	1456.56	0.3306	1.85257	1.58
50.1354	850.58	0.2480	1.81958	0.92
50.9207	594.12	0.2480	1.79335	0.64
52.2480	265.87	0.2480	1.75088	0.29
53.1413	459.94	0.4133	1.72353	0.50
54.3283	192.33	0.4959	1.68865	0.21
55.2303	268.32	0.3306	1.66319	0.29
58.6813	370.64	0.3306	1.57334	0.40
67.2019	296.24	0.3306	1.39308	0.32
78.8018	145.38	0.6048	1.21356	0.16

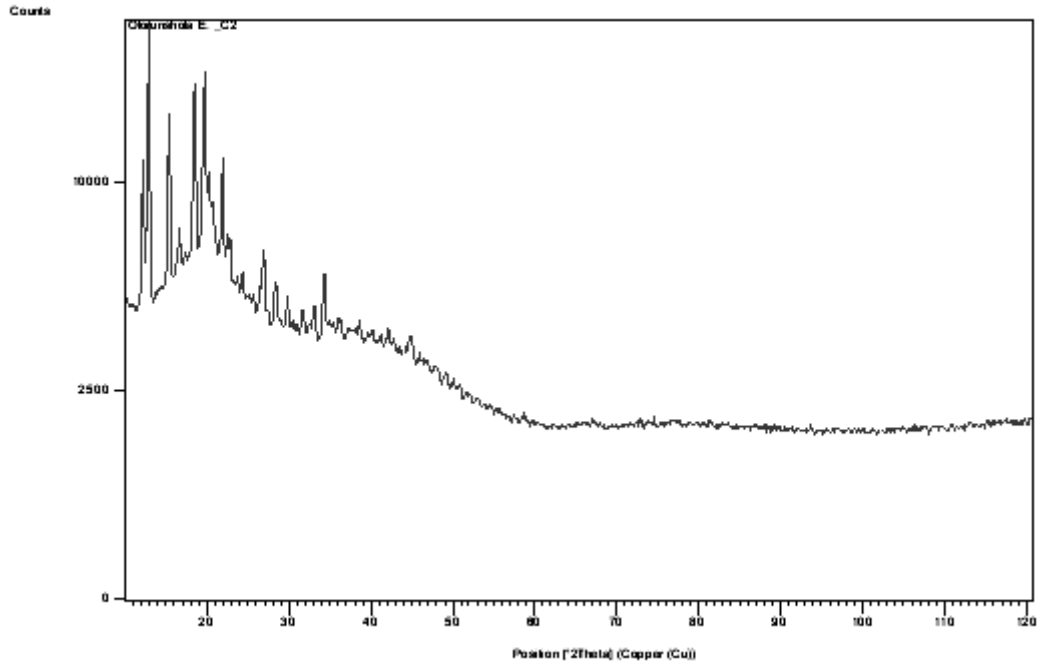
A 2.11 X-RAY DIFFRACTION PATTERN OF ARTESUNATE SODIUM + CASHEW GUM



Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
12.2234	4001.74	0.1653	7.24109	32.37
12.9760	12363.61	0.3306	6.82276	100.00
15.4388	5584.50	0.2480	5.73948	45.17
16.7185	1969.41	0.2480	5.30293	15.93
18.5463	8344.10	0.2480	4.78422	67.49
19.7751	8606.89	0.2480	4.48962	69.61
20.8231	5118.61	0.2480	4.26597	41.40
21.9744	4934.53	0.2480	4.04501	39.91
22.8164	1922.99	0.3306	3.89760	15.55
24.4091	942.76	0.2480	3.64677	7.63
26.4836	1363.09	0.2480	3.36565	11.02
28.4483	1002.88	0.3306	3.13751	8.11
29.9065	732.15	0.2480	2.98777	5.92
31.0707	241.06	0.2480	2.87842	1.95
31.7371	476.27	0.2480	2.81949	3.85
33.1646	679.11	0.2480	2.70132	5.49
34.3753	1543.01	0.2480	2.60890	12.48
36.4727	685.97	0.2480	2.46355	5.55
38.6192	372.96	0.2480	2.33142	3.02
42.3615	1143.32	0.2480	2.13372	9.25
45.0427	468.44	0.6048	2.01108	3.79

A 2.12 X-RAY DIFFRACTION PATTERN OF ARTESUNATE SODIUM + PROSOPIS GUM

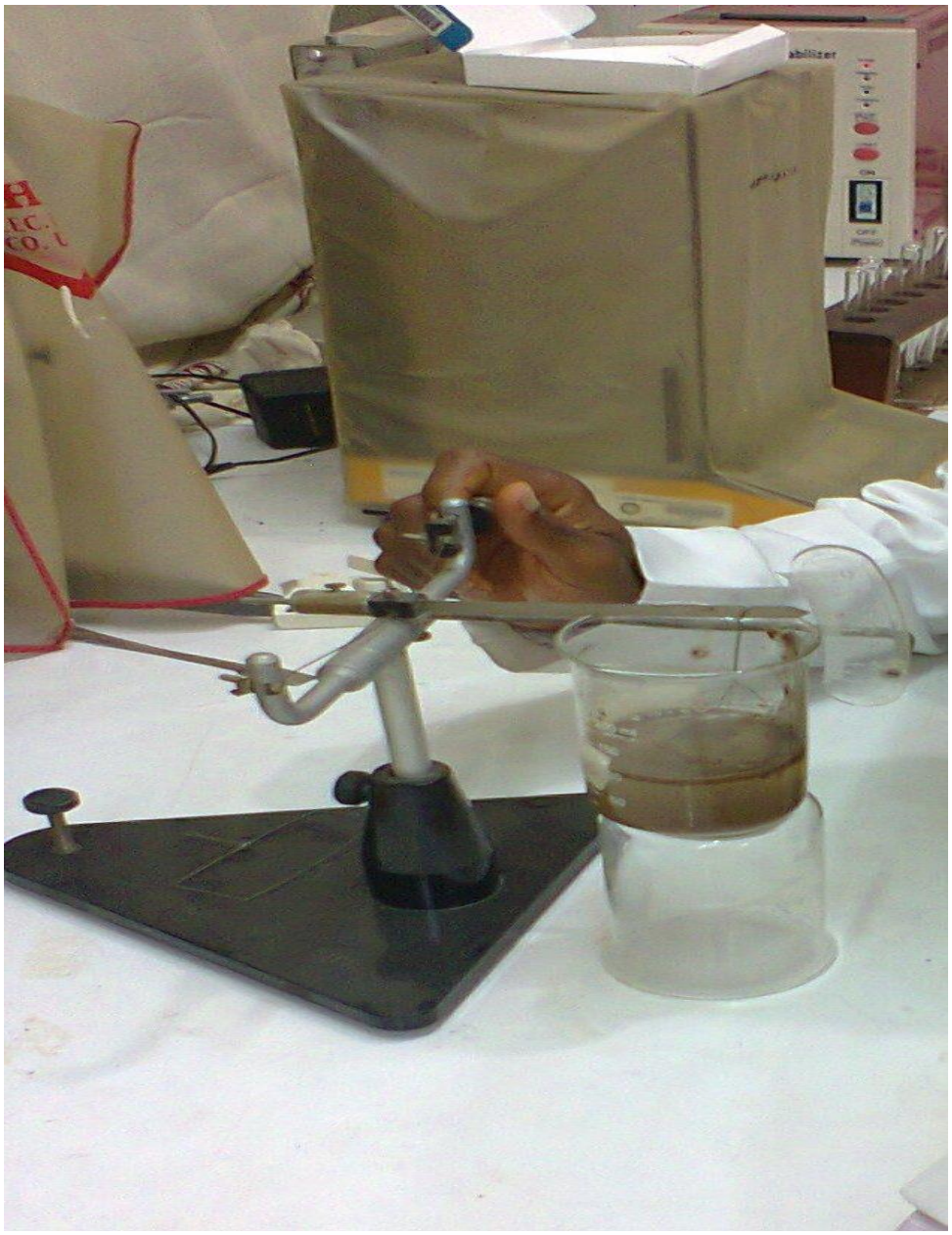


Peak List

Pos.[°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
12.1775	5577.16	0.2480	7.26825	37.47
12.9312	14886.17	0.2480	6.84630	100.00
15.3863	8294.32	0.2480	5.75895	55.72
16.6577	2498.95	0.2480	5.32214	16.79
18.4969	9974.96	0.2480	4.79689	67.01
19.7127	10332.38	0.3306	4.50370	69.41
20.2719	4896.93	0.1653	4.38071	32.90
21.9047	5933.63	0.2480	4.05772	39.86
22.8592	2253.35	0.2480	3.89041	15.14
24.3812	1112.69	0.2480	3.65088	7.47
26.9248	2277.02	0.3306	3.31149	15.30
28.4117	1323.18	0.3306	3.14147	8.89
29.8310	991.55	0.2480	2.99517	6.66
31.6677	794.26	0.3306	2.82551	5.34
33.1234	1080.93	0.2480	2.70459	7.26
34.3156	2152.43	0.3306	2.61330	14.46
38.6081	484.48	0.2480	2.33207	3.25
42.1835	425.42	0.3306	2.14231	2.86
44.8002	734.25	0.4959	2.02307	4.93
48.2120	354.53	0.7056	1.88602	2.38
49.1721	334.54	0.6048	1.85602	2.25

A 3.1 SURFACE TENSION OF VARIOUS GUM DISPERSIONS

Concentration	Surface Tension (mN/m)					
(% w/v)	CSG	KYG	ACG	AFG	PRG	SCMC
0.00	71.9±2.01	71.9±2.01	71.9±2.01	71.9±2.01	71.9±2.01	71.9±2.01
0.10	65.9±1.04	71.9±0.00	60.6±1.20	71.9±0.00	71.9±0.00	50.7±0.00
0.25	57.8±1.14	67.6±2.01	47.9±1.17	69.1±1.20	55.0±2.34	50.7±1.17
0.50	55.0±0.00	60.6±0.00	47.9±1.14	69.1±1.14	55.0±0.00	50.7±1.17
0.75	55.0±1.14	55.0±0.00	47.9±0.00	69.1±0.00	55.0±1.14	
1.00	55.0±0.00	55.0±0.00	47.9±1.14	69.1±1.17	55.0±1.14	

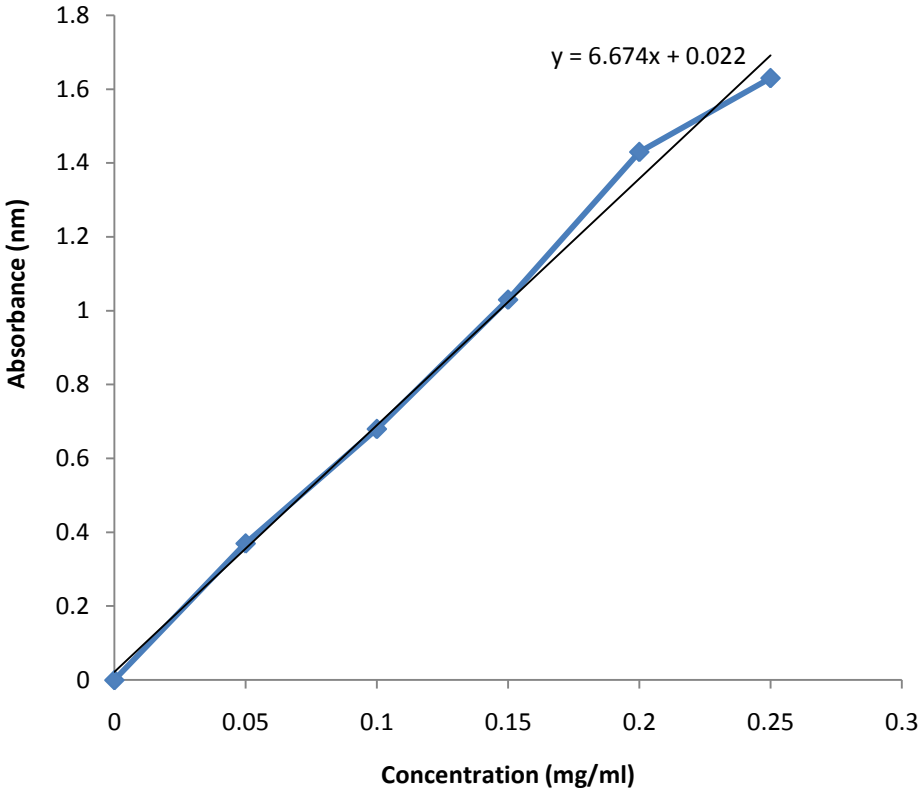


A 4.1 Experimental Set-Up for Surface Tension Determination using Searls Tensiometer

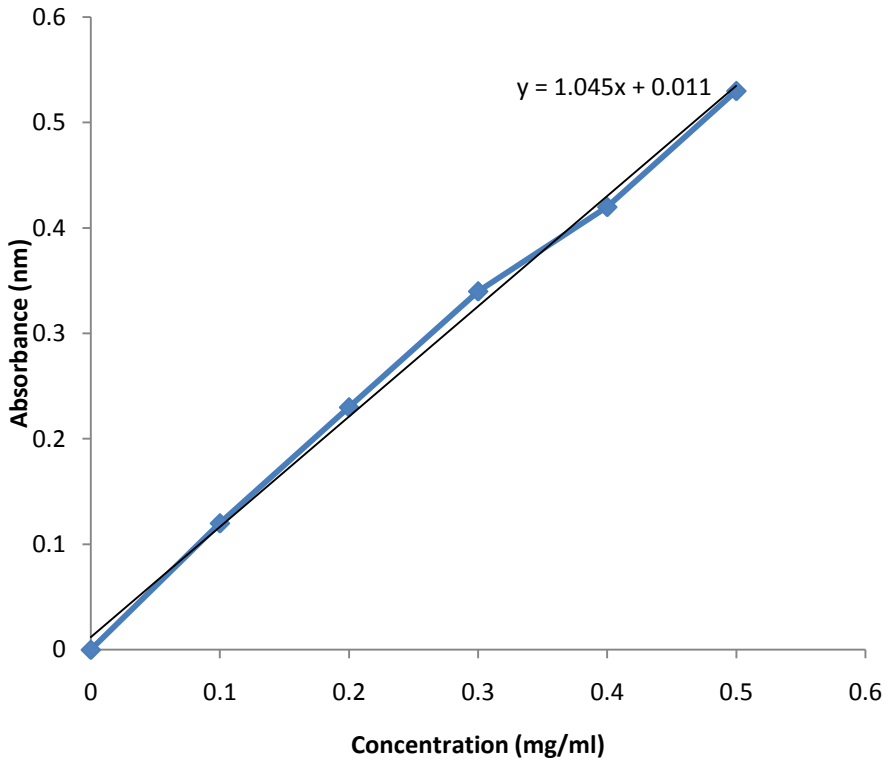




A 4.2 Experimental Set-Up for Permeation Studies using USP Dissolution Apparatus and Isolated Pig Intestine



A 5.1 Beer - Lambert's Plot of Artemether



A 5.2 Beer – Lambert's Plot of Artesunate Sodium

A 6.1 STATISTICAL ANALYSIS OF pH OF 2 % $^{W}/_{V}$ GUM DISPERSIONS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	67.26	< 0.001
CSG vs ACG	58.77	< 0.001
CSG vs AFG	47.56	< 0.001
CSG vs PRG	81.86	< 0.001
CSG vs SCMC	127.72	< 0.001
KYG vs ACG	126.02	< 0.001
KYG vs AFG	114.81	< 0.001
KYG vs PRG	149.12	< 0.001
KYG vs SCMC	194.98	< 0.001
ACG vs AFG	11.21	< 0.001
ACG vs PRG	23.10	< 0.001
ACG vs SCMC	68.96	< 0.001
AFG vs PRG	34.31	< 0.001
AFG vs SCMC	80.17	< 0.001
PRG vs SCMC	45.86	< 0.001

A 6.2 STATISTICAL ANALYSIS OF RELATIVE DENSITY OF 2 % $^{W}/_{V}$ GUM DISPERSIONS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	2.31	NS
CSG vs ACG	0.86	NS
CSG vs AFG	0.58	NS
CSG vs PRG	2.02	NS
CSG vs SCMC	59.76	< 0.001
KYG vs ACG	1.44	NS
KYG vs AFG	2.89	NS
KYG vs PRG	4.33	NS
KYG vs SCMC	57.45	< 0.001
ACG vs AFG	1.44	NS
ACG vs PRG	2.89	NS
ACG vs SCMC	58.89	< 0.001
AFG vs PRG	1.44	NS
AFG vs SCMC	60.33	< 0.001
PRG vs SCMC	61.78	< 0.001

NS = Not significant (P > 0.05)

A 6.3 STATISTICAL ANALYSIS OF ANGLE OF REPOSE OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	9.80	< 0.001
CSG vs ACG	2.77	NS
CSG vs AFG	9.31	< 0.001
CSG vs PRG	8.87	< 0.001
CSG vs SCMC	18.89	< 0.001
KYG vs ACG	7.04	< 0.01
KYG vs AFG	19.12	< 0.001
KYG vs PRG	18.68	< 0.001
KYG vs SCMC	28.69	< 0.001
ACG vs AFG	12.08	< 0.001
ACG vs PRG	11.64	< 0.001
ACG vs SCMC	21.66	< 0.001
AFG vs PRG	0.44	NS
AFG vs SCMC	9.58	< 0.001
PRG vs SCMC	10.02	< 0.001

NS = Not significant (P > 0.05)

A 6.4 STATISTICAL ANALYSIS OF FLOW RATE OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	13.30	< 0.001
CSG vs ACG	1.41	NS
CSG vs AFG	7.94	< 0.01
CSG vs PRG	11.04	< 0.001
CSG vs SCMC	19.08	< 0.001
KYG vs ACG	11.89	< 0.001
KYG vs AFG	21.23	< 0.001
KYG vs PRG	24.34	< 0.001
KYG vs SCMC	32.38	< 0.001
ACG vs AFG	9.31	< 0.001
ACG vs PRG	12.45	< 0.001
ACG vs SCMC	20.49	< 0.001
AFG vs PRG	3.11	NS
AFG vs SCMC	11.45	< 0.001
PRG vs SCMC	8.04	< 0.01

NS = Not significant (P > 0.05)

A 6.5 STATISTICAL ANALYSIS OF BULK DENSITY OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	1.97	NS
CSG vs ACG	14.81	< 0.001
CSG vs AFG	46.10	< 0.001
CSG vs PRG	51.26	< 0.001
CSG vs SCMC	66.22	< 0.001
KYG vs ACG	12.84	< 0.001
KYG vs AFG	48.07	< 0.001
KYG vs PRG	53.23	< 0.001
KYG vs SCMC	68.19	< 0.001
ACG vs AFG	60.91	< 0.001
ACG vs PRG	66.07	< 0.001
ACG vs SCMC	81.03	< 0.001
AFG vs PRG	5.16	< 0.05
AFG vs SCMC	20.12	< 0.001
PRG vs SCMC	14.96	< 0.001

NS = Not significant (P > 0.05)

A 6.6 STATISTICAL ANALYSIS OF TAPPED DENSITY OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	2.46	NS
CSG vs ACG	5.33	< 0.05
CSG vs AFG	40.84	< 0.001
CSG vs PRG	46.33	< 0.001
CSG vs SCMC	60.23	< 0.001
KYG vs ACG	7.78	< 0.01
KYG vs AFG	38.09	< 0.001
KYG vs PRG	43.87	< 0.001
KYG vs SCMC	57.78	< 0.001
ACG vs AFG	45.87	< 0.001
ACG vs PRG	51.66	< 0.001
ACG vs SCMC	65.56	< 0.001
AFG vs PRG	5.79	< 0.05
AFG vs SCMC	19.69	< 0.001
PRG vs SCMC	13.90	< 0.001

NS = Not significant (P > 0.05)

A 6.7 STATISTICAL ANALYSIS OF MOISTURE CONTENT OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	0.09	NS
CSG vs ACG	0.17	NS
CSG vs AFG	0.46	NS
CSG vs PRG	3.54	NS
CSG vs SCMC	9.43	< 0.001
KYG vs ACG	0.26	NS
KYG vs AFG	0.37	NS
KYG vs PRG	3.45	NS
KYG vs SCMC	9.34	< 0.001
ACG vs AFG	0.63	NS
ACG vs PRG	3.71	NS
ACG vs SCMC	9.60	< 0.001
AFG vs PRG	3.08	NS
AFG vs SCMC	8.97	< 0.001
PRG vs SCMC	5.89	< 0.05

NS = Not significant (P > 0.05)

A 6.8 STATISTICAL ANALYSIS OF MOISTURE SORPTION CAPACITY OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	9.92	< 0.001
CSG vs ACG	10.60	< 0.001
CSG vs AFG	4.54	NS
CSG vs PRG	11.96	< 0.001
CSG vs SCMC	37.81	< 0.001
KYG vs ACG	0.68	NS
KYG vs AFG	14.46	< 0.001
KYG vs PRG	2.05	NS
KYG vs SCMC	27.89	< 0.001
ACG vs AFG	15.14	< 0.001
ACG vs PRG	1.36	NS
ACG vs SCMC	27.21	< 0.001
AFG vs PRG	16.50	< 0.001
AFG vs SCMC	42.35	< 0.001
PRG vs SCMC	25.85	< 0.001

NS = Not significant (P > 0.05)

A 6.9 STATISTICAL ANALYSIS OF SWELLING CAPACITY OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	26.30	< 0.001
CSG vs ACG	4.78	< 0.05
CSG vs AFG	77.05	< 0.001
CSG vs PRG	194.48	< 0.001
CSG vs SCMC	239.91	< 0.001
KYG vs ACG	31.09	< 0.001
KYG vs AFG	50.75	< 0.001
KYG vs PRG	168.18	< 0.001
KYG vs SCMC	213.61	< 0.001
ACG vs AFG	81.83	< 0.001
ACG vs PRG	199.26	< 0.001
ACG vs SCMC	244.70	< 0.001
AFG vs PRG	117.43	< 0.001
AFG vs SCMC	162.86	< 0.001
PRG vs SCMC	45.43	< 0.001

A 6.10 STATISTICAL ANALYSIS OF SOLUBILITY OF THE GUMS IN WATER

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	16.43	< 0.001
CSG vs ACG	5.05	< 0.05
CSG vs AFG	39.74	< 0.001
CSG vs PRG	42.29	< 0.001
CSG vs SCMC	37.06	< 0.001
KYG vs ACG	11.38	< 0.001
KYG vs AFG	23.31	< 0.001
KYG vs PRG	25.86	< 0.001
KYG vs SCMC	20.63	< 0.001
ACG vs AFG	34.69	< 0.001
ACG vs PRG	37.24	< 0.001
ACG vs SCMC	32.02	< 0.001
AFG vs PRG	2.55	NS
AFG vs SCMC	2.67	NS
PRG vs SCMC	5.23	< 0.05

NS = Not significant (P > 0.05)

A 6.11 STATISTICAL ANALYSIS OF PARTITION COEFFICIENT OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	0.12	NS
CSG vs ACG	0.09	NS
CSG vs AFG	5.71	< 0.05
CSG vs PRG	6.64	< 0.01
CSG vs SCMC	7.34	< 0.01
KYG vs ACG	0.02	NS
KYG vs AFG	5.83	< 0.05
KYG vs PRG	6.76	< 0.01
KYG vs SCMC	7.47	< 0.01
ACG vs AFG	5.81	< 0.05
ACG vs PRG	6.74	< 0.01
ACG vs SCMC	7.44	< 0.01
AFG vs PRG	0.69	NS
AFG vs SCMC	1.63	NS
PRG vs SCMC	0.70	NS

NS = Not significant (P > 0.05)

A 6.12 STATISTICAL ANALYSIS OF PHENOL INDEX OF THEGUMS

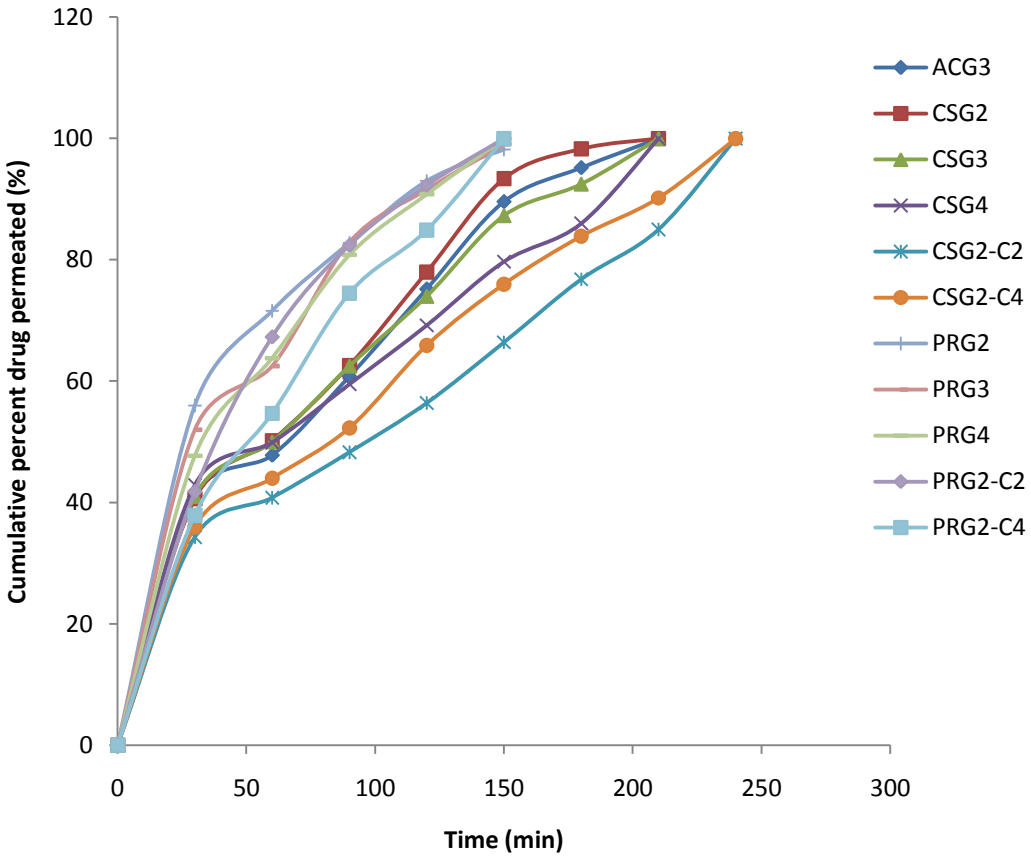
COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	0.58	NS
CSG vs ACG	6.52	< 0.01
CSG vs AFG	20.84	< 0.001
CSG vs PRG	15.87	< 0.001
CSG vs SCMC	6.72	< 0.01
KYG vs ACG	5.94	< 0.05
KYG vs AFG	20.25	< 0.001
KYG vs PRG	15.29	< 0.001
KYG vs SCMC	6.13	< 0.01
ACG vs AFG	14.31	< 0.001
ACG vs PRG	9.35	< 0.001
ACG vs SCMC	0.19	NS
AFG vs PRG	4.97	< 0.05
AFG vs SCMC	14.12	< 0.001
PRG vs SCMC	9.15	< 0.001

NS = Not significant (P > 0.05)

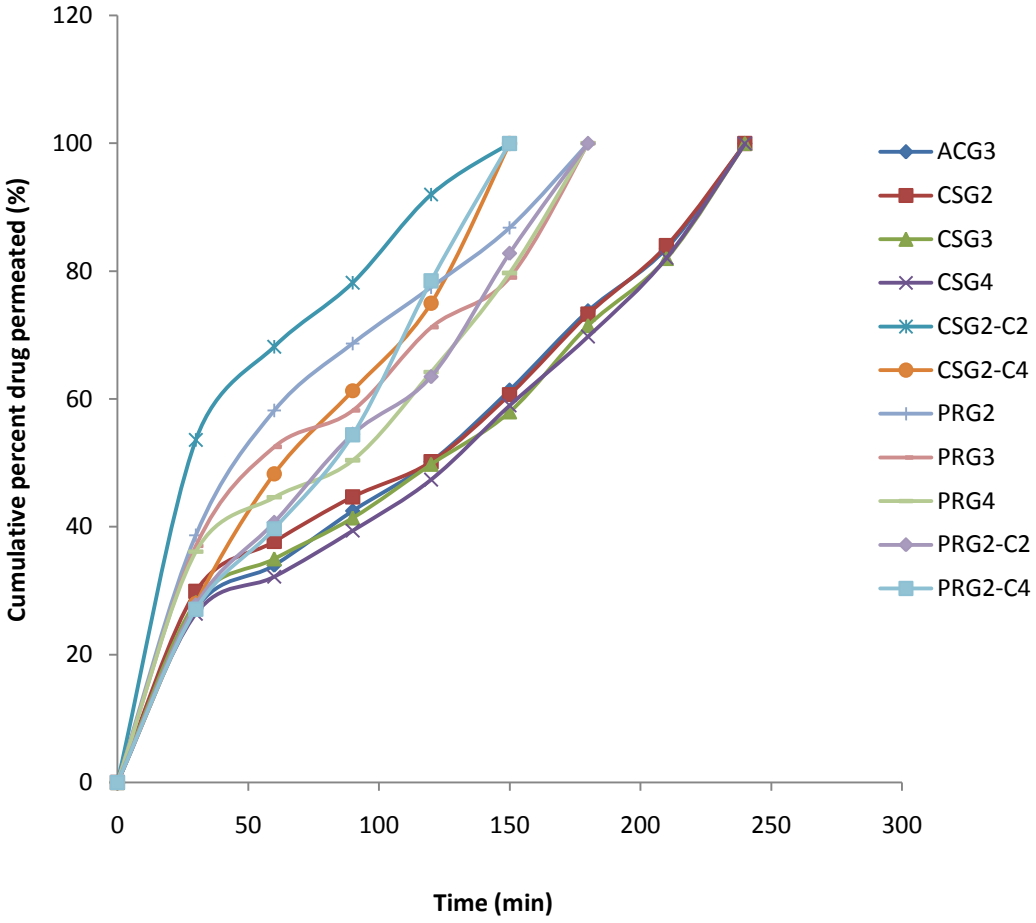
A 6.13 STATISTICAL ANALYSIS OF HLB VALUES OF THE GUMS

COMPARISON	***Q – VALUE***	***P – VALUE***
CSG vs KYG	0.59	NS
CSG vs ACG	6.52	< 0.01
CSG vs AFG	20.86	< 0.001
CSG vs PRG	15.88	< 0.001
CSG vs SCMC	6.72	< 0.01
KYG vs ACG	5.93	< 0.05
KYG vs AFG	20.27	< 0.001
KYG vs PRG	15.28	< 0.001
KYG vs SCMC	6.13	< 0.01
ACG vs AFG	14.33	< 0.001
ACG vs PRG	9.35	< 0.001
ACG vs SCMC	0.19	NS
AFG vs PRG	4.98	< 0.05
AFG vs SCMC	14.13	< 0.001
PRG vs SCMC	9.15	< 0.001

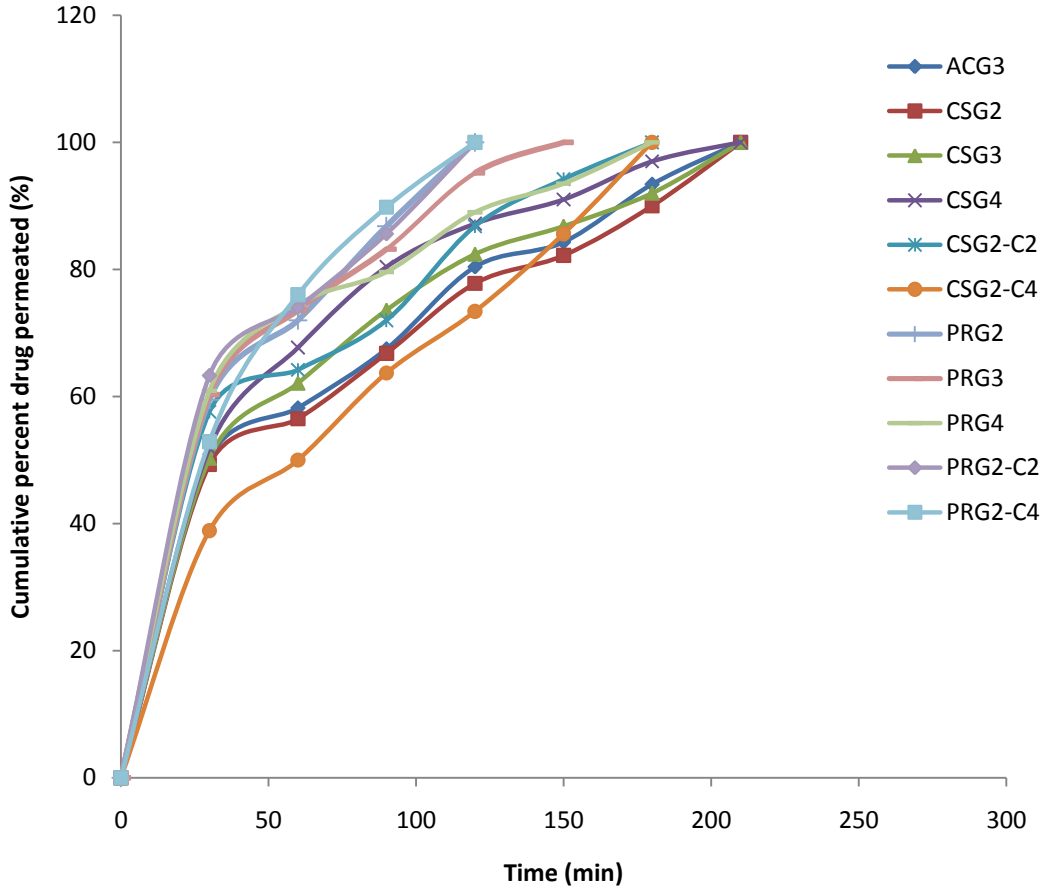
NS = Not significant (P > 0.05)



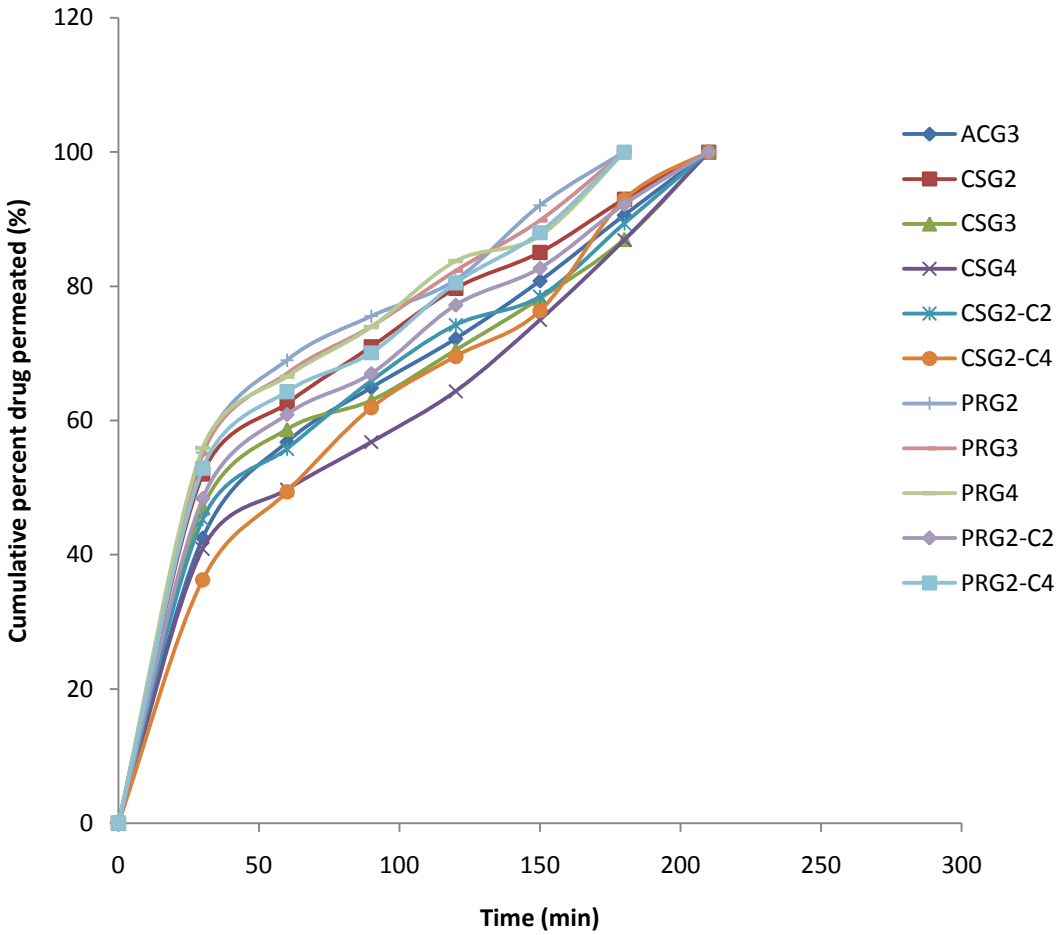
A 7.1 Permeation Profile of Artemether under Simulated Gastric Fluid Condition.



A 7.2 Permeation Profile of Artemether under Simulated Intestinal Fluid Condition.



A 7.3 Permeation Profile of Artesunate Sodium under Simulated Gastric Fluid Condition.



A 7.4 Permeation Profile of Artesunate Sodium under Simulated Intestinal Fluid Condition