Compatibility study of cashew and prosopis gums with some artemisinin derivatives

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ABSTRACT

Introduction: Drug - excipient compatibility study is important to pre-formulation and is carried out to ensure that there is no adverse interaction between the drug and any excipient. This study was aimed at investigating the compatibility of cashew gum (CSG) and prosopis gum (PRG) with artemether (ATM) and artesunate (ATS).

Methods: Interactions between each drug and each excipient were investigated by taking the differential scanning thermograms (DSC), the Fourier transform infrared (FTIR) spectra and X-ray diffraction (XRD) patterns of pure drugs, pure gums and drug/gum mixtures.

Results: The presence of cashew gum and prosopis gum had similar effects of reducing the melting point and increasing the recrystallization temperature of artemether but they had no noticeable effect on the melting point of artesunate. While cashew gum caused shifts of the peaks in the FTIR spectra of both drugs, prosopis gum caused reduction in the height of the peaks; but no new peak was formed in any of the interactions.

Conclusion: This work has shown that no new compound was formed from interactions of the two drugs with either of the two gums. Therefore, the two gums are compatible with the two artemisinin derivatives and could be investigated as delivery agents for these drugs.

Keywords: cashew gum, prosopis gum, artemether, artesunate, compatibility.

INTRODUCTION

Artemisinin is a sesquiterpene lactone endoperoxide. It is the active component of a herbal remedy that has been in use as an antipyretic in China for over two millennia [1]. It is insoluble and its use is somehow limited. Therefore, derivatives have been developed to increase solubility and to improve antimalarial efficacy. The most important of these derivatives are the water-soluble artesunate and the lipid-soluble artemether [2,3]. Artemether and artesunate are effective agents for the treatment of multidrug-resistant *P. falciparum* malaria. The high prevalence of malaria in the tropics [4] coupled with the World Health Organization's recommendation of artemisinin-based combination therapy for malaria is responsible for wide use of artemisinins [2].

Gums are widely employed in different types of pharmaceutical formulations. In solid dosage form, they are used as binders in immediate release tablets and as matrix formers in controlled release ones [5]. In liquid dosage forms, they are used as suspending agents, emulsifying agents and solubilizing agents [6]. Therefore, they

are versatile pharmaceutical excipients that can be investigated for formulation of the widely used artemisinins.

Cashew gum has been suggested for use as an agglutinant for capsules and pills in place of gum Arabic [7]. The gum, utilized as a binder in paracetamol tablet formulations was reported to impart better mechanical strength to the tablets compared to povidone and gelatin [8]. Aceclofenac gel containing 5 % $^{w}/_{w}$ cashew gum was found to be suitable for topical application [9]. Prosopis gum has been investigated for bioadhesive delivery of theophylline. The results showed that the gum was highly bioadhesive compared to sodium carboxymethylcellulose and that it could be used to deliver theophylline in a bioadhesive dosage form. It was also shown to impart high mechanical strength to tablets [10].

Gums exist widely in nature and can be expressed as exudates, seed gums, seaweed gums or as pectin [11]. Cashew gum exudes naturally from the plant while the gum in prosopis is obtained from the seed. Cashew gum is a highly branched galactan polymer comprising chains of 1, 3 linked β-D-galactopyranosyl units interspersed with β-1, 6-linkages while prosopis gum is a hemicellulose [7,12]. Hence, the two polymers have different physicochemical properties and may exhibit different interactions with drugs. Also, artemether and artesunate are different derivatives of artemisinin and might be affected in different ways by the same excipient.

The use of artemether and artesunate has greatly increased; being the most commonly used artemisinin derivatives in artemisinin-based combination therapy for malaria. Cashew and prosopis plants are abundantly available in the tropics and their gums have been shown to be useful glycopolymers for tablet formulation. This work was aimed at assessing the compatibility of the two glycopolymers with the two artemisinin derivatives. It is a pre-formulation study carried out in respect of artemether and artesunate tablet formulations using cashew and prosopis gums as binders.

MATERIALS AND METHODS

Materials

The materials used were: artemether powder (Afrab Chem. Ltd., Lagos, Nigeria), artesunate powder (IPCA Laboratory, India), cashew gum extracted from exudates of *Anacardium occidentale L*. using the method as described by Ofori-Kwakye *et al*. [13]; and prosopis gum extracted from seeds of *Prosopis africana* using the method as described by Adikwu *et al*. [14].

Differential scanning calorimetry (DSC)

The DSC analyses of pure drug, gum and 1:1 drug/gum mixtures were carried out using DSC – 204FI machine (NETZSCH Co., Germany). The procedure involved placing 3 mg sample in an A1 40 µL crucible. The scanning was done at 20 ^{o}C/min heating rate over a temperature range of 0 – 500 ^{O}C under nitrogen environment.

Fourier transform infrared (FTIR) spectroscopy

Samples of each drug, each gum and 1:1 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 at scanning range of 350 to 5,000 cm^{-1} using a spectrophotometer (model 8400S, Shimadzu Corporation, Kyoto - Japan).

X-ray diffraction (XRD)

Powder X-ray diffraction patterns of each drug, each gum and 1:9 drug/gum mixtures were obtained using an X-ray diffractometer (PANalytical Spectris Pvt. Ltd., Singapore). The recording was done using a copper target at voltage of 40 KV and a current of 30 mA over scanning range of 10 to 120 $^{0}2\Theta$.

RESULTS

Cashew gum and artemether

The DSC thermograms of pure artemether, cashew gum and 1:1 mixture of the drug and the gum are illustrated in Figure 1. 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 cashew gum showed two endotherms with peaks at 70 ^{O}C and 305 ^{O}C respectively. In the thermogram of 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, cashew gum and 1:1 mixture of artemether and cashew gum are illustrated in Figure 2. 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 X-ray diffraction spectra of the pure drug, gum and 1:9 mixture of the drug and the gum are illustrated in Figure 3. The XRD 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 $^{0}2\Theta$. The peaks in artemether / cashew gum spectrum were of lower intensity compared to those of the pure drug but no new peak was formed in the artemether / cashew gum spectrum.

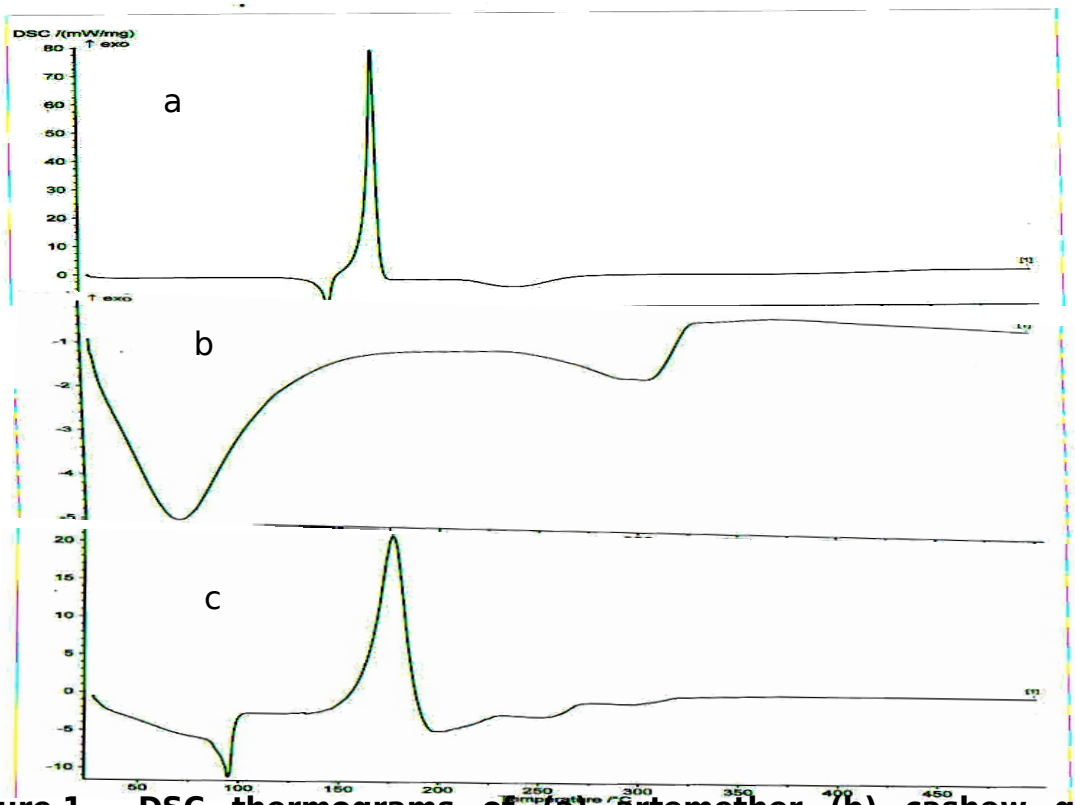

Figure 1 DSC thermograms of (a) artemether (b) cashew gum (c) artemether + cashew gum

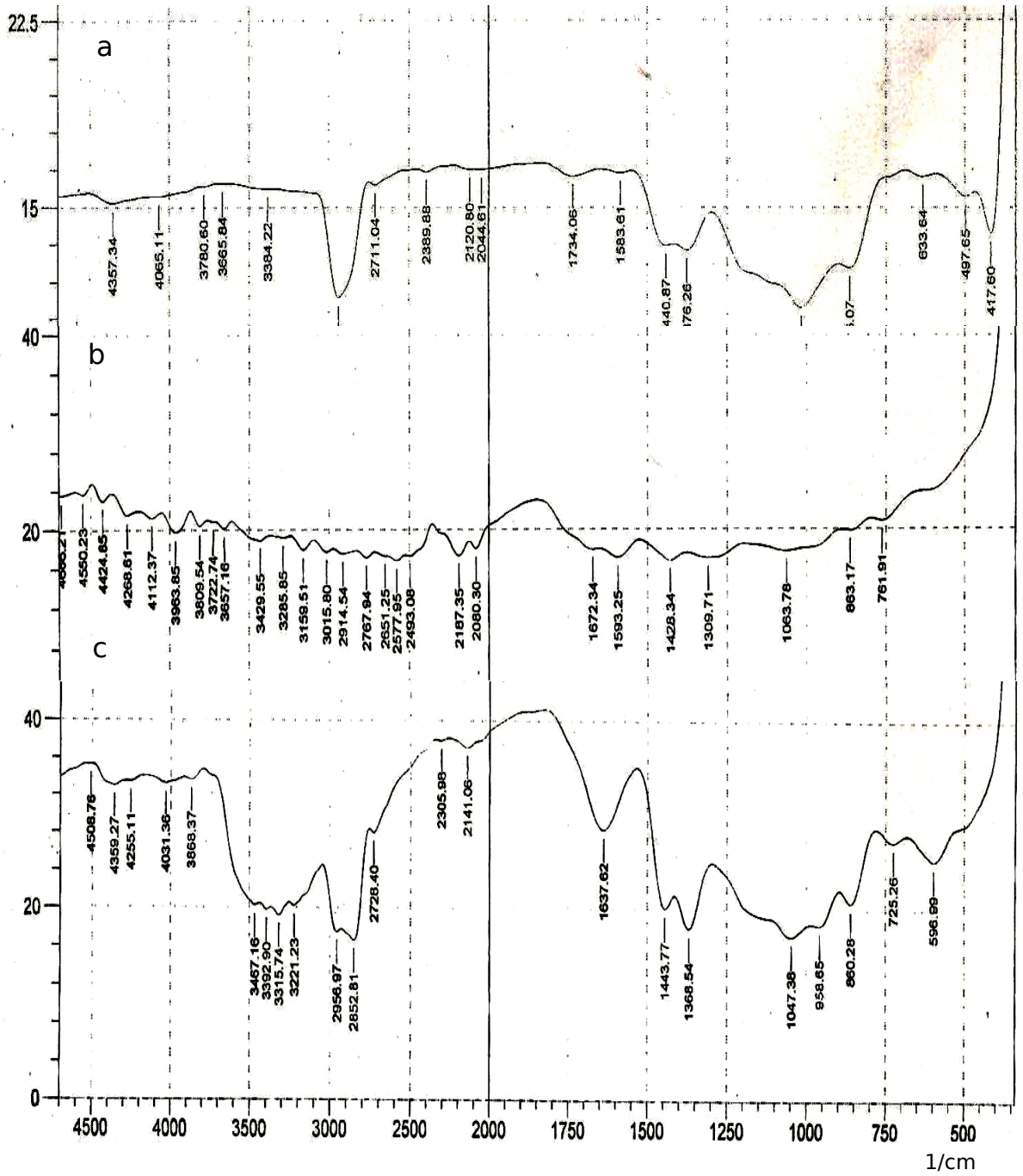

Figure 2 FTIR spectra of (a) artemether (b) cashew gum (c) artemether + cashew gum

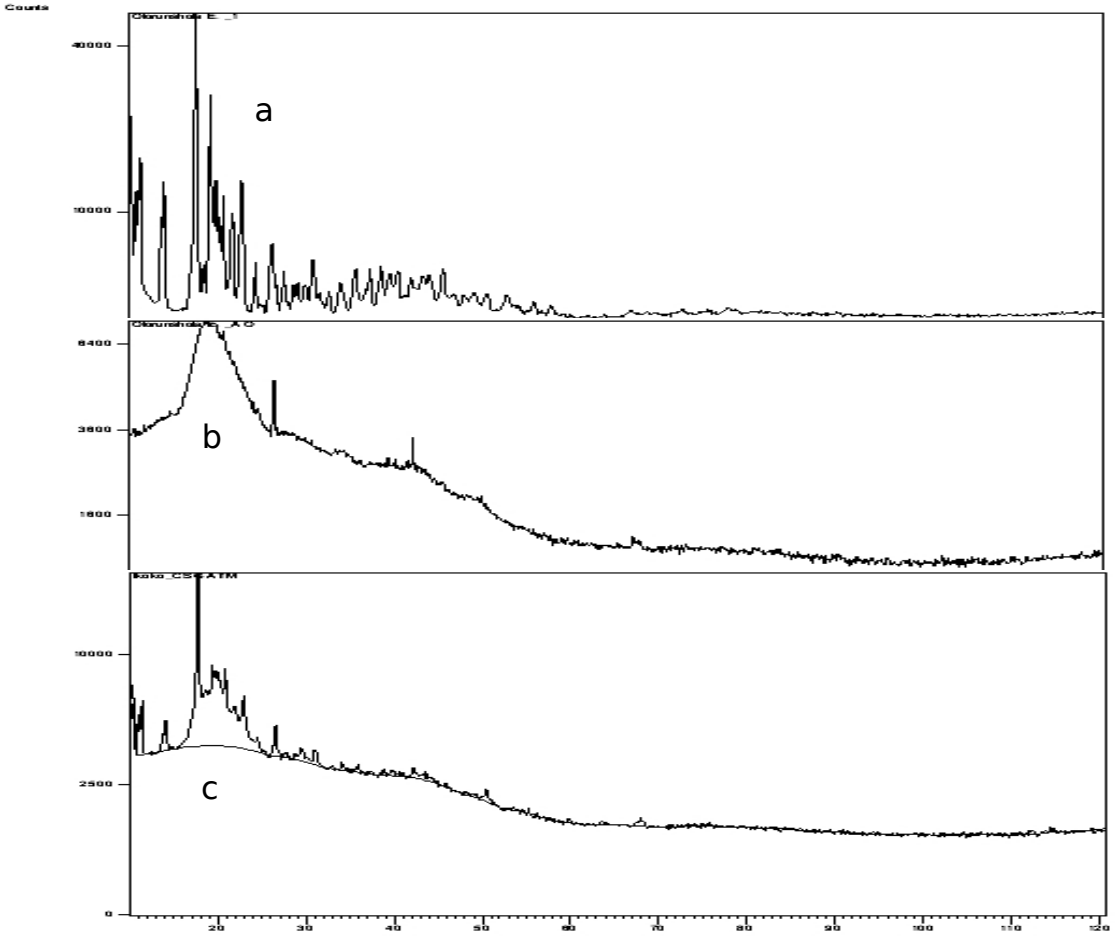

Figure 3 XRD patterns of (a) artemether (b) cashew gum (c) artemether + cashew gum

Prosopis gum and artemether

The DSC thermograms of the pure drug, gum and mixture of the drug and the gum are illustrated in Figure 4. 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, prosopis gum and mixture of artemether and prosopis gum are illustrated in Figure 5. 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, gum and mixture of the drug and the gum are illustrated in Figure 6. There was elevation of the base line of the peaks of artemether when it was combined with the gum.

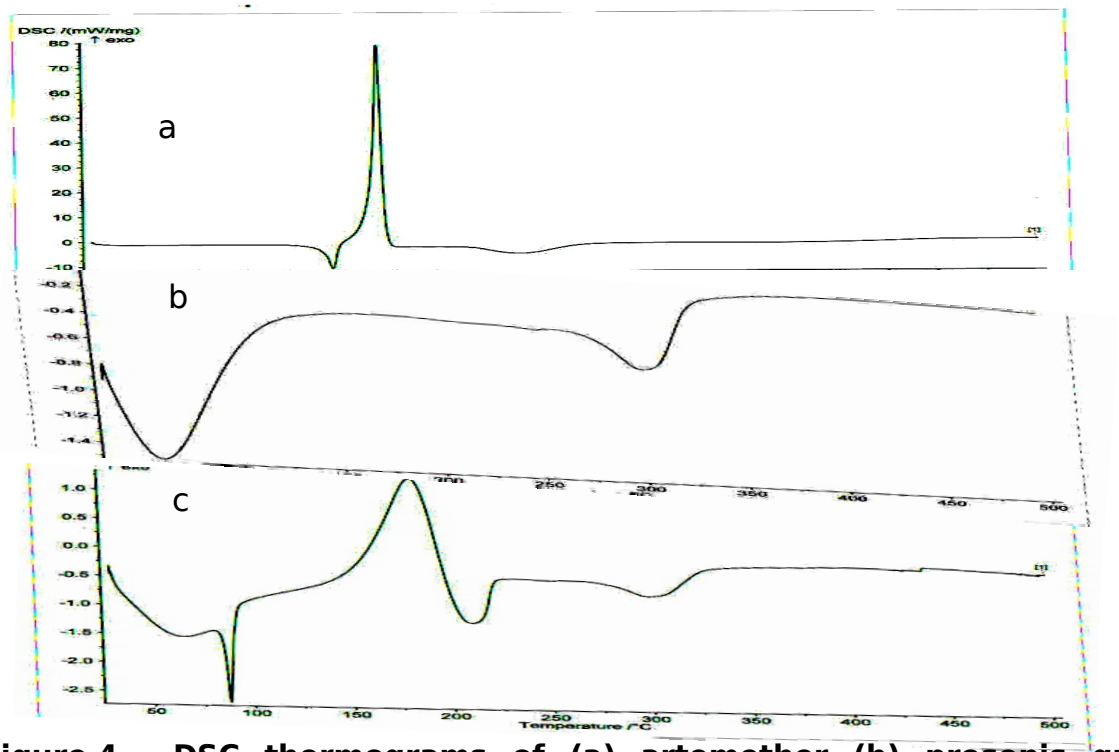

Figure 4. DSC thermograms of (a) artemether (b) prosopis gum (c) artemether + prosopis gum.

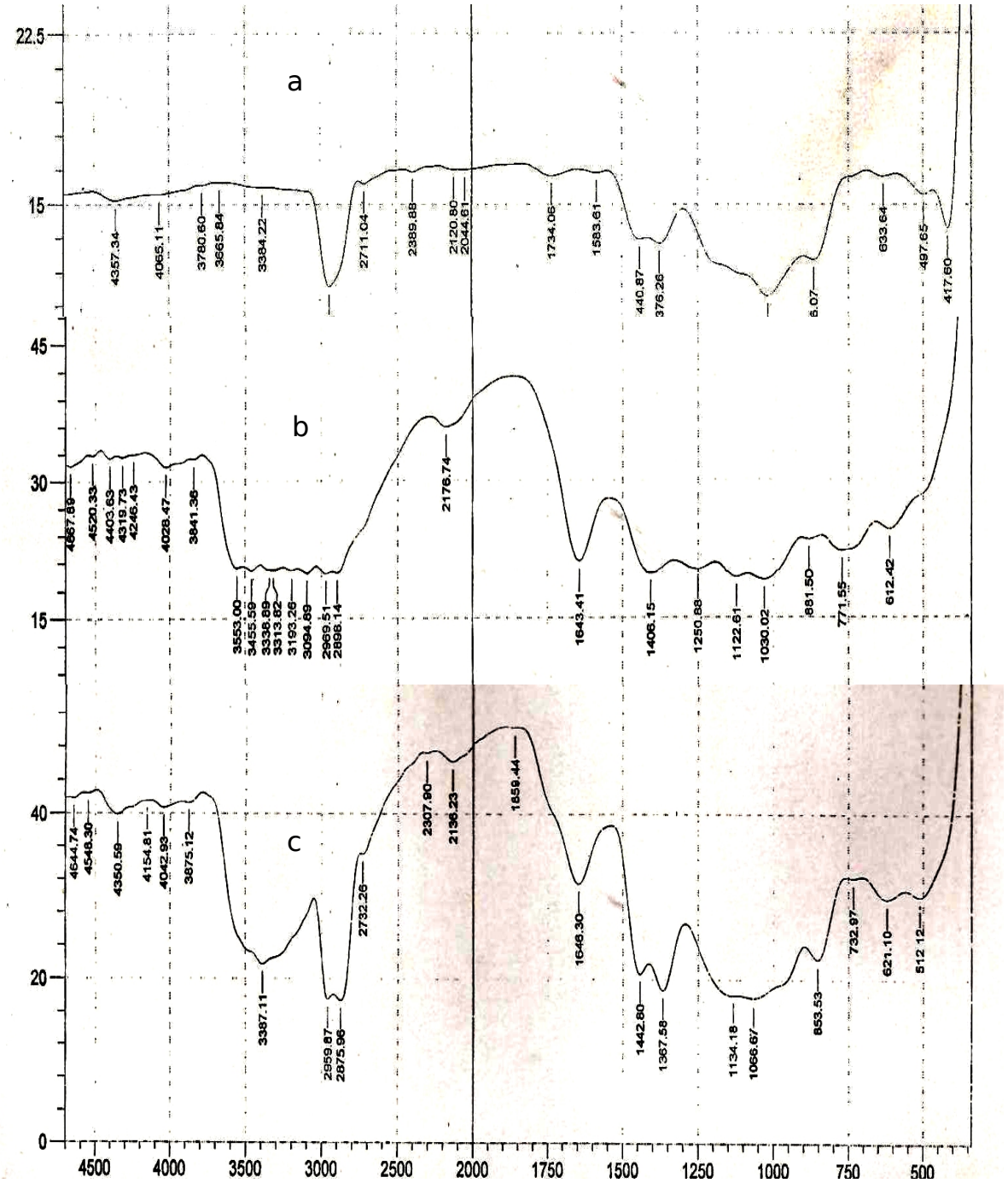

Figure 5 FTIR spectra of (a) artemether (b) prosopis gum (c) artemether + prosopis gum

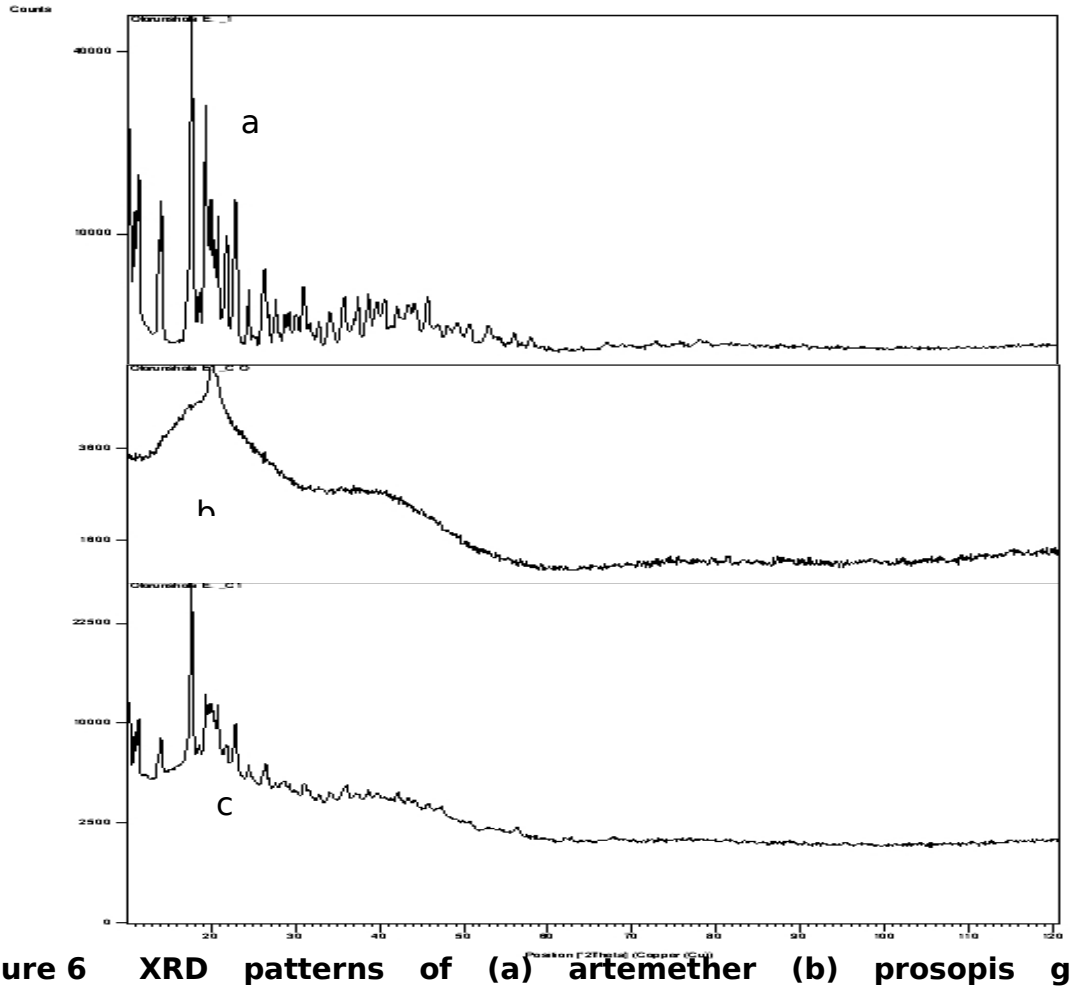

Figure 6 XRD patterns of (a) artemether (b) prosopis gum (c) artemether + prosopis gum.

Cashew gum and artesunate

The DSC thermograms of pure artesunate, cashew gum and mixture of the drug and the gum are illustrated in Figure 7. The thermogram of the pure drug 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 – 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 artesunate, cashew gum and mixture of artesunate and cashew gum are illustrated in Figure 8. There was a positive shift of peaks of artesunate appearing after 1250 cm^{-1} when it was combined with the gum. The XRD patterns of the pure drug, the gum and mixture of the drug and the gum are illustrated in Figure 9. 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.

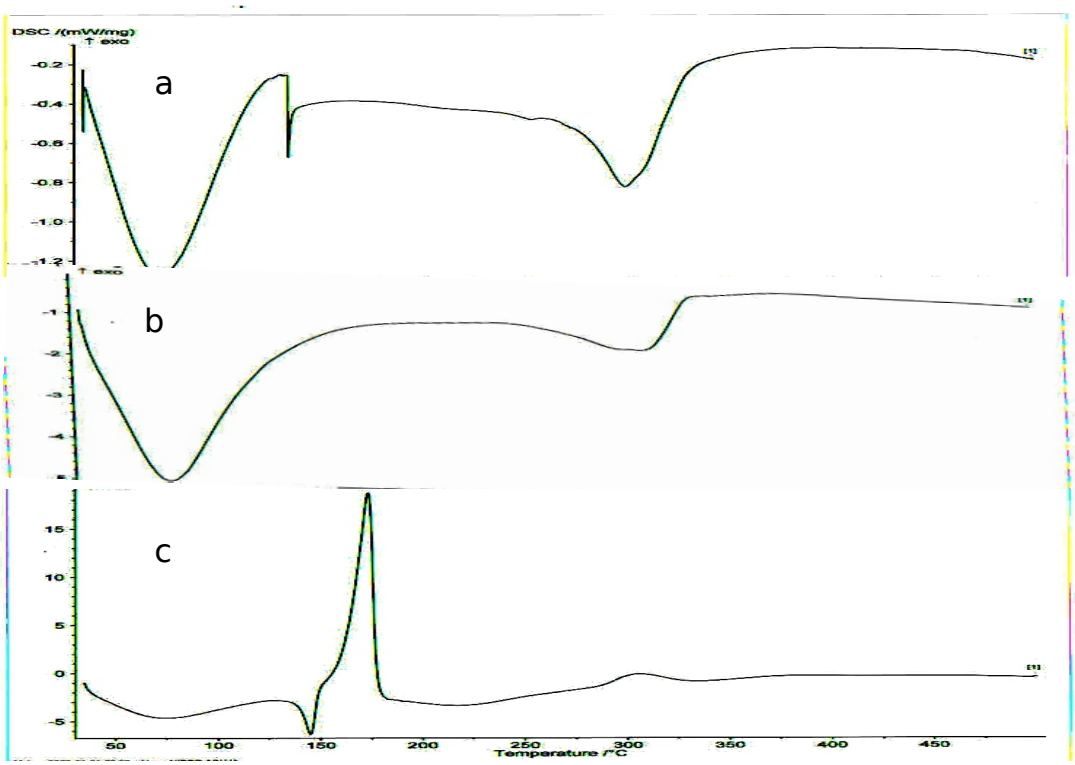

Figure 7 **DSC thermograms of (a) artesunate (b) cashew gum (c) artesunate + cashew gum**

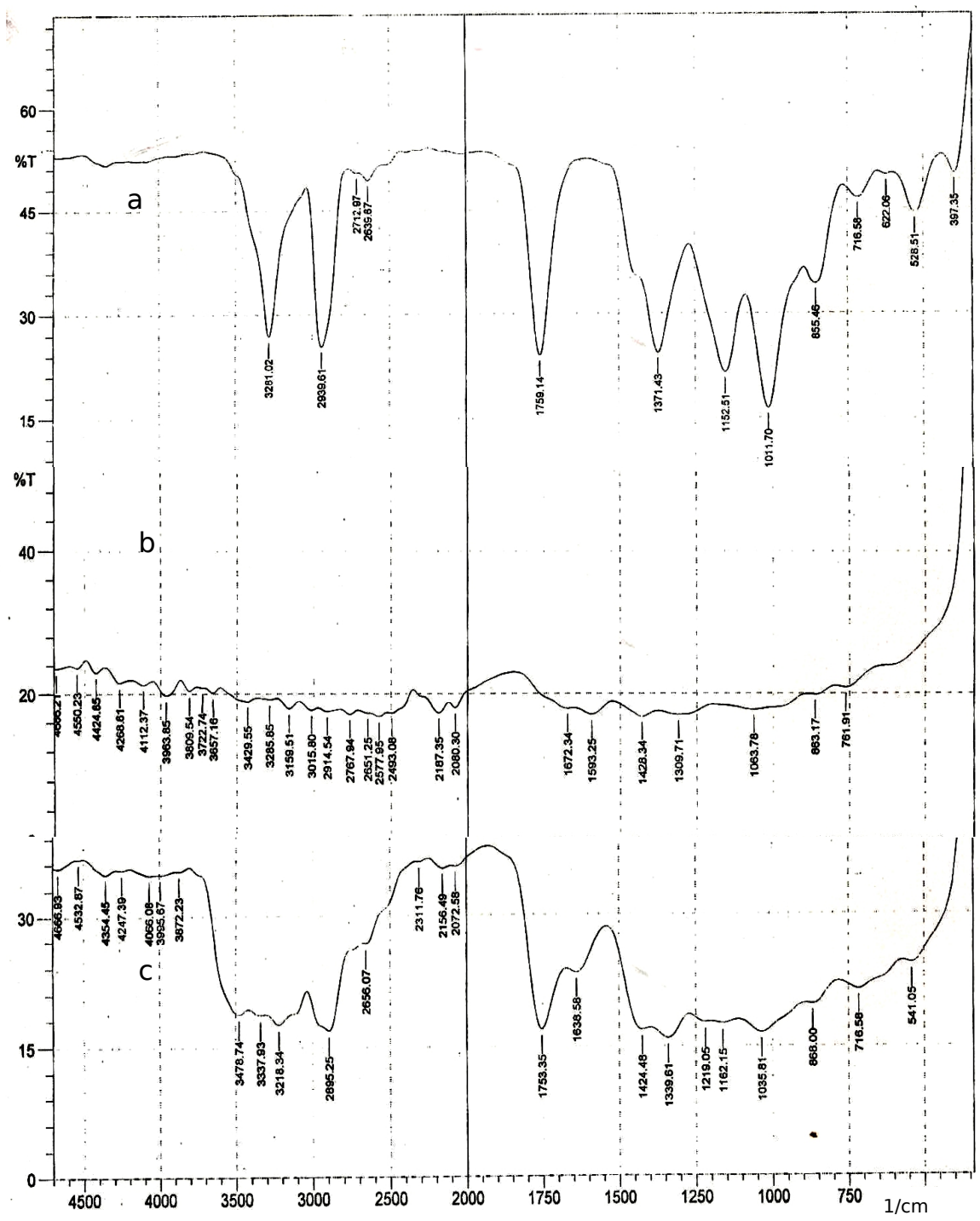

Figure 8 FTIR spectra of (a) artesunate (b) cashew gum (c) artesunate + cashew gum

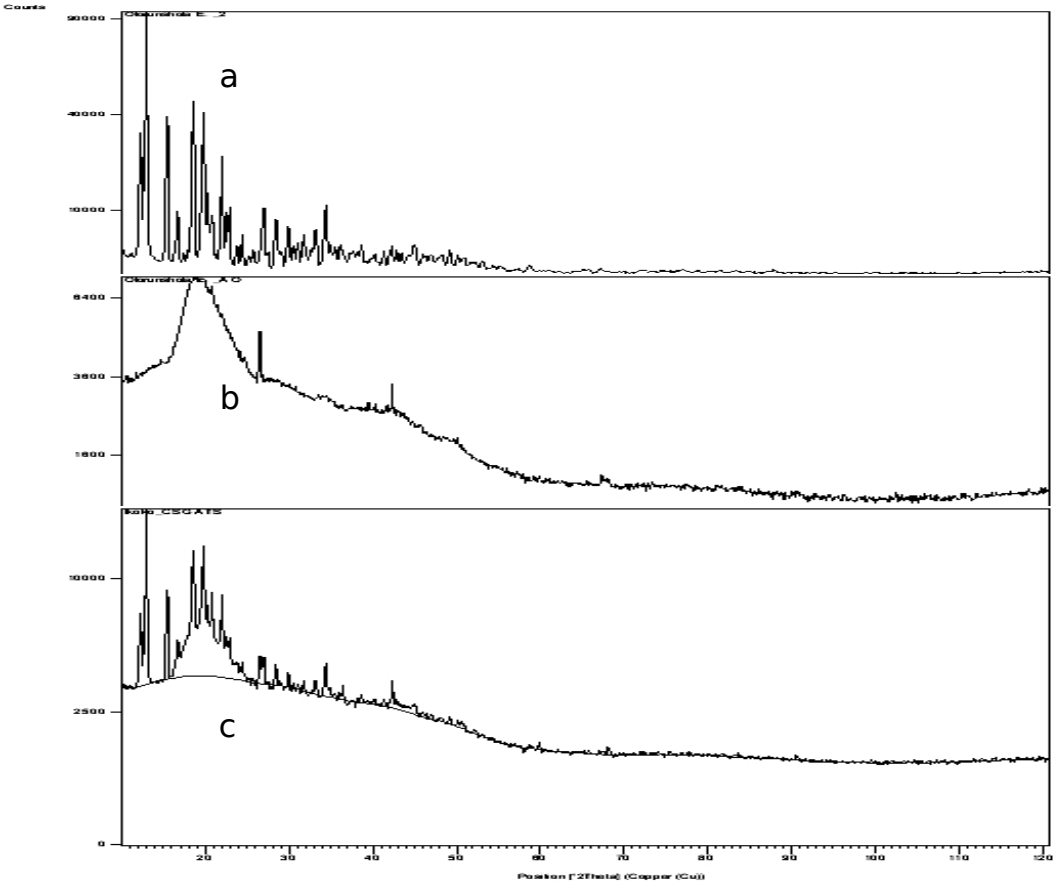

Figure 9 XRD patterns of (a) artesunate (b) cashew gum (c) artesunate + cashew gum.

Artesunate and prosopis gum

The DSC thermograms of artesunate, prosopis gum and drug - polymer (1:1) mixture are shown in Figure 10. The thermogram of pure artesunate 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 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 – 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 artesunate, prosopis gum and 1:1 mixture of artesunate and prosopis gum are shown in Figure 11. 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 12. There were slight changes in the position and d-spacing of the peaks of the drug - polymer mixture but no new peak was formed.

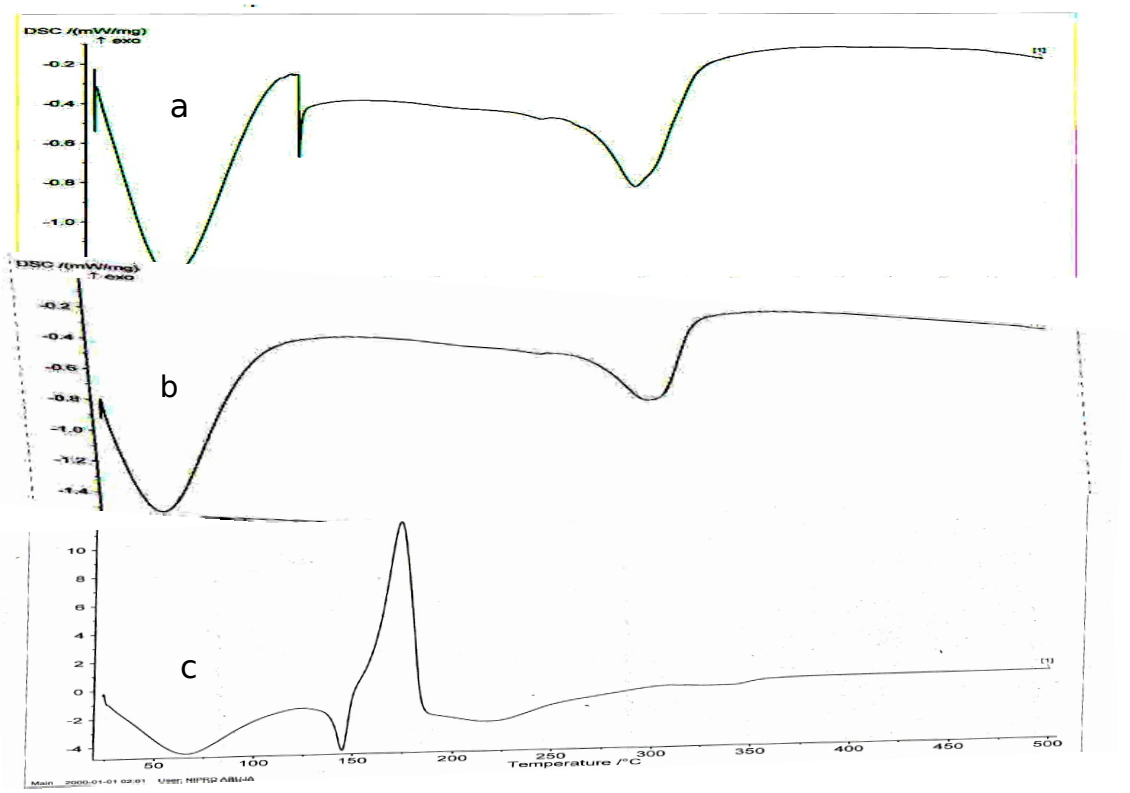

Figure 10 DSC thermograms of (a) artesunate (b) prosopis gum (c) artesunate + prosopis gum

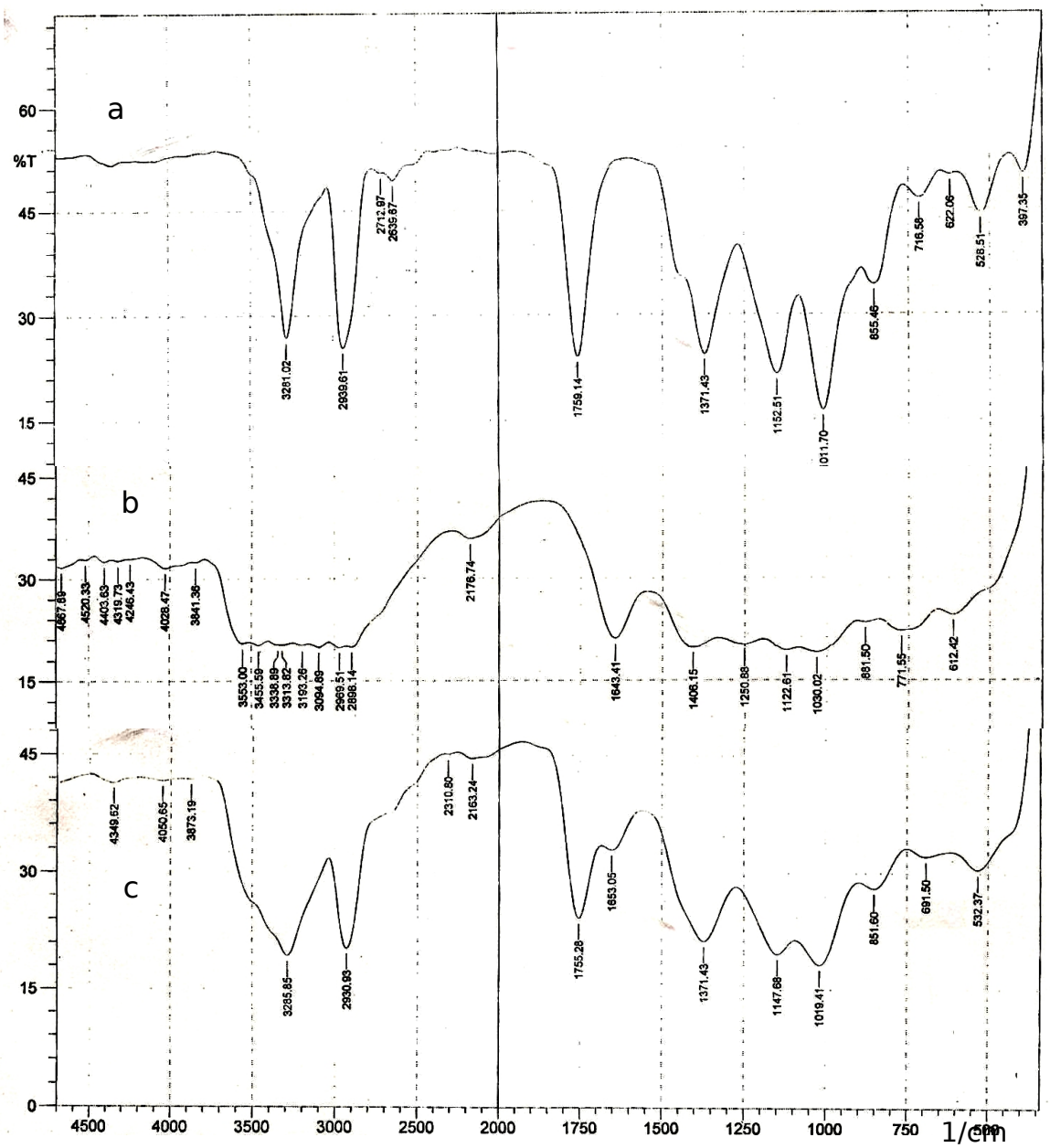

Figure 11 FTIR spectra of (a) artesunate (b) prosopis gum (c) artesunate + prosopis gum

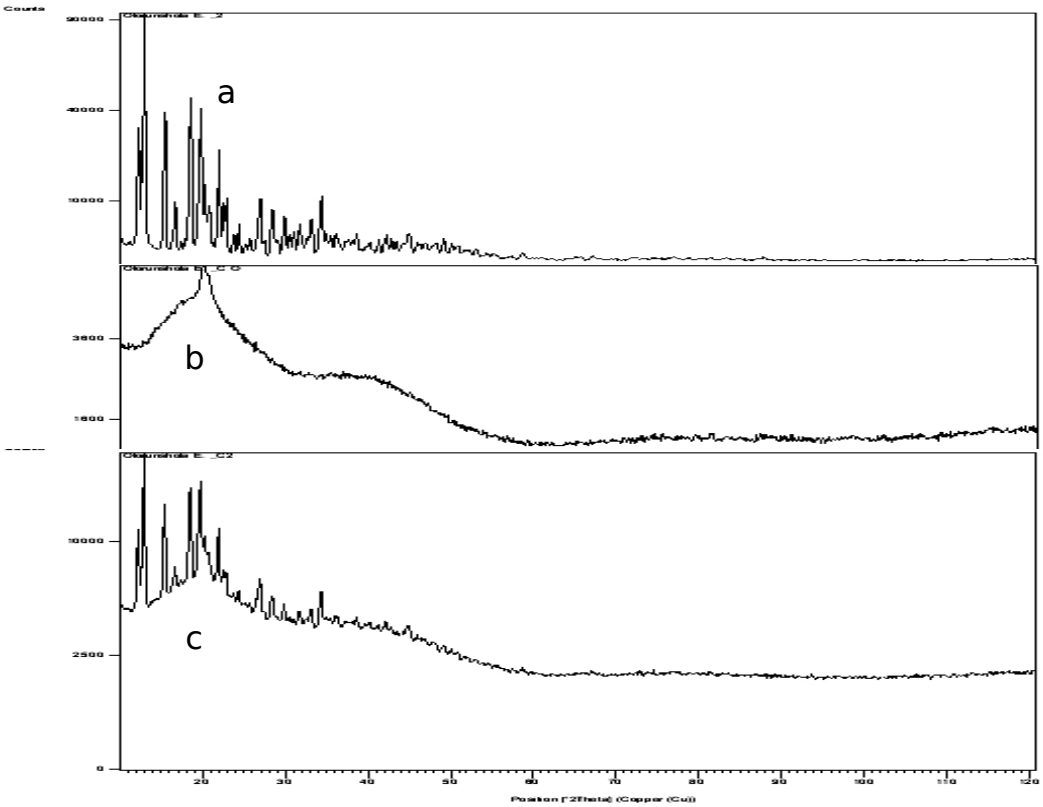

Figure 12 XRD patterns of (a) artesunate (b) prosopis gum (c) artesunate + prosopis gum.

DISCUSSION

The first endotherm in the thermogram of artemether can be ascribed to melting of the drug being that the drug is in the crystalline form. The melting point of the drug was 125 ^{O}C based on the peak of the endotherm [15]. The exotherm can be ascribed to recrystallization of the drug while the diffuse endotherm (225 to 250 ^{O}C) can be ascribed to its second melting.

The first transition, an endotherm which peaked at 95 ^{O}C, in the thermogram of cashew gum/artemether mixture can be ascribed to melting of the drug and

enthalpy relaxation of the gum [16]. 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 the drug from 165 ^{O}C to 175 ^{O}C. The second endotherm (200 to 300 ^{O}C) which is a diffuse one without a clearly defined peak 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 866.07 cm^{-1} in the FTIR spectrum of artemether 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. 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 [17].

All the major peaks observed in the FTIR spectrum of artemether were retained 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 pronounced peak at 20 $^{0}2\Theta$ in the XRD pattern of pure cashew gum is typical of amorphous organic substance [18]. 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.

The first endotherm in the thermogram of artemether / prosopis gum mixture can be ascribed to enthalpy relaxation of prosopis gum and melting of artemether [16]. The presence of prosopis gum reduced the melting point of artemether from 125 ^{O}C to 85 ^{O}C. The 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 [19].

Prosopis gum and cashew gum had similar effects of lowering the melting point and raising the 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.

All the major peaks observed in the FTIR spectrum of pure artemether were retained in the presence of prosopis gum (Figure 5). However, there were slight changes in the location of the peaks. There was 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 [17]. 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 from 1,440.87 cm^{-1} to 1,442.80 cm^{-1}.

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 6). 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.

The first endotherm (with peak at 70 ^{O}C) in the thermogram of artesunate can be ascribed to the enthalpy relaxation of the drug while the exotherm (with peak at 120 ^{O}C) 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.*[20]. Melting point of 132 – 135 ^{O}C was reported by these researchers.

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 – cashew gum mixture can be attributed to enthalpy relaxation of cashew gum and that of artesunate [16] while 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. The exotherm can be attributed to recrystallization of artesunate 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.

The peak at 855.46 cm^{-1} in the FTIR spectrum of artesunate 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 [17].

The presence of cashew gum in the artesunate / cashew gum mixture resulted in shifts in the FTIR peaks of the drug. There was a positive shift for peaks appearing after 1,250 cm^{-1} (Figure 8). 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 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 major peaks of XRD of pure artesunate and artesunate / 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/cashew gum mixture. Therefore, no new compound was formed from interaction of cashew gum with artesunate.

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 – prosopis gum mixture can be ascribed to the enthalpy relaxation of prosopis gum and that of artesunate [16]. 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 while the last endotherm can be ascribed to melting of prosopis gum [15]. The melting point of prosopis gum was significantly reduced by the presence of artesunate.

All the major peaks observed in the FTIR spectrum of pure artesunate were observed in the spectrum of artesunate / prosopis gum mixture and 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 were found in the spectrum of artesunate / prosopis gum mixture. However, the corresponding peaks were found in the spectrum of prosopis gum. These include: the peaks at 1653.05 cm^{-1}, 3873.19 cm^{-1}, 4050.65 cm^{-1} and 4349.62 cm^{-1} (Figure 11).

All the major peaks in the XRD pattern of pure artesunate were observed in the pattern of artesunate / prosopis gum mixture. There were slight changes in the position and d-spacing of the peaks. These can be attributed to the presence of prosopis gum – an amorphous substance [18]. The greatest extent of dislocation was observed in the peak at position 20.84 $^{0}2\Theta$ of artesunate spectrum in the presence

of the gum. There was elevation of the base level and hence reduction in the intensity of the peaks in artesunate / prosopis gum mixture. There was no new peak in the spectrum of artesunate / prosopis gum mixture showing that no new compound was formed from the mixture of the drug and the glycopolymer.

This study is a pre-formulation study and further work as formulation study can be carried out using the glycopolymers and the drugs. If the glycopolymers are to be used for the formulation of artemisinin-based combination therapy, there is a need to investigate any possible adverse interaction between the glycopolymer and the non-artemisinin antimalarial to be combined before the actual formulation.

CONCLUSION

No adverse interaction was observed in any of the drug – gum combinations. Therefore, the two gums are compatible with artemether (a lipid-soluble artemisinin) and artesunate (a water-soluble hemisuccinate artemisinin) and the gums could be investigated for the delivery of these drugs.

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