

Optimization of artesunate delivery by formulation in a delayed release prosopis hemicellulose matrix

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ABSTRACT

This study was aimed at formulating artesunate in a hemicellulose – based matrix for an optimized delivery. Artesunate (ATS) tablets containing varying concentrations of prosopis gum (PRG) in the range of 1 to 4% w/w were formulated. Tablets containing 3% w/w standard acacia gum (ACG) were also formulated to serve as a control. Tablet density, tensile strength, swelling index and swelling time were determined. Drug release and permeation were also studied. There were no significant differences in tablet density and in swelling index but tensile strength and swelling time increased significantly with increase in concentration of PRG. Rate of drug release from tablets containing 3% w/w ACG was faster than those containing same concentration of PRG. Tablets containing 4% w/w PRG brought forth cumulative drug release of 27.2%, 57.0% and 78.6% in 30 min, 60 min and 120 min respectively. All PRG batches brought forth complete drug permeation within 180 min. Prosopis gum at concentration of 4% w/w can delay the release of artesunate so that 57.0 to 78.6% of the drug is released at the gastric region while 21.4 to 43.0% is released at the intestinal region of the gastrointestinal tract for optimized delivery of the drug.

INTRODUCTION

Artemisinin and its derivatives are generally effective in treating severe and multi-drug resistant forms of *Plasmodium falciparum* malaria (Augustijns *et al.*, 1996). The World Health Organization's recommendation of artemisinin – based combination therapy for malaria has led to increased and wide use of this class of antimalarial (Chen, 2014). They are rapidly absorbed with peak plasma level occurring in 1 – 2 hours. They have half-lives of 1 – 3 hours (Rosenthal, 2004). The major physicochemical challenge with artemisinin, the parent compound, is its poor solubility which led to the search for the derivatives with better solubility and better antimalarial efficacy.

Artemether (which is lipid-soluble) and artesunate (which is water-soluble) are the two most commonly used of the derivatives (Rosenthal, 2004). The metabolism of artesunate to dihydroartemisinin is strongly pH-dependent and the drug is less stable at acidic pH (Olliaro *et al.*, 2001). In the stomach (pH 1.2), it has a half-life of less than 1 hour while at neutral pH, the half-life is over 7 hours (Olliaro *et al.*, 2001). Hence, the drug is short-lived when the dissolution occurs in the stomach; and delaying the dissolution will lead to prolonged and pronounced antimalarial activity.

Enteric coating is the most common method of protecting drugs from gastric environment to ensure dissolution in the intestine (Tirpude and Puranik, 2011). However, high cost and technology are some of the challenges of coating over conventional tableting. Therefore, a search for appropriate excipient for conventional tableting that will enable delayed release of artesunate is a good alternative to enteric coating.

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Hemicellulose hydrogels had been shown to be useful for controlled drug delivery. Afzelia gum, a xyloglucan hemicellulose, was shown to be a hydrogel with potential for use as a sustained delivery excipient (Builders *et al.*, 2009). Wheat straw hemicellulose was used for controlled delivery of acetylsalicylic acid and theophylline (Sun *et al.*, 2013). The polymer experienced swelling at the gastric pH but disintegrated and dissolved at higher pH to release the drugs. The hydrogel protected the drugs from the acidic environment of the stomach.

Prosopis gum from *Prosopis africana* seed is a hemicellulose consisting of xylose, galactose, glucose and fructose as the major monosaccharide units (Attama *et al.*, 2000) and could delay the release of artesunate from tablet when used for the drug delivery. Characterization of the gum in a previous work (Olorunsola *et al.*, 2016) showed that the presence of prosopis gum had no noticeable effect on the melting point of artesunate as revealed in their differential scanning thermograms. However, the FTIR spectroscopy showed that the presence of the polymer caused reduction in the height of the peaks in the spectrum of artesunate; but no new peak was formed in the interactions. This study is aimed at delaying the release of artesunate by formulation in prosopis hemicellulose matrix for the purpose of optimizing the delivery of the drug.

MATERIALS AND METHODS

Materials

The materials used were: artesunate powder – ATS (IPCA Laboratory, India), *Acacia senegal* gum - ACG (BDH Chemicals, Poole, England), lactose (Surechem Products Ltd., England), magnesium stearate (Riedel-De Haen, Germany), maize starch B.P (BDH Chemicals, Poole, England), talc (BDH Chemicals, Poole, England) and prosopis gum which was extracted and characterized in our previous work (Olorunsola *et al.*, 2016).

Ethical approval

Ethical approval for experimentation involving laboratory animal was obtained from Ethics Committee of Faculty of Pharmacy, University of Uyo, Uyo, Nigeria (protocol number UU/PH/002). The pig was housed in a cross-ventilated room and later sacrificed in accordance with internationally accepted laboratory animal use and the guidelines and rules for animal experimentation.

Preparation of tablets

Artesunate granules containing varying gum concentrations as matrix former (1.0, 2.0, 3.0 and 4.0% w/w) were prepared by wet granulation. A batch containing 3% w/w of standard acacia gum as control was also produced. The preparations were such that 275 mg tablet contained 50 mg of artesunate and varying concentrations of polymer as shown in Table 1. The artesunate powder, lactose and maize starch B.P were weighed individually and dry-mixed for 5 min and then moistened

with mucilage of the polymer. The wet mass was screened through a 2.0 mm sieve, dried in a hot air oven (Gallenkamp, Germany) at 60 °C for 1 h and screened again through a 1.0 mm sieve. Talc and magnesium stearate were weighed and gently blended with the dried granules over a period of 3 min. The resulting granules were tableted at 30 KN compaction force using a single punch (size 8.00 mm) tableting machine (Erweka, Germany).

Table 1: Formula of artesunate tablets.

Ingredient	B A T C H E S				
	ACG3	PRG1	PRG2	PRG3	PRG4
Artesunate powder (%)	18.20	18.20	18.20	18.20	18.20
Maize starch B.P (%)	10.00	10.00	10.00	10.00	10.00
Lactose (%)	66.80	68.80	67.80	66.80	65.80
Acacia gum (%)	3.00	-	-	-	-
Prosopis gum (%)	-	1.00	2.00	3.00	4.00
Talc (%)	1.50	1.50	1.50	1.50	1.50
Magnesium stearate (%)	0.50	0.50	0.50	0.50	0.50

Evaluation of tablets

Compact density

The dimensions (diameter and thickness) of the tablets were determined using digital caliper (Z 540-1, USA) while the masses were determined using Mettler analytical balance. Compact density, CD, was calculated using equations (1) and (2).

$$CD = \frac{m}{V} \quad (1)$$

$$V = \pi r^2 t \quad (2)$$

Where m = mass of compact, V = volume, r = radius and t = thickness of tablet.

Tensile strength

The tensile strength, T, of tablet was determined using hardness tester (PTB 301, Pharmatest Switzerland) and by applying equation (3) as applied by Odeku *et al.* (2005).

$$T = 2F/\pi dt \quad (3)$$

Where F is the load needed to cause fracture, d is tablet's diameter and t is the thickness.

Swelling properties

The swelling properties of tablets were determined using the modified form of the method described by Ngwuluka *et al.* (2015). Tablet was weighed and dropped in a beaker containing 50 ml of 0.1 N HCl. The swollen tablet was removed from the medium at 15 min intervals over a period of 2 h, the medium was blotted out and the tablet was reweighed. The highest weight obtained and the last time swelling was observed were recorded. The swelling index was calculated using equation (4).

$$\text{Swelling index} = (W_t - W_o)/W_o \quad (4)$$

Where W_t is the highest weight obtained which occurred at time t; and W_o is the initial weight of tablet.

Dissolution characteristics

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 N hydrochloric acid thermostatically maintained at 37.0 ± 0.5 °C. The apparatus was set to a rotational speed of 100 rpm for 2 h. Samples (10 ml) were taken at 20 min intervals with subsequent replacement with equal volume of the dissolution medium. Each withdrawn sample was filtered and diluted with pure dissolution medium. The absorbance of samples was taken at 216 nm (USP Medicine Compendium, 2013) using a UV spectrophotometer (UNICO Shanghai Instrument, China). A graph of cumulative percent drug released was plotted against time.

Permeation characteristics

Simulated intestinal fluid (SIF) was prepared using the method as described by Adikwu *et al.* (2005). The permeation study was carried out using the modified method of Sharma *et al.* (2013). Each segment of the pig intestine was tied at one end and filled with 5 ml of simulated intestinal fluid (pH 6.8). The tablet was introduced into the donor compartment and then tied at the other end. The donor chamber was subsequently immersed into a dissolution apparatus containing 900 ml of the receptor medium of the same composition as the donor medium. The temperature was maintained at 37 ± 0.5 °C and the apparatus was set to operate for 6 h.

Aliquots (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 an ultraviolet spectrophotometer (UNICO Shanghai Instrument, China) at 216 nm. A graph of cumulative percent drug permeated was plotted against time. The time for 95% drug permeation ($t_{95\%}$) was read from the plot. Value of steady state drug flux (J) was calculated using the equation:

$$J = \frac{dQ}{dt A} \quad (5)$$

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 percent drug permeated versus time. The permeation coefficient (K_p) was calculated using the equation:

$$K_p = \frac{J}{C} \quad (6)$$

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

Data analysis

All measurements were taken in triplicates and presented as mean \pm S.E.M. Data analysis was done using one-way analysis of variance 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.

RESULTS AND DISCUSSION

Physical properties of tablets

Some physical properties of the tablets are shown in Table 2. There was no significant difference in the density of tablets containing different concentrations of gum. However, the tensile strength increased with increase in concentration of prosopis gum; and the tensile strength of tablet containing PRG3 was higher than that of ACG3.

Table 2: Some physical properties of tablets (n = 3, mean \pm S.E.M).

Batch	Density (g/cm^3)	Tensile strength (MN/m^2)
ACG3	1.11 ± 0.01	0.82 ± 0.08
PRG1	1.09 ± 0.01	0.73 ± 0.01
PRG2	1.10 ± 0.04	0.92 ± 0.04
PRG3	1.10 ± 0.01	0.95 ± 0.01
PRG4	1.12 ± 0.03	1.11 ± 0.06

ACG3= 3% w/w acacia gum, PRG1= 1% w/w prosopis gum, PRG2= 2% w/w prosopis gum, PRG3= 3% w/w prosopis gum, PRG4= 4% w/w prosopis gum.

Tablet density is an inverse measure of the volume (size) of the compact. This parameter can be influenced by both compaction factors and the physical properties of the material to be compacted (Alderborn, 2007). To minimize variation in compaction factors, compaction was carried out at 30 KN (based on the pilot study) for all the batches. There was no significant difference in the density of tablets containing different concentration of the gums (Table 2). Hence, the concentration of the hemicellulose (prosopis gum) had no significant effect on the tablet size and density. Densification is a process of volume reduction which occurs as pressure is applied to a powder bed (Alebiowu and Itiola, 2003).

Compaction process can result in consolidation (volume reduction), elastic deformation, plastic deformation or brittle fracture (Bodga, 2002). On application of the compaction pressure of 30 KN, the extent of volume reduction was not significantly different. Hence, the polymer concentration has no significant effect on the extent of densification.

The tensile strength of the tablets increased with increased in concentration of PRG. Tensile strength depends on the amount of plastic deformation which occurs during compaction (Odeku and Itiola, 2007). Therefore, concentration of PRG contributed more to plastic deformation rather than to volume reduction as pressure was applied. Tensile strength is a reliable means of measuring tablet strength because it takes into consideration the tablet dimensions (Halenius *et al.*, 2014).

Swelling characteristics

The swelling characteristics of tablets are shown in Table 3. Swelling was not obtained for tablet containing ACG but the tablet dissolved within 2 min after being introduced into the medium. Swelling index and swelling time increased with increase in the concentration of PRG.

Prosopis gum, like other hemicelluloses, is a swellable polymer (Sun *et al.*, 2013). The proportion of the gum used in

relation to the tablet (1 - 4% w/w) was small and this could be responsible for the insignificant difference in the swelling index. However, there was a significant difference in the swelling time; and the time increased with increase in the polymer concentration. The swelling time was taken as the last time swelling was observed. After the swelling time, the weight of the tablet continued to decrease until the tablet finally dissolved.

Table 3: Swelling characteristics of tablets (n = 3, mean \pm S.E.M).

Batch	Swelling index	Swelling time (min)
ACG3	-	-
PRG1	1.13 \pm 0.02	20.00 \pm 5.00
PRG2	1.17 \pm 0.03	55.00 \pm 5.00
PRG3	1.18 \pm 0.03	75.00 \pm 0.00
PRG4	1.25 \pm 0.04	85.00 \pm 5.00

ACG3= 3% w/w acacia gum, PRG1= 1% w/w prosopis gum, PRG2= 2% w/w prosopis gum, PRG3= 3% w/w prosopis gum, PRG4= 4% w/w prosopis gum.

Drug release profile

The dissolution profiles of tablets are shown in Figure 1. Tablets containing 3% w/w ACG brought forth drug release of 75% within 30 min and complete drug release within 1 h. There was 90.7%, 82.3%, 66.5% and 57.0% cumulative drug release in 1 h from tablets containing PRG1, PRG2, PRG3 and PRG4 respectively. Also, there was complete drug release in 2 h from tablets containing PRG1 and PRG2; and 85.7% and 78.6% within same period from PRG3 and PRG4 respectively.

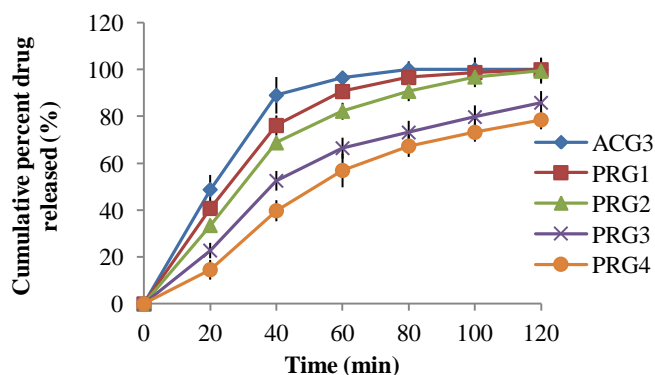


Fig. 1: Dissolution profile of artesunate tablets containing different gum concentrations.

Acacia gum is only suitable for immediate release formulation as it gave complete drug release within 1 h (Figure 1). The gastric residence time (GRT) in normal individuals is 5 min to 2 h (Ashford, 2007). About 79% drug release was obtained from formulation PRG4 at 2 h (upper limit of GRT) and 57% drug release in the gastric region and 43% release in the intestinal region are obtainable from PRG4 in an average individual. There is a need for the use of moderate concentration of PRG as 4% w/w to prevent excessive delay of onset of action. Since artesunate has a prolonged half-life at higher pH (Tirpude and Puranik, 2011), the antimalarial activity of the drug will be prolonged when substantial amount of the drug is released in the intestine.

Permeation profile

The graph of cumulative percent drug permeated versus time of permeation is shown in Figure 2 while the permeability data are shown in Table 4. The steady state drug flux was reached in 30 min for ACG3 and 60 min for PRG1, PRG2, PRG3 and PRG4. Cumulative percent drug permeated in 60 min decreased with increase in concentration of PRG but the steady state drug flux increased with increase in concentration of PRG. The time for 95% drug permeated for tablets containing PRG was not significantly different.

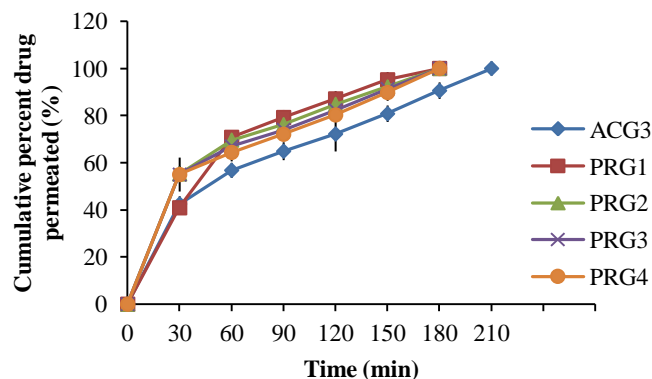


Fig. 2: Permeation profile of artesunate tablets containing different gum concentrations.

Table 4: Permeability data of tablet formulations (n = 3, mean \pm S.E.M).

Batch	Drug flux ($\mu\text{g}/\text{cm}^2 \cdot \text{s}$)	Permeation coefficient $\times 10^{-6}$ (cm/s)	Time for 95% permeation (min)
ACG3	0.17 \pm 0.03	16.65 \pm 3.11	195.33 \pm 6.76
PRG1	0.14 \pm 0.01	14.41 \pm 1.05	154.00 \pm 7.56
PRG2	0.15 \pm 0.03	15.19 \pm 3.11	160.67 \pm 5.00
PRG3	0.19 \pm 0.01	18.72 \pm 0.68	168.67 \pm 7.34
PRG4	0.22 \pm 0.04	22.03 \pm 4.23	170.33 \pm 5.34

ACG3= 3% w/w acacia gum, PRG1= 1% w/w prosopis gum, PRG2= 2% w/w prosopis gum, PRG3= 3% w/w prosopis gum, PRG4= 4% w/w prosopis gum.

The steady state drug flux was reached earlier for tablet containing ACG. The delayed release and delayed steady state drug flux from prosopis gum matrices can be linked to the high binding strength of the gum and its hemicellulosic nature (Attama *et al.*, 2000). However, the permeation coefficient at steady state increased with increase in concentration of prosopis gum. Hemicelluloses experience more of swelling at gastric pH but disintegrate and dissolve at higher pH to release the incorporated drugs (Sun *et al.*, 2013). The high bioadhesive strength of prosopis gum (Attama *et al.*, 2000) was found to be favorable for permeation enhancement for already released drug. The increase in time for 95% drug permeation despite the increase in permeation coefficient (at steady state) can be linked to the delay in reaching the steady state as the concentration of the polymer was increased.

Even though the steady state drug flux was delayed when the drug was formulated in matrices of PRG, the time for 95% drug permeation was shorter compared to formulation with ACG (Figure 2). According to Suputtamongkol *et al.* (2001), artesunate has t_{max} of 90 min achieving complete absorption at about 180

min. Therefore, the eventual time of drug permeation was not adversely affected by formulation in matrix of prosopis gum. Delaying the release of the drug by formulation in this hemicellulose matrix is effective for optimizing the delivery since a substantial amount is released at the later part of GRT and in the intestine. The half-life of artesunate increases by up to seven folds between the gastric pH and intestinal pH (Olliaro *et al.*, 2001).

Formulation of artesunate in a hemicellulose matrix as a means of delaying the release of the incorporated drug has some advantages over enteric coating. The process of tableting is simpler, cheaper and less equipment is involved. Unlike in coating where the polymer is used as outer coat for the tablet, the polymer is simply mixed or granulated with other excipients before tableting in matrix formation. Also, the onset of action of drug formulated in hemicellulose matrix is not excessively delayed since part of the drug is released in the stomach while the remaining part is released in the intestine. One major challenge with polymers of natural origin is the batch to batch variation in quality. Factors that could be responsible for this variation include the geographical source, species variation and processing variables such as method of extraction and type of solvent used. Batch to batch variation has a significant effect on the performance of these polymers. Therefore, care should be taken in obtaining polymer of good quality for use in drug delivery. One of the reliable ways of detecting batch to batch variation of a polymer is by rheological evaluation of a specific concentration of dispersions of different batches (Mancini *et al.*, 1996). This method can be used to ensure the quality of prosopis gum.

CONCLUSION

Rate of drug release from a tablet containing acacia gum is faster than that of a tablet containing same concentration of prosopis gum. All the batches containing prosopis gum can achieve complete drug permeation within 180 min. The gum, at a concentration of 4% w/w can delay the release of artesunate such that 57.0 to 78.6% of the drug is released at the gastric region while 21.4 to 43.0% is released at the intestinal region where the drug has longer half-life. Therefore, the gum at this concentration can be used for optimization of the delivery of the artesunate.

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