

***Entandophragma angolense* Gum as a Novel Binder and Mucoadhesive Component in Oral Tablets**

O.A. ADETUNJI*, M.A. ODENIYI AND O.A. ITIOLA

Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Ibadan, Nigeria.

The present work reports on the mucoadhesive and mechanical properties of the water-soluble gum obtained from *Entandophragma angolense* when incorporated in oral tablets. Flat-faced chlorpheniramine maleate tablets containing the gum were formulated. The potential for chemical interaction between the gum and drug was evaluated by UV spectroscopy. The mucoadhesive, mechanical and release properties of the tablets were evaluated. The rates of water uptake and erosion were determined for the tablets. The detachment time for the tablets increased from 78.71 ± 0.43 to 84.28 ± 0.75 min, and from 33.57 ± 0.48 to 79.27 ± 4.7 min as the amount of gum per tablet was increased from 2.5 to 10.0% w/w, respectively. The drug release time for all tablets increased with binder concentration. UV spectroscopy suggested the absence of chemical interactions. The novel natural gum compared favourably with established mucoadhesive polymers namely hydroxypropylcellulose and gelatin. The mucoadhesive, mechanical and release properties were a function of polymer concentration.

Key words: *Entandophragma angolense*, chlorpheniramine maleate tablets, mucoadhesion, mechanical properties

INTRODUCTION

Mucoadhesion has been defined as the attachment of a drug carrier system to a mucosal surface [1,2,3]. Mucoadhesive drug delivery systems are developed to obtain sustained drug delivery via various mucous membranes for either local or systemic delivery of poorly absorbed drugs such as peptides and proteins [4,5,6] as well as drugs that are subject to first pass metabolism [7,8,9]. This method of drug administration is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of drugs into the systemic circulation [10,11]. Target sites include various mucous membranes such as those in the gastrointestinal tract [12], eye [13], cervix and vagina [14], and oral and nasal cavities [8,15].

Mucoadhesive polymers have been utilized in many different dosage forms such as tablets, tapes, films, patches, semisolids and powders [11]. However, sustained-release dosage forms have received most attention amongst all the controlled drug delivery systems due to their conventional usage [16]. Carrier systems that release drugs based on a time-independent rate (zero order kinetics) for an extended period of time are usually considered optimal [17]. The model membranes used for investigation of mucoadhesion vary from mouse peritoneal membranes to cellulosic paper disks impregnated with mucous gel [3,17].

A lot of attention has been given to hydrophilic polymers in the design of oral drug delivery systems due to their flexibility, cost-effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivatives such as methylcellulose, hydroxypropylmethylcellulose, and sodium carboxymethylcellulose are generally considered to be stable and safe as excipients in the development of oral controlled release dosage forms. These semisynthetic polymers are quite expensive when compared with natural polymers such as guar gum and alginates, while the natural polymers are nontoxic and readily available [18].

The present study was designed to evaluate the hydrophilic natural gum obtained from *Entandophragma angolense* (ENTA) for its binding and mucoadhesive properties in tablet formulation. The gum is an exudate from the plant *Entandophragma angolense* which is indigenous in Tropical Africa. It is expected that this natural gum will not exhibit the gastro-intestinal side effects such as gastric irritation that are usually associated with the use of synthetic mucoadhesive polymers [3,19]. The binding and mucoadhesive properties of the gum were evaluated using chlorpheniramine maleate (CPM) as a model drug.

MATERIALS AND METHODS

The materials used were chlorpheniramine maleate powder (Sigma Chemicals, St. Louis, MO, and BDH Chemicals Ltd., Poole, U.K.), lactose B.P.

*Author to whom correspondence may be addressed.

(DVM Veghel, Holland), magnesium stearate B.P., industrial castor oil and hydroxypropylcellulose (HPC) (Aqualon, Hercules Inc., USA). The gum was obtained from the early morning exudates of the barks of *Entandophragma angolense* (Family: Meliaceae; synonym: *Swietenia angolensis*), available as a tree crop in the Botanical Gardens of the University of Ibadan, Ibadan, Nigeria.

The gum was purified by filtration. It was dissolved in water and the resulting solution was filtered through muslin cloth and then freeze dried [20,21]. The bioadhesion measurement technique using the rotating cylinder method (a slightly modified dissolution apparatus described in the USP) was employed for mucoadhesion studies [22].

Two types of flat-faced tablets were prepared: uncoated tablets (type A), and tablets in which all but one face of the tablet were coated with

industrial castor oil using a modified coating technique to form type B tablets (these tablets are intended to release the drug through the uncoated face of the tablet). Wet granulation and direct compression techniques were used in preparing type A tablets for a number of formulations. Other tablet formulations were prepared by direct compression techniques only.

Direct compression

The formulae for the directly compressed tablets are listed in Table 1. They were prepared, initially, by premixing the *Entandophragma angolense* gum and chlorpheniramine maleate for about 15 min. Subsequently, lactose and castor oil were incorporated and the resulting composition mixed for a further 15 min. Magnesium stearate was then added and the mixing continued for an additional 7 min. The mixing was performed by mechanical rotation at 225 rpm.

Table 1: Formulae for direct compression of tablets

Ingredients	I	II	III	IV	V
CPM (mg)	5	5	5	5	5
Lactose (mg)	95	91	88.5	86	83.5
ENTA (% w/w)	-	2.5	5.0	7.5	10.0
Castor oil (% w/w)	1	1	1	1	1
Magnesium stearate (% w/w)	0.5	0.5	0.5	0.5	0.5

CPM = chlorpheniramine maleate; ENTA = *Entandophragma angolense*.

Wet granulation

The formulae of the tablets prepared by wet granulation are listed in Table 2. The CPM, ENTA, and lactose were mixed using a mortar and pestle and then wet massed with the water. The material was granulated using a Number 12 mesh sieve and the granules were dried at 60°C until the moisture content was about 1.5% w/w. The dried granules were resieved through a Number 16 mesh

sieve. Castor oil and magnesium stearate were then added and mixed with the dried granule by mechanical rotation at 225 rpm.

Tablet compression

The tablets were prepared using a Carver hydraulic hand press (model C, Carver Inc, Menomonee Falls, Wisconsin, U.S.A.) fitted with a pressure gauge reading up to 2.5 metric tonnes.

Table 2: Formulae for wet granulation of tablets

Ingredients	I	II	III	IV	V
CPM (mg)	5	5	5	5	5
Lactose (mg)	95	91	88.5	86	83.5
ENTA (% w/w)	-	2.5	5.0	7.5	10.0
Water	q.s.	q.s.	q.s.	q.s.	q.s.
Castor oil (% w/w)	1	1	1	1	1
Magnesium stearate (% w/w)	0.5	0.5	0.5	0.5	0.5

CPM = chlorpheniramine maleate; ENTA = *Entandophragma angolense*; q.s. = sufficient quantity.

Disintegration test

The disintegration time of type A tablets were determined in distilled water at $37 \pm 0.5^\circ\text{C}$ using Apex disintegration testing apparatus (Apex Construction Ltd., Northfleet Gravesent and Darford, Kent, U.K.). Tablets were placed on the wire mesh just above the surface of the water in the tube and the apparatus was started simultaneously with a stop clock. The tablets were kept in contact with distilled water contained in the tube. The time taken for all the tablets to disintegrate and pass through the wire mesh was recorded. Determinations were made in quadruplicate.

Crushing strength and friability tests

Ten tablets from each type A formulation were tested for diametrical crushing strength using Erweka TBH 28 hardness tester (Apparatebau GMBH, Germany). Measurements were made in quadruplicate and the crushing strength results were accepted only if the samples split clearly into two halves. A Veego tablets friability apparatus (Veego Scientific Devices, Mumbai, India) was used in determining the friability of type A tablets.

Dissolution tests

Dissolution studies were performed using a USP dissolution apparatus (basket method) at 100 rpm. The dissolution medium consisted of 900 ml of deionized water (pH 7.0) at $37^\circ \pm 0.5^\circ\text{C}$. Samples were analyzed for CPM by UV spectrophotometry using the SP6-450 UV/VIS spectrophotometer (Pye Unicam, Middlesex, England) at 262 nm. Both type A and type B tablets were tested and the experiments were performed in quadruplicate. For each formulation, the time to reach 80% CPM release ($t_{80\%}$) was calculated from the mean dissolution data.

Water uptake and erosion study

Directly compressed type B tablets were tested using 900 ml of deionized water (pH 7.0) at 37°C using a USP dissolution apparatus I. The tablets were immersed in water for varying times (without stirring) and the weights of the tablets (W_1) following equilibrium water uptake were determined using an analytical balance (Mettler, Hightstown, NJ). The tablets were dried in a hot-air oven at 40°C until the tablets attained a constant weight. Tablets were then reweighed

using the analytical balance (W_2). Water uptake and erosion were calculated using equations (1) and (2).

$$\text{Water uptake} = (W_1 - W_2)/W_2 \quad (1)$$

$$\text{Erosion} = (W_o - W_2)/W_o \quad (2)$$

Where: W_o = initial weight of the tablet

W_1 = weight of the tablet at time $t=0$

W_2 = dry weight of the tablet at time t

Chemical interaction studies

Mixtures consisting of different ratios of CPM/ENTA and either CPM or ENTA alone were scanned in the wavelength range 190-300 nm. The peak at 262 nm was monitored for any wavelength shift on a SP6-450 UV/Vis spectrophotometer (Pye Unicam, Middlesex, England).

Ex-vivo mucoadhesion studies

The studies of the mucoadhesion properties of the gum involved use of type A tablets formulated by direct compression technique. The rotating cylinder method (a slightly modified dissolution apparatus described in the USP) for mucoadhesion studies was employed [22]. A porcine intestinal segment of about 5×8 cm, obtained from the intestine of a freshly sacrificed pig by ethically acceptable means, was fixed with glue on a stainless-steel cylinder with the basolateral side of the intestine facing the cylinder. Then, the tablets containing different concentrations of the ENTA gum were pressed on the apical side and the cylinder was put into a medium containing about 100 ml of buffer medium. The rotation speed was set to 75 rpm. The time when the tablets detached completely from the mucosa was recorded.

RESULTS

Crushing strength and friability studies

The mechanical properties of type A tablets were assessed by the crushing strength and friability of the tablets. Table 3 presents values of crushing strength and friability for type A formulations, prepared by wet granulation and at a relative density of 0.90, which is representative of commercial tablets. There was an increase in crushing strength with corresponding decrease in friability values as the binder concentration for all formulations was increased. It has been established

that the presence of high concentration of binding agent leads to an increase in plastic deformation of the formulation and consequently to the formation of more solid bonds with increase in tablet strength and resistance to fracture and abrasion. The crushing strength-friability ratio (CSFR) also provides a parameter for measuring tablet strength [23]. Generally, the higher the CSFR value, the stronger the tablet. As shown in Table 3, there was an observable increase in the CSFR value of the assay tablets with increase in binder concentration.

The disintegration time values for the tablets at a relative density of 0.90 are also presented. An increase was observed in disintegration time with increase in binder concentration for all formulations, although there were no significant ($p>0.05$) differences in disintegration time between the formulations. However, all tablets passed the British Pharmacopoeia specifications for disintegration of uncoated tablets within 15 min.

Table 3: Crushing strength, friability, crushing strength-friability ratio (CSFR) and disintegration time for directly compressed tablets containing ENTA at 0.90 relative density

ENTA (% w/w)	Crushing strength	Friability (%)	CSFR	D (min)
0.0	43.27 ± 1.02	3.63 ± 0.02	11.92	4.17 ± 1.21
2.5	81.23 ± 1.31	2.53 ± 0.03	32.10	8.99 ± 1.07
5.0	87.48 ± 1.02	1.63 ± 0.02	53.66	9.72 ± 0.34
7.5	91.21 ± 2.09	0.74 ± 0.02	123.26	11.13 ± 0.25
10.0	94.17 ± 1.21	0.36 ± 0.04	261.58	12.85 ± 1.04

Values are reported as mean ± sd; n=4; D=disintegration.

Dissolution studies

The dissolution profiles of CPM from the type A tablets prepared by direct compression are shown in Figure 1. The mean $t_{80\%}$ values for both type A and type B tablets for both direct compression and wet granulation are given in Table 4. From the dissolution profiles and the $t_{80\%}$ values, it was observed that direct compression was more profound in the gradual release of CPM from the

tablets compared with tablets prepared by wet granulation. A direct relationship was noted between increasing the amounts of ENTA in the tablet and $t_{80\%}$ for directly compressed tablets.

Chemical interaction studies

Results of UV studies suggested the absence of a chemical interaction between CPM and ENTA.

Table 4: Values for $t_{80\%}$ for directly compressed and wet granulated tablets

ENTA (% w/w)	Direct compression $t_{80\%}$ (min)		Wet granulation $t_{80\%}$ (min)	
	Type A	Type B	Type A	Type B
0	9.07 ± 1.17	11.27±2.01	9.3±0.24	11.27±2.0
2.5	78.71 ± 0.43	40.61±7.53	33.57±0.48	39.28±3.9
5.0	75.73 ± 1.05	97.46±8.72	-	-
7.5	75.82 ± 0.14	103.14±4.52	-	-
10.0	84.28 ± 0.75	111.73±3.37	79.27±4.7	100.83±2.6

Values are reported as mean ± sd; n=4.

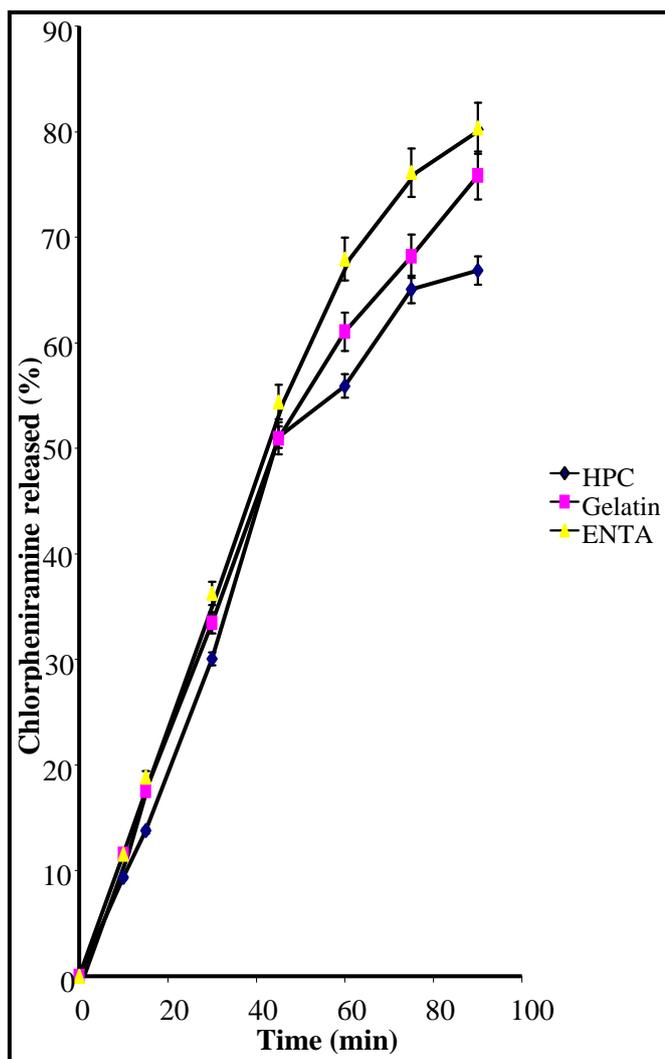


Figure 1. Drug release profile for chlorpheniramine maleate from tablet formulations containing 10.0% w/w polymer concentration.

Water uptake and erosion studies

The water uptake and erosion rates of type B tablet formulations were calculated from the slopes of the relevant linear plots and the results are listed in Table 5 and Figure 2. The initial, or instantaneous, uptake is given by the intercept of the curve with the y-axis. As the amount of ENTA was increased, the initial water uptake rate was increased, while the rate of tablet erosion was reduced.

Table 5: Erosion rates for type B tablets

ENTA (% w/w)	Initial	Rate (%/min)
0	7.46	1.71
2.5	4.78	1.45
5.0	1.37	0.37
7.5	0.62	0.31
10.0	0.18	0.18

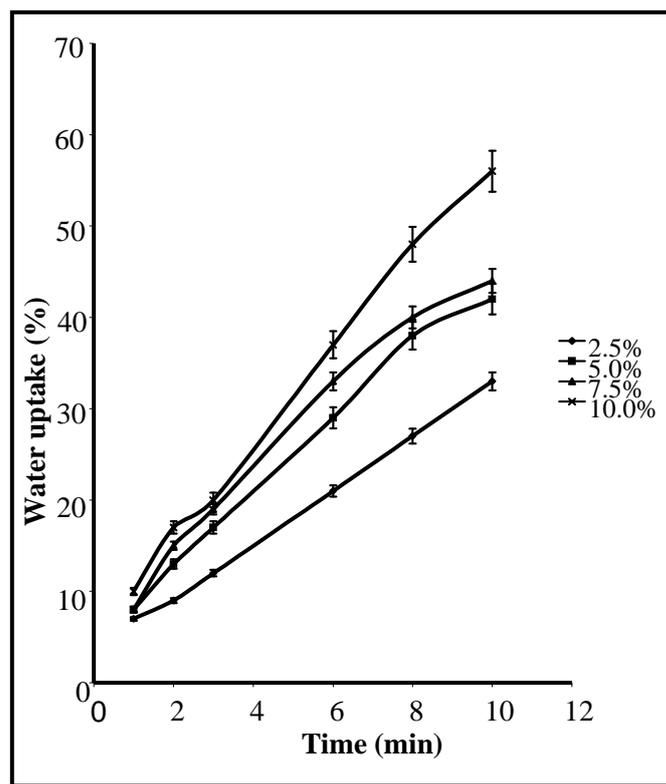


Figure 2: Graphical representation of the water uptake versus time for *E. angolense*-containing formulations of chlorpheniramine maleate at different concentrations.

Mucoadhesion studies

Figure 3 provides the results of the time observed for the mucoadhesive nature of the tablets formulated by direct compression and containing different concentrations of ENTA gum, gelatin and hydroxypropylcellulose. It was observed that the time of adhesion of the tablet to the intestine increased as the concentration was raised from 2.5% to 10.0% w/w.

DISCUSSION

Type B tablets were practically impervious to the passage of CPM. The unidirectional release of CPM, as a result of coating all surfaces of the tablet, except one flat face, was established. Direct compression technique, apart from being a simple technique, was more efficient in ensuring the gradual release of CPM from the tablets compared to tablets prepared by wet granulation. Type A tablets formulated by wet granulation, however, showed stronger mechanical properties compared with type A tablets formulated by direct compression. A direct relationship was noted between increasing the amounts of ENTA in the

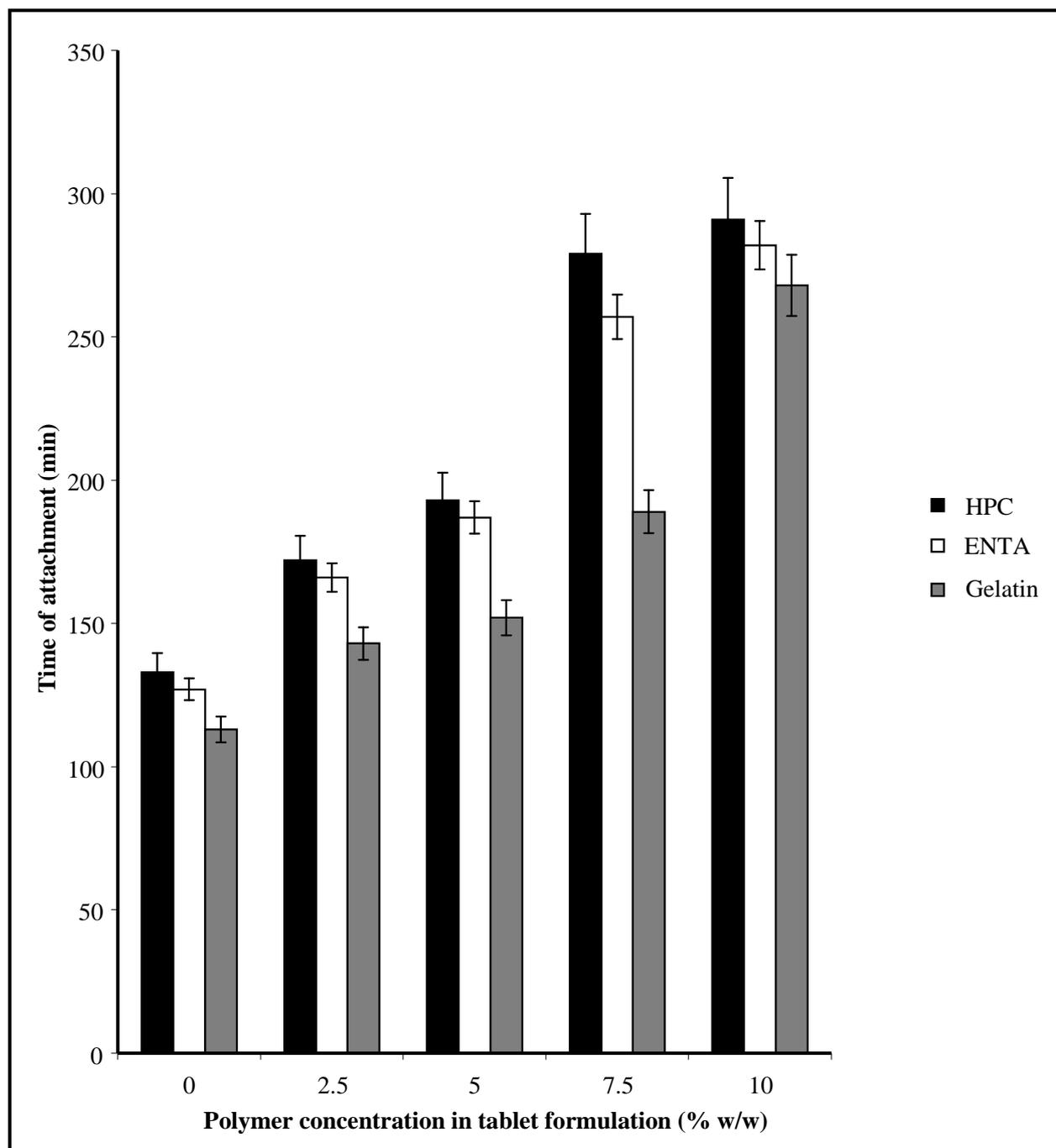


Figure 2: Values obtained for time of detachment from intestinal mucosa for ex-vivo mucoadhesive studies for chlorpheniramine maleate tablets containing *Entandophragma angolense* (ENTA), gelatin and hydroxypropylcellulose (HPC).

tablet and the $t_{80\%}$ value of CPM from directly compressed tablets. The gradual release of CPM in vitro due to the inclusion of ENTA was established by the $t_{80\%}$ values.

A linear relationship between increasing the amounts of hakea in the tablet and the $t_{90\%}$ value of CPM from directly compressed tablets has previously been demonstrated [20]. In the present study, a direct relationship was also observed

between increasing the amounts of ENTA in the tablet and the $t_{80\%}$ value of CPM from directly compressed tablets. It is noteworthy that there is potential use of the gum as a sustained release matrix with increasing concentration in tablet formulations. The reduction in the sustained-release effect of the ENTA in the tablets prepared by wet granulation values was probably due to a combination of wetting at room temperature and drying at an elevated temperature.

The amount of ENTA incorporated into the tablets was a critical factor in defining the resultant bioadhesive attachments. The experiments showed that tablets that had a higher concentration of ENTA adhered more to the porcine intestinal segment. A possible reason for this could be an increase in water uptake due to the ENTA content, which resulted in tablet swelling and consequent increase in the surface area of flexible chains responsible for increased bioadhesion time [20]. Thus, the release of CPM and the duration of mucoadhesion can be optimized by varying the amount of ENTA contained in the tablets. A similar trend was observed for the values obtained for time of detachment from porcine intestinal mucosa for CPM tablets formulated with gelatin and HPC as components. In both cases, the time of detachment increased as the gelatin and HPC concentrations increased. However, tablets that contained HPC adhered more to the porcine intestinal segment, whereas tablets containing gelatin as components adhered less on the porcine intestinal segment when compared with tablets that contained ENTA as shown in Figure 3. The rank order for mucoadhesion for the polymers was HPC > ENTA > gelatin.

Results in the present study suggest that the release of CPM and the duration of mucoadhesion can be optimized by varying the amount of gum contained in the tablet. While this observed phenomenon could have been due to a chemical interaction between gum ENTA, and the basic drug CPM, sustained release of CPM in the present study was due primarily to a gel barrier being formed and the slow relaxation of gum. This was confirmed by the lack of any chemical interaction between the two species as determined by UV spectroscopy [20].

The water uptake and erosion rate studies of the ENTA/CPM tablet formulations were aimed at determining whether the tablet would possess sufficient mucoadhesive properties and whether it can sustain the release of a drug. The ENTA/CPM tablets evaluated in the present study demonstrated an increase in water uptake and a decrease in erosion as the concentration of the ENTA was increased in the formulations. The imbibed water is initially responsible for the hydration of the polymer present in the superficial layers of the tablet, and presumably the outward diffusion of the aqueous drug was retarded, resulting in both a slower CPM release rate and slower tablet erosion.

CONCLUSION

The natural gum, *Entandophragma angolense*, may be used as a binder in achieving the formulation of CPM in oral tablets, and also for its mucoadhesive properties. The tablets produced had good mechanical and release properties with promise of sustained release with increased gum concentration. The mechanism by which CPM was released was probably due to slow relaxation of the hydrated gum. Also, the mucoadhesive properties of the gum can be modulated by altering the amount of the gum in the tablet formulation.

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