

Mucoadhesive slow-release tablets of theophylline: Design and evaluation

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Mucoadhesive tablets were prepared to evaluate the adhesive property of the gum obtained from seeds of *Caesalpinia pulcherrima* (CP) by comparing it with carbopol, hydroxy propyl methylcellulose (HPMC), and Chitosan. Physical parameters such as bulk density, tapped density, compressibility index, and Hausner's ratio values indicate good flow, the percentage of drug content was in the range of $96.4 \pm 0.97\%$, and various adhesive evaluation results reveal a good mucoadhesive property. The barium sulphate loaded tablet possesses strong mucoadhesive property, which was evident from prolonged adhesion in the same location of the stomach up to a period of 10 h, whereas the duration of adhesion found to be comparatively less with other polymers. From the results of *in vitro* and *in vivo* adhesive tests and *in vitro* release study the test agent (Gum) appears to exhibit considerable mucoadhesive property and mean residence time values when compared with tablets of carbopol, HPMC, and Chitosan.

Key words: *Caesalpinia pulcherrima*, mucoadhesive drug delivery, theophylline

INTRODUCTION

Delivery of drugs via the absorptive mucosa is easily accessible in body cavities, such as the ocular, nasal, buccal, rectal, and vaginal mucosa. It has the advantage of the dual biophysical and biochemical nature of the mucosal membrane. This readily absorbs drugs with hydrophilic and lipophilic drugs.^[1] Once the dosage form firmly sticks to the mucosal surface, its gastric residence time is prolonging until it is removed by turnover of mucins or by some other means. This is simple and yet highly innovative concept.^[2] Mucus is secreted from both non-specialized and specialized "Goblet" epithelial cells. It forms a diffusion barrier between the luminal substances. It may play important roles in immune response. They are either single-layered epithelium (stomach, small and large intestine) or multi-layered stratified epithelium (esophagus, cornea, and vagina).^[3] Mucus glycoprotein chemically consists of large peptide backbone with pendent oligosaccharide side chains whose terminal end is either sialic or sulfonic acid. The presence of sialic acid and sulfate residues and its high charge density play an important role in bioadhesion.^[4] Since the cationic form, the

D-glucosamine residue of *Caesalpinia pulcherrima* could interact with the sialic acid residues of mucin by electrostatic interaction.^[5]

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion.^[6] The most widely investigated group of mucoadhesive is hydrophilic macromolecules containing numerous hydrogen bonds forming groups,^[7,8] the so-called first-generation mucoadhesive. The presence of hydroxyl, carboxyl, or amine groups on the molecules favors adhesion. As typical hydrocolloid, glues if the formed adhesive joint is allowed to dry then they can form very strong adhesive bonds.^[9,10] Typical examples are carbomers, Chitosan, sodium alginate, and the cellulose derivatives. These were used initially as they are available "off-the-shelf" with regulatory approval, but in the last few years, new enhanced materials have been developed.^[11] In the present study, an attempt has been made to investigate the mucoadhesive property of the gum extracted from the seeds of *C. pulcherrima* belonging to family Fabaceae.^[12] The seeds are non-toxic and used variously as indigenous medicines in the Guiana's and S. America for stomachache, gall bladder problems, and kidney stones among other ailments.^[13] Theophylline an anti-

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DOI: 10.4103/0973-8398.63979

asthmatic drug that would be a suitable drug for the study since the condition of asthma will be worst during night hours.^[14]

MATERIALS AND METHODS

Materials

Theophylline, hydroxy propyl methylcellulose (HPMC) (Caplin Point, Pondicherry, India), talc, magnesium stearate (S.D. fine chemicals, Mumbai), barium sulphate, methanol (HPLC Grade) (E.Merck India., Mumbai), Chitosan (sigma, Germany), carbopol (Sigma, Mumbai), seeds of *C. pulcherrima* collected in and around Erode District (Tamilnadu). All other ingredients used were of analytical grade.

Method

Extraction and physicochemical characterization of gum obtained from the seeds of Caesalpinia pulcherrima

500 g of the seeds were collected, washed thoroughly with hot water, and soaked in 1 L of distilled water for 12 h.^[15] The tegument (an outer covering of the seeds) removed and the white portions of the kernels were separated. Then the seeds were ground to a fine powder mixed with 500 mL of

water to form a paste by continuous stirring for few minutes and kept aside for 12 h. The slurry was filtered through a muslin cloth. The filtrate was collected and kept undisturbed in a refrigerator for 12 h. The filtrate was precipitated by the addition of three volumes of acetone by stirring continuously for 15 min and the precipitated gum was washed thrice with acetone and dried in a vacuum drier, powdered, and passed through the sieve number 120 and kept in desiccator for further studies.

pH measurement

A 2% w/v dispersion of the gum was used for the study.^[16] Measurement of pH was carried out using a pH meter (Elico Li-120). The mean of three determinations was calculated and noted [Table 1].

Swelling studies of the natural adhesive agent

Discs of the gum were prepared by compressing (hardness-3 kg/cm²) in a cadmach single punch tablet machine. Each disc was 1.5 mm thick and 14 mm in diameter. The initial weights of the disc were recorded then placed in 500 mL of water, pH 1.2 and pH 7.4 buffer solution where allowed to swell at body temperature.^[17] At regular time intervals, the swollen discs were carefully removed, blot dried, and the weight gain was recorded. Water sorption is calculate using the formula:

$$\text{Swelling index} = [(w_2 - w_1) / w_1]$$

Where

w_1 → weight of natural adhesive agent before swelling and

w_2 → weight of natural adhesive agent after swelling.

The experiment repeated three times and the mean was calculated.

Mucoadhesive studies

Detachment force method

To characterize the mucoadhesive strength, the detachment force method was used.^[18] Mouth of a glass vial fixed with a fresh section of animal tissue from fundus portion of goat intestine, facing mucosal side out and kept in simulated gastric fluid (pH 1.2) without pepsin. Kept another portion of mucus side of exposed tissue over a rubber stopper and secured with an aluminum cap. The mucoadhesive tablet placed on the exposed mucus layer (later case), kept in contact with the former tissue which is connected with a pan in which the weight can be raised. At specific intervals, applied weight and the force required to detach measured for mucoadhesive strength [Table 4] [Figure 1].

Table 1: Results of physical parameters

Parameter	Results
	Caesalpinia pulcherrima gum
pH	6.5±0.5
Swelling index (after 6 h)	18.09±0.34
with, distilled water	13.33±0.28
pH – 1.2	12.12±0.29
pH – 7.4	
Viscosity (1% w/v)	
at 37°C	1.1158 Poise
45°C	0.9139 Poise
60°C	0.5090 Poise
Solubility	Hot water
Percentage yield	4.6% w/w of powder material

Table 2: Formula for oral mucoadhesive tablet (each tablet weighing 200 mg)

Ingredients	Quantity per tablet (mg)		
	F1CL	F2CL	F3CL
Theophylline	25	25	25
Natural mucoadhesive agent (CL)	25	50	75
Dicalcium phosphate	148	123	98
Magnesium stearate	1	1	1
Talc	1	1	1

Table 3: Results of powder parameters

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio
Caesalpinia pulcherrima	0.400±0.05	0.454±0.04	12.000±1.50	1.136±0.4

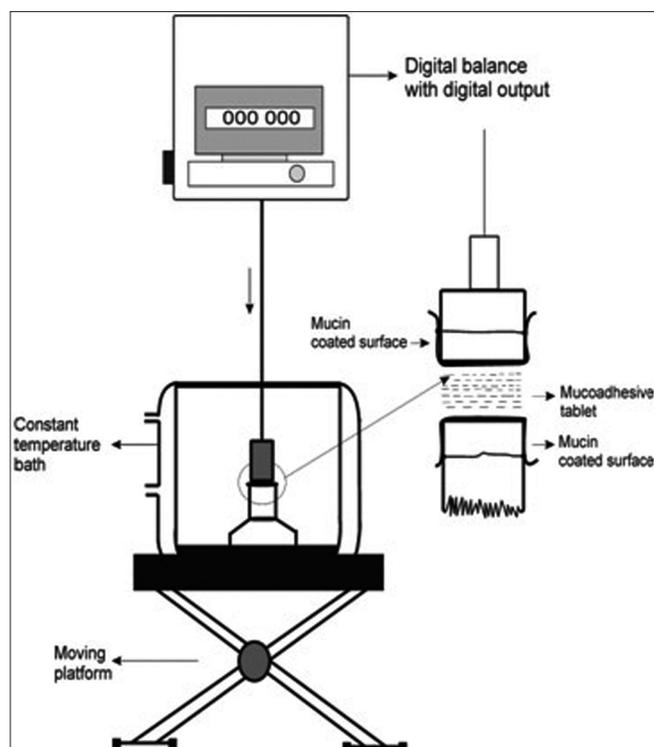


Figure 1: Mucoadhesive testing system by the detachment force method

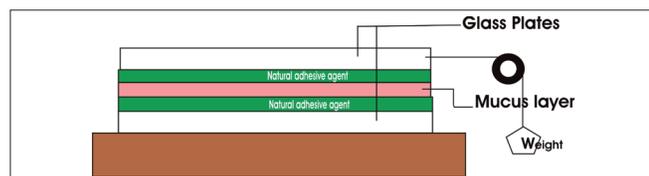


Figure 2: Shear stress measurement

Table 4: Different methods for mucoadhesive evaluation

Polymer	Time (min)	Shearing stress	Wilhelmy method	Detachment force
Test agent CP	15	236.79±5.6	1.35±0.3	42.1±0.7
	30	241.40±4.7	1.48±0.4	71.2±0.8
	60	284.21±6.0	1.70±0.5	88.4±1.2
Chitosan (g)	15	232.74±4.8	1.13±0.5	30.2±1.0
	30	242.90±5.0	1.24±0.6	58.6±0.8
	60	286.15±5.6	1.60±0.5	72.9±1.0
Carbopol (g)	15	203.63±4.6	1.16±0.6	26.0±1.1
	30	227.89±5.4	1.20±0.5	52.4±1.0
	60	273.77±4.4	1.52±0.3	65.4±1.6
HPMC (g)	15	191.46±5.6	0.76±0.4	18.6±0.9
	30	220.45±4.8	1.15±0.5	34.0±0.8
	60	257.44±6.6	1.26±0.4	50.6±1.6

Standard deviation = Mean of six values (n=6)

Shear stress measurement

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel

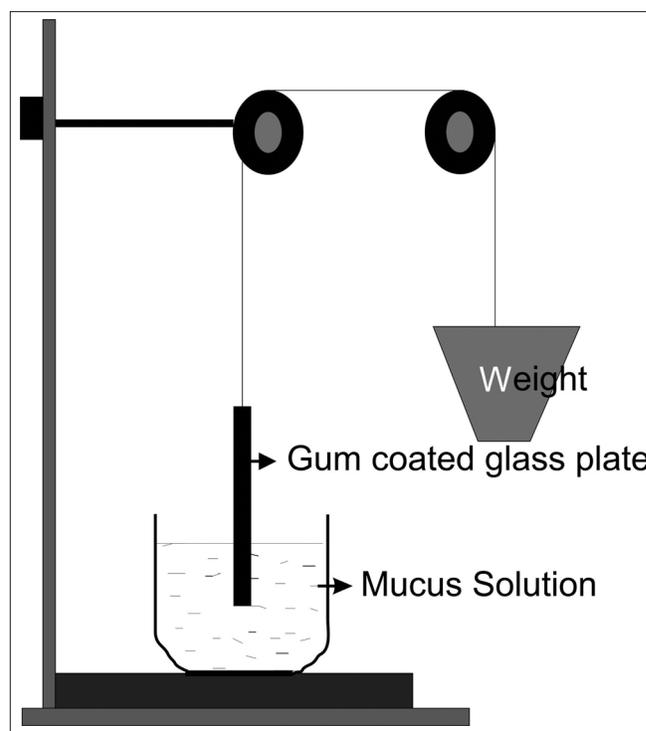


Figure 3: Wilhelmy plate method

to their place of contact of adhesion. The test was done by coating either side of the two slides with natural adhesive agent followed by the second layer coated with mucous layer.^[17] Mucus forms thin film between the two natural adhesive coated slides the test measures the force required to separate the two surfaces. In present study was used weight with reference to force [Table 4] [Figure 2].

Wilhelmy plate method

A small glass plate (2×5cm) was coated with 1% w/v of the mucoadhesive agent. The mucus gel was taken from goat intestine kept in a suitable container, where the above-mentioned glass plate can be kept in contact with gel in a balanced condition and the temperature was maintain at 30°C. Nylon thread was attached at one end of the glass plate. Provision was given to raise the weight (4) at the other end. At specified intervals, weight was added to detach the coated glass plate (2) from gel and the force required to pull the plate out of the gel (3) was determined under experimental condition. Six plates were tested for each material and the average weights required were calculated^[19,20] [Table 4] [Figure 3].

Preparation of mucoadhesive tablet

Theophylline mucoadhesive tablets were prepared using Cadmach[®] tablet machine by the wet granulation technique. The drug to adhesive agent ratio used was 1:1, 1:2 and 1:3 [Table 2].

In vitro release study

The *in vitro* release studies of theophylline 100 mg oral mucoadhesive tablet were carried out according to U.S.P

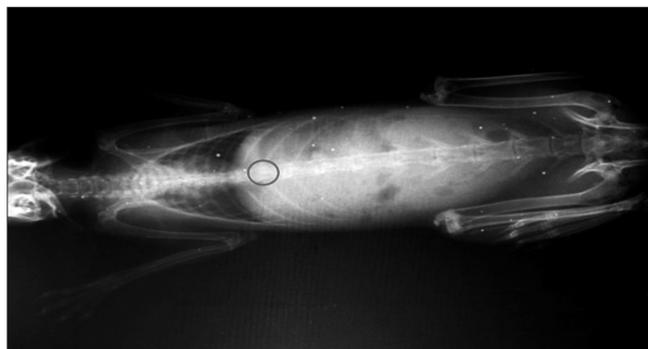


Figure 4: After second hour



Figure 5: After fourth hour



Figure 6: After sixth hour



Figure 7: After tenth hour

apparatus 2 (paddle method). 100 mg tablets were taken in 900 ml of acidic buffer (pH 1.2) maintained at 37°C and rotated at 50 rpm. At specific time intervals 5 ml of the sample withdrawn from the dissolution media and equal volume of media was replaced immediately. Withdrawn samples were filtered, suitably diluted and analyzed spectrophotometrically at 272 nm.

In vivo bio adhesive study

To study the bioadhesive character and mean residence time of the natural polymer in the stomach, barium sulphate loaded tablet was used. Two healthy rabbits weighing 2.5 kg were selected and administered orally with the tablet. X-ray photograph was taken at different time intervals shown in the Figures 4-7. (Animal ethical committee No: JSSCP/ IAEC/ M.PHARM/ PH. CEUTICS/ 05/ 2007 – 2008.)

RESULTS AND DISCUSSION

C. pulcherrima (CP) seeds isolated yielded 4.6% w/w of natural mucoadhesive agent. Physicochemical characters of selected natural mucoadhesive agent are given in Table 1, which is self-explanatory.

To determine swelling capacity of the gum, the discs prepared with the compression force of 3 kg/cm² were kept constant. Swelling index indicates higher in water at 6 h than with other buffer solution given in Table 1. An index of three is an indication of test polymer having good bioadhesive character.^[21]

Flow parameters from the tabular column indicates a good free flowing character of the polymer which is evident from the results of Angle of repose, Compressibility index and Hausner's ratio.

Drug content of the formulation was found to be $96.4 \pm 0.97\%$ [Table 3].

The adhesive strength of CP determined from shearing stress was found to be 254.13 ± 6.0 g. The mean detachment force between the natural adhesive agent and mucosal area was found 67.23 ± 1.2 g. Similarly, in the Wilhelmy plate method after the specified contact time, the mean weight required for pulling the plate out of the fresh mucus gel was 1.51 ± 0.5 g. From the tabular column, it is evident that the test agent shows a comparable adhesive strength with that of other polymers.

In vitro release studies [Figure 8] show 50% of the drug released from first 3 h and the remaining drug release was in a sustained manner in the next 7 h. Release shows improvement in sustaining property while increasing the natural adhesive agent concentration. F3CP (1:3) ratio shows more sustaining action up to 10 h (97%).

For the *in vivo* test, the rabbits received barium sulfate-loaded matrix tablet, which possessed strong mucoadhesive property that revealed by X-ray photographs at different time intervals. The tablet resists disintegration for longer period (upto 10 h) in the same location of stomach, which shows that the tablet

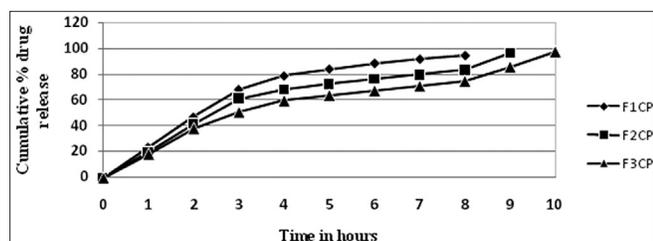


Figure 8: *In vitro* release profile of *Caesalpinia pulcherrima* formulation

has the residence time of up to 10 h. It may be due to the strong adhering property of the gum that has been proved by *in vitro* adhesive studies also.

CONCLUSION

The natural adhesive agent studied in our laboratory was obtained from *Caesalpinia pulcherrima* plant seeds. Better correlation found was between the results of the detachment force measurement in different models and *in vivo* studies. *Caesalpinia pulcherrima* was found to have mucoadhesiveness in *in vitro* and *in vivo* models and it acts as a better mucoadhesive agent in the extended drug delivery system designing through mucoadhesion to combat the crisis of nocturnal asthmatic attacks that too with lesser adverse effects during the treatment regime and also with more patient compliance. Further, the study will be extending to find out the stability and pharmacokinetics in future.

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Source of Support: Nil, **Conflict of Interest:** None declared.