Original Article

Evaluation of *Calendula* mucilage as a mucoadhesive and controlled release component in buccal tablets

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Abstract

Mucoadhesive drug delivery systems were developed to sustain drug delivery via various mucus membranes for either local or systemic delivery of poorly absorbed drugs such as peptides and proteins as well as drugs that are subjected to high first-pass metabolism. The present study was undertaken to use isolated *Calendula* mucilage as a mucoadhesive agent and to formulate controlled release buccoadhesive tablets with an intention to avoid hepatic first-pass metabolism as well as to enhance residence time of drug in the buccal cavity. The mucilage was isolated from the *Calendula* petals by aqueous extraction method and characterized for various physiochemical parameters as well as for its adhesive properties. By using direct compression technique, tablets were prepared containing dried mucilage and chlorpheniramine maleate (CPM) as a model drug. Three batches of tablets were prepared and evaluated containing three mucoadhesive components namely Methocel K4M, Carbopol 974P and isolated *Calendula* mucilage in 16.66%, 33.33 % and 50 % (1:2:3 ratio) resulting in 9 different formulations. FTIR studies between mucilage and CPM suggested the absence of a chemical interaction between CPM and *Calendula* mucilage. The results of the study showed that the isolated mucilage had good physicochemical and morphological characteristics and tablets conformed to the pharmacopoeial specifications. Also *in vitro* release studies showed controlled action of drug with increasing the concentration of the isolated *Calendula* mucilage as a mucoadhesive agent in the formulations. Permeability studies indicated that permeability behavior was not statistically different (P>0.05) by changing the mucoadhesive component. The formulated mucoadhesive tablets for buccal administration containing 75 mg *Calendula* mucilage showed controlled drug release. Thus, mucoadhesive natural *Calendula* mucilage based buccal tablets for controlled release were successfully formulated.

Keywords: *Calendula*; Natural polymers; Chlorpheniramine maleate; Controlled release; Mucoadhesive

INTRODUCTION

Free availability, relatively low cost, nontoxicity, ease of manufacturing, favorable *in vivo* performance, and versatility in controlling the release of drugs with a wide range of physicochemical properties are some of the imperative factors which may contribute to the successful and widespread use of polymeric systems. There is a continued need to develop new, safe, and effective polymers although a variety of polymeric substances are available to serve as mucoadhesive and controlled release component (1).

Natural polymers are easily available and when employed in controlled release drug delivery systems have some advantages such as bioacceptability, biocompatibility, bio-degradability and nontoxicity. Mucilages are most commonly used adjuvant in pharmaceutical preparations as binding, disintegrating, sus-pending, emulsifying and sustaining agents because of their low cost, ready availability, non-toxicity and non-irritancy (2,3). They consist of sugar and uronic acid units. They swell in water and form a gel (1).

Calendula officinalis L. (var. *prolifera* Hort) commonly known as pot marigold, is an aromatic annual plant that belongs to the Asteraceae (Compositae) family (4).

Calendula is native to the Mediterranean area (some believe it comes from Egypt) although it is widely spread throughout the world as an ornamental plant (5).

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On chemical analysis, the *Calendula* flowers were found to contain a volatile oil, many bitter chemical principles, different types of carotenoids, a lot of mucilage, plant resin, all kinds of polysaccharides, plant acids, variety of alcoholic compounds, saponins as well as other glycosides and different kinds of sterols (6).

Mucoadhesive drug delivery systems were developed to sustain drug delivery via various mucus membranes for either local or systemic delivery of poorly absorbed drugs such as peptides and proteins (7-9) as well as drugs that are subjected to high first-pass metabolism (10-12). Target sites include various mucus membranes such as the gastrointestinal tract (13,14), eye (15), cervix (16), vagina (17), nasal cavities (18) and oral cavities (8,9,19,20). Mucoadhesive agents also increase residence time of the delivery system and provide intimate contact between the dosage form and the mucus membrane of interest, leading to increased drug transport. Such a method of drug delivery is less invasive and serves as an alternate to the parenteral administration.

Most of the mucoadhesive materials are either synthetic or natural, hydrophilic or water-insoluble polymers and are capable of forming numerous hydrogen bonds because of the presence of carboxyl, sulfate, hydroxyl and amino functional groups. Formation of hydrogen bonds amongst the functional groups of the polymers and mucosal layer plays an important role. In general, stronger the hydrogen bonding, stronger is the adhesion. Various synthetic materials tested for mucoadhesion include Carbopol 934P, Carbopol 974P, sodium carboxymethyl cellulose (Sodium CMC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polymethyl methacrylates (PMMA), and polycarbophil, whereas natural materials tested for mucoadhesive properties include carageenan, xanthan gum, sodium alginate, gelatin, acacia, and tragacanth (21). All mucoadhesive materials interact with oligosaccharide molecules in the mucus layer that covers the mucosal epithelial surface.

The simplest dosage forms for delivery of drugs through the mucosa of the oral cavity are the conventional formulations like lozenges,

troches, gels, oral rinses, or mouthwashes would be (22,23). However, these conventional dosage forms have two major disadvantages which consist of an initial burst of activity followed by a rapid decrease in concentration (24,25) and limited stability due to the constant flow of saliva and the mobility of the involved tissues. Buccal mucoadhesive formulations which control the drug release are expected to overcome these problems.

The buccal cavity has a very limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery (26).

In the present study, an attempt was made to isolate and characterize the mucilage from *Calendula* flowers and also to evaluate the mucilage for its controlled release and mucoadhesive properties. Chlorpheniramine maleate was used as a model drug to evaluate the sustained-release potential of the mucilage. It has been used extensively as an antihistamine for symptomatic relief of the common cold and allergy (27).

MATERIALS AND METHODS

Materials

Chlorpheniramine maleate was received as gift sample from Alembic Ltd. Vadodara, Gujarat. Flowers were procured from local nursery of Vadodara. Ethyl alcohol, Methocel K4M, Carbopol 974P were procured form Loba Chem (Mumbai, India) and used as received. All other reagents used were of analytical grade.

Isolation of mucilage from Calendula flowers

The *Calendula* flowers and the petals were sun dried for 10 days. The dried petals were soaked in water for 5–6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Ethanol (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 35°C, collected, grounded, passed through a # 80 sieve and stored in a desiccator till use (28,29).

Characterization of isolated Calendula mucilage

The isolated dried mucilage was studied for percentage yield and characterized for various physiochemical parameters such as solubility, weight loss on drying (30), thin layer chromatography (31,32), viscosity, pH, swelling index and total carbohydrate content (33,34).

Compatibility study

Mixtures consisting of different ratios of CPM/*Calendula* mucilage, and either CPM or *Calendula* mucilage alone were subjected to FT-IR analysis using a model BRUKER ALPHA T FT-IR spectrophotometer (Bruker Optik GmbH, Germany).

Comparative mucoadhesive characterization of Calendula mucilage with Methocel K4M, Carbopol 974P as standard polymers; shear stress measurement

Different concentrations of the mucoadhesive agent solution, such as, 1, 2, and 3% w/v, using Methocel K4M, Carbopol 974P, and a natural isolated *Calendula* mucilage were prepared. Shear stress was calculated by self-fabricated apparatus made of wooden board with scale and two glass slides having two pans on the both sides mounted on a pulley. An excess of prepared solution was placed between two glass slides and 1000 g weight was placed on glass slide for 5 min to compress the sample to uniform thickness. Weight (250 g) was added to the pan. The weight required to separate two slides was taken as a measure of shear stress (35).

Formulation and evaluation of buccal tablets containing Calendula mucilage, Methocel K4 M and Carbopol 974 P

Three batches of tablets each containing 8 mg of CPM as model drug were prepared changing the quantity of mucoadhesive component (16.66%, 33.33% and 50%) by direct compression method using flat face 6-mm punch (Rimek Mini Press-I machine), resulting in 9 different formulations (CF1, CF2, CF3 for Carbopol 974P; CMF1, CMF2, CMF3 for *Calendula* mucilage; HF1, HF2, HF3 for Methocel K4M). The tablet weight was adjusted to 150 mg. (Table 4). The prepared tablets were evaluated for average thickness, hardness, friability test, weight variation test and mucoadhesive strength measurement (36,37).

Dissolution testing

Dissolution studies were performed using a USP dissolution apparatus 2 (paddle method) at 50 rpm. The dissolution medium consisted of 900 ml phosphate buffer (pH 6.8) at 37°C. Samples (sampling interval 60 min) were analyzed for CPM by UV spectrophotometer at 262 nm. Tablets were tested and the experiments were performed in triplicate. For each formulation, the time to reach 90% of CPM release (*t*90%) was calculated from the mean dissolution data according to the respective dissolution curve.

The tablet was designed to absorb water and swell, changing into a gelling mass that would release a high percentage of the drug before disintegration occur. Therefore the drug release from a tablet can be considered as release from a swelling matrix rather than a release from a disintegrating matrix. The release kinetics of each tablet can be assessed by inserting the experimental data in the semi-empirical equation $M_t/M_\infty = Kt^n$ where M_t/M_∞ is the fractional amount of the drug at the time t, K is a kinetic constant of the system which indicates rate of the release and the n is the release exponent, indicative of the mechanism of release. Values for n and K for each system were obtained from the logarithmic plot of the fractional release against the time, considering data between the first withdrawal at 30 min and the one corresponding to the release of

60% of the dose (38). The slope of the line is *n* while log *K* is the intercept. The values of n and K were calculated by regression analysis and the statistical parameter R^2 was established to evaluate the fitting of the semi-empirical equation to the release kinetics.

Mucoadhesion studies

The aim of this study was to quantitate the force of detachment (mucoadhesive strength) of CPM buccal tablets applied to freshly excised goat buccal mucosa as a model membrane. The force of detachment was measured in grams by using self fabricated apparatus (modified physical balance.

In Vitro drug permeation

The *in vitro* buccal drug permeation studies of CPM through the goat buccal mucosa were done by using modified Franz diffusion cell at 37 °C ± 0.5 °C (diameter of 1.5 cm with a diffusional area of 1.76 cm^2). Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed in donor compartment with the core facing the mucosa and the compartments clamped together. The receptor compartment (15 ml capacity) was filled with phosphate buffer of pH 6.8. The temperature of media was maintained at 37 ± 0.5° C with the help of temperature controlled water jacket and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. A 2 ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 262 nm using a UV spectrophotometer. The volume of release media was maintained by adding equal volume of the fresh media after every sampling.

A test on the reference suspension was carried out by placing 2 ml of the suspension in the donor compartment. The suspension was obtained by adding an excess of drug in purified water at room temperature. The system was heated up to 50° C in order to dissolve the drug and then equilibrated at 37° C ± 0.5° C for 24 h (40,41).

Permeation through the membrane can be considered as a passive diffusion process and can be described by Fick's law equation:

$$Js = dQr/ Adt$$

where, Js is the steady-state buccal mucosa flux in mcg/cm^2 per h, dQr is the change in quantity of material passing through the membrane into the receptor compartment expressed in mcg, A is the active diffusion area in cm^2, and dt is the change in time in hours. The steady state flux of CPM through the goat buccal mucosa was calculated from the slope of the linear portion of the cumulative amount permeated through the membrane per unit area versus time plot. For the CPM suspension the permeability coefficient was calculated using the equation:

$$Kp = Js/ Cd$$

where, Kp is the permeability coefficient, Js is the flux calculated at the steady-time and Cd is the donor concentration (42).

RESULTS

The mucilage was isolated and characterized for various physicochemical properties. The results are shown in Table 1.

Fig. 1 depicts the results of compatibility study. The FT-IR spectrum of *Calendula* mucilage showed broad characteristics peak at 2424.98 cm^{-1} due to O-H intramolecular hydrogen bonding, sharp peaks at 1621.94 cm^{-1} C-C bond stretching vibrations, 1202 cm^{-1} is

Table 1. Physicochemical parameters of *Calendula* flower mucilage

S. No.	Parameter	Observation
1	color	Greenish brown
2	Solubility with water	Colloidal solution formed
3	pH (1% w/v)	6.3
4	Loss on drying	4.2 %
5	Swelling index	19.5
6	Test for carbohydrates (Molish test)	Positive
7	Test for Tannins (Ferric chloride test)	Negative
8	Viscosity (3.0 % solution in water)	1290 cp
9	Total carbohydrates content	79.08 %
10	Thin layer chromatography	Spot corresponding to glucose and mannose
11	Percentage yield	11%
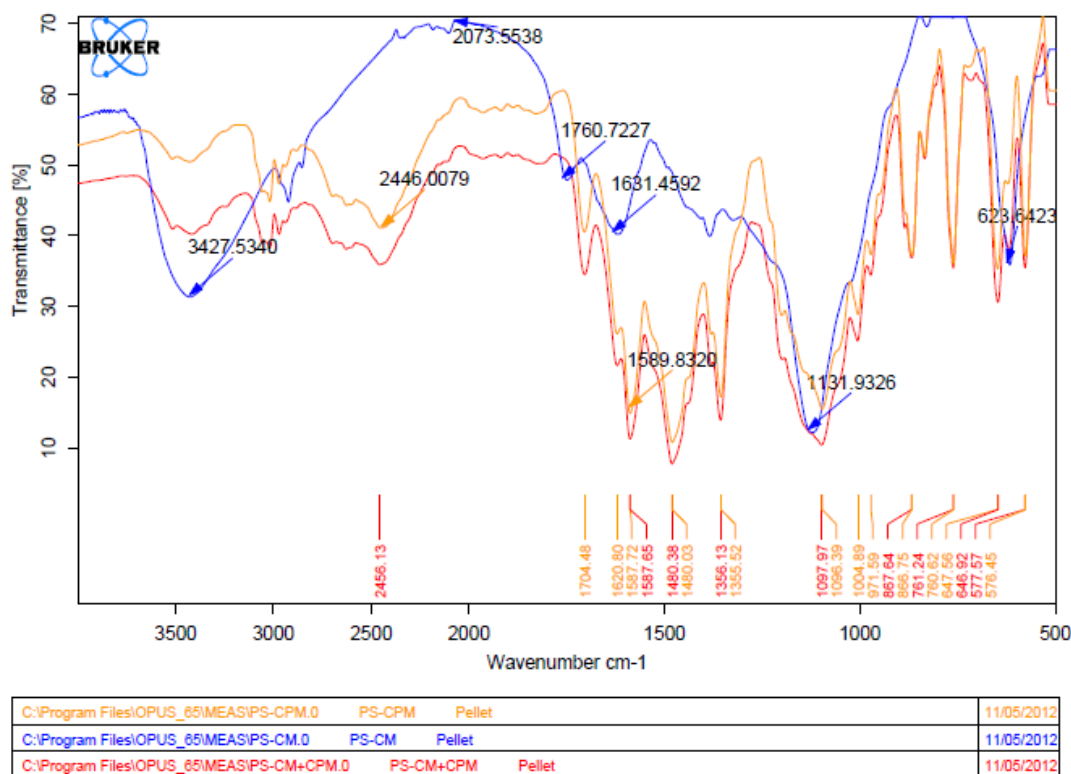
Fig. 1. FT-IR spectra of CPM-*Calendula* mucilage (CM).

Table 2. Shear stress measurement

Name of the polymer	Contact time (min)	Weight required[a] (g)
Carbopol 974P	5	23.5 ± 1.2
	10	48.0 ± 1.3
	15	70 ± 1.4
	30	84.5 ± 1.2
Calendula mucilage	5	27.5 ± 1.7
	10	43 ± 1.5
	15	60.0 ± 1.3
	30	70.5 ± 1.1
Methocel K4M	5	28.0 ± 1.2
	10	44.5 ± 1.2
	15	58.5 ± 2.0
	30	71.5 ± 1.5

[a]Each value represents the mean ± S.D. n=3

present due to C-N aliphatic vibrations and 616.28 cm^{-1} is due to C=C bending vibrations. The FT-IR spectrum of CPM showed characteristic bands at 3018 cm^{-1} aromatic C-H stretching vibrations, 2453 cm^{-1} due to C-H stretching of alkane, 1704 cm^{-1} due to C=O stretch, 1620 due to C=C stretching, 1587 cm^{-1} due to C=N stretching, 1480 cm^{-1} due to C-H stretching, 1335 cm^{-1} due to C-H bending vibrations. A sharp band can be observed at 866 and 834 due to C-C stretching vibration of maleate and 760 cm^{-1} due to C-Cl stretching vibration.

While demonstrating shear stress measurement *Calendula* mucilage was found to possess comparable and remarkable adhesiveness to that of Methocel K4M and less adhesiveness than Carbopol 974P within 60 min. The results of shear stress measurement are shown in Table 2.

Three batches of tablets each containing 8 mg of CPM as model drug were prepared with different quantity of mucoadhesive component (16.66 %, 33.33 % and 50 %) by direct

compression method, resulting in 9 different formulations (Table 3). The results of evaluation of tablets are shown in Table 4. The thickness, hardness, average weight and drug content percent of all formulations CF1, CF2, CF3, CMF1, CMF2, CMF3, HF1, HF2, and HF3 was in the range of 2.20 ± 0.3 to 2.45 ± 0.05 mm, 4 to 6 Kg/Cm^2, 148 ± 0.81 to 151 ± 0.86, 97.5 ± 0.5 to 99.7 ± 0.6 respectively and friability percentage in all these formulations was found to be less than 0.1%.

The results for mucoadhesion studies are shown in Table 5. The mucoadhesive strength of *Calendula* mucilage was comparable to that of Methocel K4M.

The percentage of drug released from tablets containing the different mucoadhesive agents at different concentrations is depicted in Figs. 2, 3, and 4. The values of *n*, *K* and R^2 of these release rates are represented in Table 6.

Fig. 5 depicts the comparative drug release between tablets containing the three mucoadhesive polymers, at highest concentration (formulation CF3, CMF3, HF3). The permeation profile of the CPM suspension in water is shown in Fig. 6, while Figs. 7, 8, and 9 show permeation profiles of tablets. Permeation tests from the CPM suspension showed a Kp value of 8.99×10^{-2} corresponding to a flux of 0.1799 mcg $\times$ cm^{-2} $\times$ h^{-1}. The fluxes and Kp values in these profiles are reported in Table 7 that also shows the values for the CPM suspension in water.

Table 3. Composition of tablets

S. No.	Ingredients	Quantity/Tab (mg)		
		CF1; MF1; HF1	CF2; MF2; HF2	CF3; MF3; HF3
1	Drug (CPM)	8	8	8
2	Dicalcium Phosphate	115	90	65
3	Mucoadhesive Component[a] (16.66	25	50	75
4	Magnesium Stearate	1	1	1
5	Talc	1	1	1

[a]Carboxyvinyl polymer (Carbopol 974P) or natural *Calendula* mucilage or Hydroxypropy lmethylcellulose (Methocel K4M) result in 9 formulations as CF1, CF2, CF3 for Carbopol 974P; CMF1, CMF2, CMF3 for *Calendula* mucilage; HF1, HF2, HF3 for Methocel K4M.

Table 4. Evaluation of tablets

Parameter	Carbopol 974P			*Calendula* mucilage			Methocel K4M		
	CF1	CF2	CF3	CMF1	CMF2	CMF3	HF1	HF2	HF3
Avg Weight (mg)[a]	149 ± 0.82	148.66 ± 0.94	148 ± 0.82	150.66 ± 0.47	152 ± 0.82	149.66 ± 0.47	148 ± 0.82	150 ± 0.82	151 ± 0.82
Hardness (Kg / Cm^2)[a]	5 ± 0.81	5.1 ± 0.62	6 ± 0.81	4 ± 0.81	5.3 ± 0.47	6.1 ± 0.62	5.2 ± 0.52	5.1 ± 0.32	5.1 ± 0.23
Drug content (%)[a]	99.8 ± 0.40	97.2 ± 0.50	98.4 ± 0.50	99.8 ± 0.40	98 ± 1.1	98.6 ± 0.30	99 ± 0.40	98.1 ± 0.20	99 ± 0.30
Thickness (mm)[a]	2.11 ± 0.02	2.10 ± 0.03	2.40 ± 0.01	2.30 ± 0.04	2.40 ± 0.05	2.15 ± 0.02	2.28 ± 0.05	2.36 ± 0.01	2.33 ± 0.03
Friability (%)	Less than 0.1% in all formulations								

[a]Each value represents the mean ± S.D. n=3

Table 5. Mucoadhesive strength determination

Formulation	Mucoadhesive strength[a] (g)
HF1	28.30 ± 1.09
HF2	32.41 ± 1.79
HF3	40.50 ± 1.05
CF1	30.31 ± 1.15
CF2	37.80 ± 1.98
CF3	43.40 ± 1.82
CMF1	29.60 ± 1.78
CMF2	35.39 ± 1.91
CMF3	42.72 ± 1.89

[a]Each value represents the mean ± S.D. n=3

Table 6. n and *k* values of the different tablets

Para-meters	Carbopol 974P			*Calendula* mucilage			Methocel K4M		
	CF1	CF2	CF3	CMF1	CMF2	CMF3	HF1	HF2	HF3
K (cm $\times$ h^{-1}) [a]	-1.1143 ± 0.03652	-1.114 ± 0.09582	-1.1322 ± 0.17380	-1.0914 ± 0.02340	-0.8426 ± 0.06717	-1.114 ± 0.10210	-1.0599 ± 0.12210	-0.8463 ± 0.07984	-0.4757 ± 0.08746
n[a]	0.4641 ± 0.01601	0.4727 ± 0.04583	0.4578 ± 0.07822	0.4704 ± 0.01160	0.3759 ± 0.04213	0.4727 ± 0.04738	0.4628 ± 0.05164	0.378 ± 0.03870	0.4757 ± 0.03775
R^2	0.9626	0.9917	0.9874	0.9722	0.9696	0.9917	0.9809	0.9686	0.9904

[a]Each value represents the mean ± S.D. n=3

Table 7. Flux (Js) and Kp values of CPM from tablets and from the suspension in purified water

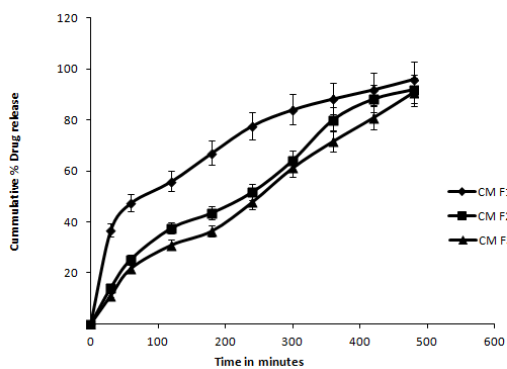| Para-meters	Carbopol 974 P			*Calendula* mucilage			Methocel K4M			CPM Suspension in Purified water
	CF1	CF2	CF3	CMF1	CMF2	CMF3	HF1	HF2	HF3	
Js (mcg $\times$ cm^{-2} $\times$ h^{-1})	0.0247 ± 0.021	0.1413 ± 0.011	0.5938 ± 0.044	0.0252 ± 0.004	0.2326 ± 0.031	0.8907 ± 0.027	0.0310 ± 0.045	0.22608 ± 0.044	0.8907 ± 0.083	0.22607 ± 0.027
Kp[a]	0.0157 ± 0.015	0.02296 ± 0.031	0.04658 ± 0.034	0.01519 ± 0.032	0.0241 ± 0.036	0.02306 ± 0.039	0.0190 ± 0.024	0.02306 ± 0.033	0.0230 ± 0.037	0.02300 ± 0.033

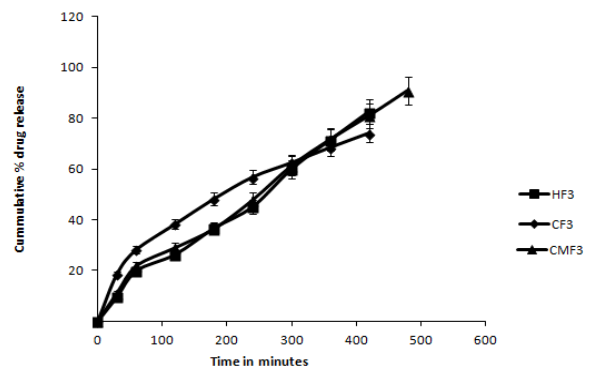[a]Each value represents the mean ± S.D. n=3
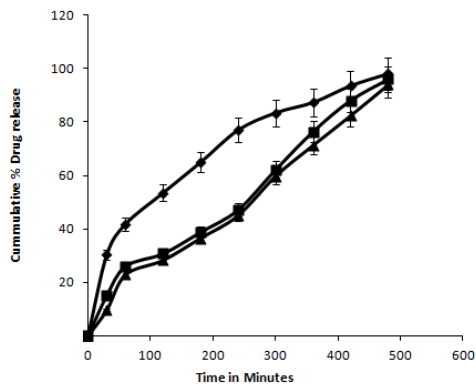
Fig. 2. Release profile of tablets containing Methocel K4M in 16.66 %, 33.33 % and 50 % quantity.
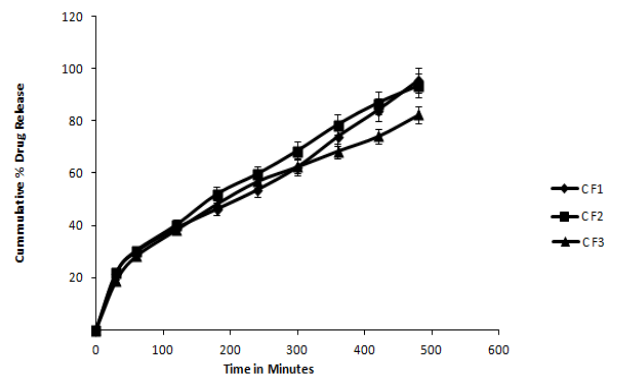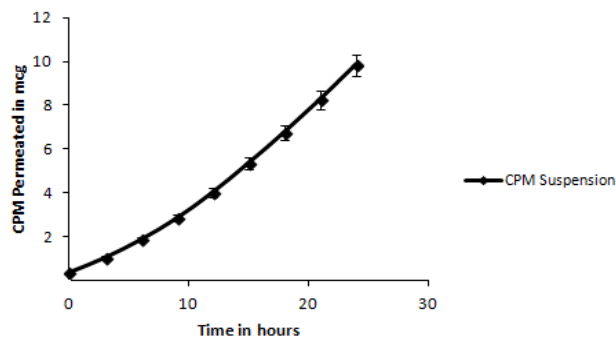

Fig. 3. Release profile of tablets containing Carbopol 974P in 16.66 %, 33.33 % and 50 % quantity.
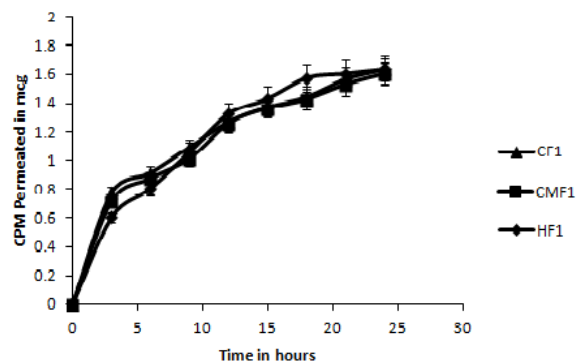

**Fig. 4.** Release profile of tablets containing *Calendula* mucilage in 16.66 %, 33.33 % and 50 % quantity.

Fig. 5. Comparison between release profile of tablets containing Methocel K4M, Carbopol 974P and *Calendula* mucilage at higher quantity.
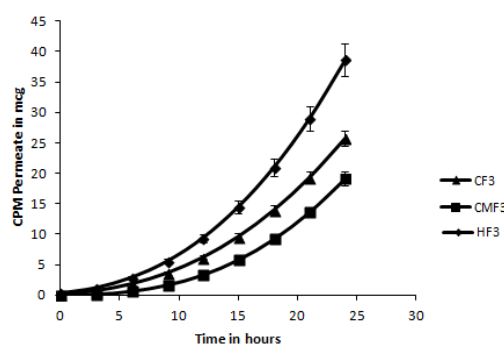
45

Fig. 6. Cumulative amount of permeated CPM from a saturated solution in purified water.

Fig. 7. Cumulative amount of permeated CPM from the tablets (CF1, CMF1 and HF1) containing Carbopol 974P, *Calendula* mucilage and Methocel K4M.
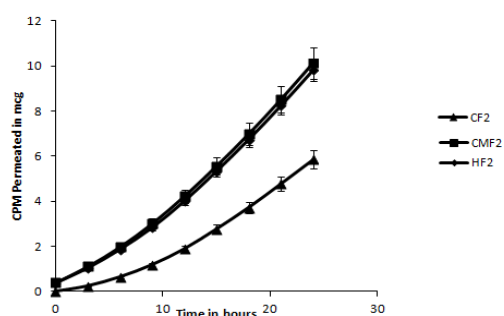
Fig. 8. Cumulative amount of permeated CPM from the tablets (CF2, CMF2 and HF2) containing Carbopol 974P, *Calendula* mucilage and Methocel K4M.

Fig. 9. Cumulative amount of permeated CPM from the tablets (CF3, CMF3 and HF3) containing Carbopol 974P, *Calendula* mucilage and Methocel K4M.

DISCUSSION

The main aim of this work was to isolate and evaluate mucilage from *Calendula* flowers for its controlled release and mucoadhesive properties in buccal tablets. Carbopol 974P, Methocel K4M and natural *Calendula* mucilage were selected as buccoadhesive polymers. *Calendula* flowers yielded 10-11% w/w mucilage using alcohol as mucilage precipitating solvent. The isolated mucilage was characterized for various physicochemical properties and specifications were set as per the Pharmacopoeial guidelines (34). The mucilage was found to be water miscible and it formed colloidal solution in water. The mucilage was tested for presence of carbohydrates and a positive result was obtained. Total carbohydrates content was found to be 79.08%. The pH was found 6.3, indicating that the *Calendula* mucilage might not irritate the epithelium and

mucus membrane of oral cavity (30-34). All other physicochemical parameters conferred to the pharmacopoeial guidelines.

Results of FT-IR spectroscopy studies suggested the absence of a chemical interaction between CPM and *Calendula* mucilage.

All the formulations pass test for weight variation, hardness, content uniformity and show acceptable results with respect to drug content (99.7 ± 0.6) and friability percent.

The mucoadhesive characteristics were affected by ratio of mucoadhesive agents. Due to a higher concentration of the isolated *Calendula* mucilage in formulation CMF3, it showed more mucoadhesive strength than CMF1 and CMF2. The highest mucoadhesive strength may be due to possibility of proper hydration and erosion of natural polymer adhered to mucosal surface with strong bond which have been supported by maximum mucoadhesive force.

From the R^2 values, it is observed that the semi-empirical equation described by Ritger and Peppas is able to fit the release from tablets containing all the three polymers. The polymers showed a better modulation capacity, with a release on average, of 37 and 39% respectively during two h. This aspect is shown by the comparison between tablets containing three mucoadhesive polymers, at highest concentration (formulations CF3, CMF3, HF3) in Fig. 4. Tablets containing Methocel K4M and *Calendula* mucilage showed a controlled release, characterized by an exponent n that changed according to the type of mucoadhesive polymer. For tablets containing Methocel K4M, n was between 0.4759 ± 0.01 and 0.4827 ± 0.07 and for *Calendula* mucilage between 0.4880 ± 0.01 and 0.4787 ± 0.03. An "n" value of 0.5 indicates a Fickian process that describes release of a drug from a matrix governed by diffusion.

Tablet permeation profiles are lower than those obtained from the suspension (tablet fluxes as a whole fell under 0.0575 ± 0.002 and 0.1789 ± 0.033 mcg $\times$ cm^{-2} $\times$ h^{-1}) which can be explained when considering that CPM present in tablets must be dissolved and released before permeation occurs. From the comparison of profiles of different tablets, it is observed that changing the mucoadhesive component, permeability behavior was not statistically different (P>0.05). The higher fluxes shown by Methocel K4M and *Calendula* mucilage can be explained by its rapid deaggregation. On the other hand, in all tablets, the cumulative amount of permeated CPM increased in respect to the concentration of the mucoadhesive polymer, probably because an increase in the mucoadhesive component allowed a closer contact between the tablet and the mucosa.

CONCLUSION

FTIR studies showed that there was no interaction between the CPM and the *Calendula* mucilage. The CPM release kinetics showed that tablets containing *Calendula* mucilage were the better formulations because they showed a prolonged drug release with linear kinetics, comparable to Methocel K4M.

Permeability tests indicated that all tablets showed a satisfactory drug permeability flux, compared with the flux from a saturated solution of drug in water. The permeability behavior was not statistically different (P>0.05) on changing the mucoadhesive component.

In conclusion, the developed mucoadhesive tablets for buccal administration containing *Calendula* mucilage (CMF3) showed controlled drug release.

Our future studies will be directed at determining the bioavailability of CPM from the prototype *Calendula* mucilage based buccal tablets following application to the buccal mucosa of rabbits.

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